CLINICAL STUDY PROTOCOL

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

NCT Number: NCT03772041

PRT NO.: 263-102-00003

Version Date: 27 March 2020 (Version 3.0)

Otsuka Pharmaceutical Co., Ltd.

Investigational Medicinal Product

OPC-61815

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Protocol No. 263-102-00003

CONFIDENTIAL – PROPRIETARY INFORMATION

Clinical Development Phase:	3
Sponsor:	Otsuka Pharmaceutical Co., Ltd.
Immediately Reportable Event	Otsuka Pharmaceutical Co., Ltd. Department of Pharmacovigilance Email: IRE_263-102-00003@otsuka.jp
Amendment 2 Approval: Amendment 1 Approval: Approval:	27 Mar 2020 15 Mar 2019 26 Sep 2018
Date of Translation:	9 Jun 2020

Protocol Synopsis

Name of Sponsor: Otsuka Pharmaceutical Co., Ltd. Name of Investigational Medicinal Product: OPC-61815	Protocol No.: 263-102-00003
Protocol Title:	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
Clinical Phase/Trial Type:	Phase 3/Confirmatory Trial
Treatment Indication:	Congestive heart failure (CHF) patients with volume overload despite having received diuretics other than vasopressin antagonists
Objective(s):	Primary: 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 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
Trial Design:	Multicenter, randomized, double-blind, active-controlled, parallel group, non-inferiority trial
Subject Population:	Male and female CHF patients age 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 The sample size was set at a total of 288 subjects, comprising 144 subjects in each group.
Inclusion/Exclusion Criteria:	**Inclusion criteria (screening period):** 1) Patients receiving any of the following oral diuretics (including patients planning to initiate treatment during the run-in period) • Loop diuretics equivalent to furosemide tablet or fine granules at a dose of 40 mg/day or higher

- Concomitant use of a loop diuretic and a thiazide diuretic (including thiazide analogs) at any dose
- Concomitant use of a loop diuretic and an aldosterone antagonist or potassium-sparing diuretic agent at any dose

Note: See Table 3.4-1 for the types and doses of concomitant diuretics

2) Patients with CHF in whom lower limb edema, pulmonary congestion, or jugular venous distension due to volume overload is present. Patients with pulmonary congestion may be enrolled if pulmonary congestion is confirmed by chest x-ray performed within 14 days prior to informed consent.
3) Male and female patients age of 20 to 85, inclusive, at the time of informed consent
4) Patients who are currently hospitalized or who are able to be hospitalized from the day before the run-in period (on Day −4) until the end of the treatment period
5) Patients who are capable of taking oral tablets
6) Patients who are capable of giving consent

Inclusion criteria (run-in period):

7) Patients with lower limb edema, jugular venous distension (on Day −1 of the run-in period), or pulmonary congestion (confirmed by chest x-ray during the run-in period)
8) Patients who have received diuretics with no change in dose or regimen during the run-in period
9) Patients with no more than 1.0 kg change in body weight over the 2 days (Day −2 and −1 of the run-in period) prior to initial administration of the investigational medicinal product (IMP)

Exclusion criteria:

1) Patients with acute heart failure
2) Patients with mainly noncardiogenic congestive symptoms
3) Patients who are on a ventricular assist device
4) Patients who have any of the following diseases, complications, or conditions:
   - Suspected hypovolemia
   - Hypertrophic cardiomyopathy (excluding dilated

phase)
- Valvular disease with significant valvular stenosis
- Hepatic encephalopathy with difficulty in adequate fluid intake

5) Patients who have experienced acute myocardial infarction within 30 days prior to the screening examination
6) Patients with a definite diagnosis of active myocarditis or amyloid cardiomyopathy
7) Patients who have any of the following diseases, complications, or conditions:
   - Poorly controlled diabetes mellitus
   - Anuria
   - Dysuria associated with urinary tract obstruction, calculus, or tumor
8) Patients who have any of the following medical histories:
   - History of sustained ventricular tachycardia or ventricular fibrillation within 30 days prior to the screening examination (for patients without an implantable cardioverter defibrillator)
   - History of cerebrovascular disease (excluding asymptomatic cerebral infarction) within 6 months prior to the screening examination
   - History of hypersensitivity or idiosyncratic reaction to benzazepines or benzazepine derivatives such as the ingredients of OPC-61815, tolvaptan, mozavaptan hydrochloride, and benazepril hydrochloride
9) Patients who are severely obese (body mass index [BMI]: body weight [kg]/height $[m]^2$) exceeding 35 kg/m^2
10) Patients with supine systolic blood pressure of <90 mmHg
11) Patients with any of the following abnormalities in laboratory test results:
    Total bilirubin: >3.0 mg/dL, serum creatinine: >3.0 mg/dL, serum sodium: <125 mEq/L or >147 mEq/L, serum potassium: >5.5 mEq/L
12) Patients with current symptoms or a history of hepatic impairment (including patients with aspartate

	aminotransferase [AST] or alanine aminotransferase [ALT] exceeding 3 times the upper limit of the reference range at the screening examination) 13) Patients who are unable to sense thirst or who have difficulty with fluid intake 14) Female patients who are breast-feeding or who have a positive pregnancy test result prior to receiving investigational product (IMP) 15) Sexually active males or women of childbearing potential (WOCBP) who do not agree to practice birth control or remain abstinent during the trial and for 30 days after the final IMP administration. 16) Patients who have received tolvaptan within 28 days prior to the screening examination 17) Patients who have participated in a clinical trial in which they received OPC-61815 18) Patients who have participated in another clinical trial and received another IMP within 30 days prior to the screening examination 19) Patients who are otherwise judged to be ineligible by the investigator or subinvestigator
Trial Site(s):	Approximately 55 sites in Japan
Investigational Medicinal Product(s), Dose, Dosage regimen, Treatment period, Formulation, Mode of Administration:	The IMPs administered in this trial will be a lyophilized formulation containing 16 mg of OPC-61815 or placebo in a vial and tolvaptan 15-mg tablet or placebo tablet. 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. Once daily, first either tolvaptan 15-mg tablet or placebo tablet will be orally administered, followed immediately by 1-hour intravenous administration of either OPC-61815 injection at 16 mg or placebo injection. The treatment period will be 5 days.
Trial Assessments:	Efficacy: Body weight, congestive symptoms (lower limb edema, pulmonary congestion, jugular venous distension, hepatomegaly, cardiothoracic ratio, pulmonary rales, and cardiac third sound), and New York Heart Association (NYHA) classification Pharmacokinetic: Blood sampling for plasma concentrations of OPC-61815 free form and tolvaptan (OPC-41061) Pharmacodynamics: Daily urine volume, daily fluid intake,

	serum sodium concentration, serum potassium concentration, serum osmolality, biomarker measurements (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 I), and urine osmolality Safety: Adverse events, clinical laboratory tests (including pregnancy test), physical examination, vital signs (blood pressure, pulse rate, and body temperature), and 12-lead electrocardiography (ECG) Screening/Other: Medical and medication history, physical examination, laboratory tests, vital signs, body weight, urine pregnancy test, and DNA storage
Criteria for Evaluation:	**Primary Endpoint:** Change in body weight from baseline (before IMP administration on Day 1) at time of final IMP administration (day after final IMP administration) **Secondary Endpoints:** Congestive symptoms (lower limb edema, pulmonary congestion, jugular venous distension, hepatomegaly, cardiothoracic ratio, pulmonary rales, and cardiac third sound) and NYHA classification **Pharmacokinetic Endpoint:** Plasma concentrations of OPC-61815 free form and tolvaptan (OPC-41061) **Pharmacodynamic Endpoints:** Daily urine volume, daily fluid intake, daily fluid balance, serum sodium concentration, serum potassium concentration, serum osmolality, biomarker measurements (plasma concentrations of AVP and BNP, plasma renin activity, and serum concentrations of NT-proBNP and troponin I), daily urine sodium excretion, daily urine potassium excretion, and urine osmolality **Safety Endpoints:** Adverse events, clinical laboratory tests (including pregnancy test), physical examination, vital signs (blood pressure, pulse rate, and body temperature), and 12-lead ECG

Statistical Methods:	**Statistical Methods for the Primary Endpoint:** The primary endpoint is change in body weight from baseline (before IMP administration on Day 1) at the time of final IMP administration. Main analysis will be performed using an ANCOVA model with treatment as the fixed effect factor and body weight at baseline as a covariate. The least-square mean of the difference between the OPC-61815 16-mg injection group and the tolvaptan 15-mg tablet group and its two-sided 95% confidence interval (CI) 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 confidence interval does not exceed 0.48. **Rationale for 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 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).
Trial Duration:	Planned duration of the clinical trial: Jan 2019 to Jul 2020 Planned duration of trial participation for each subject: Maximum of 22 days (screening [4 to 7 days before start of IMP administration], 3 days for run-in period, 6 days for treatment period, and post-treatment follow-up at 7 to 10 days after final IMP administration)

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List of Abbreviations

Abbreviation	Definition
ADPKD	Autosomal dominant polycystic kidney disease
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AVP	Arginine vasopressin
BMI	Body mass index
BNP	Brain natriuretic peptide
cAMP	Cyclic adenosine 3',5'-monophosphate
CHF	Congestive heart failure
CI	Confidence interval
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EU	European Union
FAS	Full analysis set
GCP	Good Clinical Practice
hCG	Human chorionic gonadotropin
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IMP	Investigational medicinal product
IRB	Institutional review board
IRE	Immediately reportable event
IWRS	Interactive Web Response System
Ki	Inhibition constant
LOCF	Last Observation Carried Forward
NYHA	New York Heart Association
NT-proBNP	N-terminal fragment of brain natriuretic peptide precursor
PAP	Prostatic acid phosphatase
PPK	Population pharmacokinetic
PQC	Product quality complaint
QTc	QT corrected for heart rate
SAE	Serious adverse event
SD	Standard deviation
SIADH	Syndrome of inappropriate secretion of antidiuretic hormone

TEAE	Treatment-emergent adverse event
TRACP-5b	Tartrate-resistant acid phosphatase 5b
ULN	Upper limit of normal
US	United States
WOCBP	Women of childbearing potential

List of Pharmacokinetic Parameters

Abbreviation or term	Unit	Definition
AUC_{∞}	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
CL	L/h	Total body clearance of drug from the plasma
C_{max}	ng/mL	Peak (maximum) plasma concentration of the drug
$t_{1/2,z}$	h	Terminal-phase elimination half-life
t_{max}	h	Time to maximum plasma concentration
V_z	L	Apparent volume of distribution during the terminal phase (λz)

1 Introduction

Tolvaptan is an arginine vasopressin (AVP) V_2 receptor antagonist synthesized by Otsuka Pharmaceutical Co., Ltd. (Otsuka Pharmaceutical). It promotes water excretion (aquaresis) without affecting electrolyte excretion, by specifically inhibiting the binding of AVP to V_2-receptor at distal parts of the nephron. Congestive heart failure (CHF) is manifested by dyspnoea, orthopnoea, jugular venous distension, and other symptoms[1], and treated primarily with diuretics.[2] Conventional diuretics (mainly loop diuretics) exert their diuretic effect by increasing electrolyte excretion in the urine. This mechanism of action makes them difficult to be a therapeutic option for patients with decreased serum electrolyte levels. Because conventional diuretics can also impair renal function at high dose levels, a dose increase is not always an option even in patients with insufficient response. In contrast, an add-on diuretic effect can be expected with tolvaptan because of its mechanism of action, which differs from those of other conventional diuretics. Moreover, tolvaptan does not lower serum electrolyte levels and has little effect on renal function, making it an option for patients in whom dose increases or prolonged treatment with conventional diuretic is unsuitable.

In Japan, tolvaptan was approved under the trade name of Samsca® Tablets for "the treatment of volume overload in heart failure when adequate response is not obtained with other diuretics (eg, loop diuretics)" in 2010, for "the treatment of fluid retention in hepatic cirrhosis when adequate response is not obtained with other diuretics (eg, loop diuretics)" in 2013, and for "suppression of progression of autosomal dominant polycystic kidney disease (ADPKD) in patients with increased kidney volume and a rapid rate of increase" in 2014. Outside Japan, tolvaptan has received approvals for the following indications: "the treatment of clinically significant hypervolemic and euvolemic hyponatremia, including patients with heart failure and Syndrome of Inappropriate Antidiuretic Hormone (SIADH)" in the United States (US) in 2009, "the treatment of hyponatremia secondary to SIADH in adults" in the European Union (EU) in 2009, "slowing the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with CKD stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease" in the EU in 2015, and "slowing kidney function decline in adults at risk of rapidly progressing ADPKD" in the US in 2018 (in overseas marketed under the name of Jinarc in the EU and Jynarque in the US). Tolvaptan is currently approved in more than 40 countries and regions.

Tolvaptan has been administered to patients in clinical settings as an oral aquaretic agent as a useful treatment option for heart failure patients with volume overload despite having received other conventional diuretics. However, in clinical practice, there is a demand for intravenously injectable aquaretic drugs that have similar effects to tolvaptan and can be administered intravenously are needed for heart failure patients when oral administration is not feasible/desirable, eg, due to impaired consciousness, decreased absorption of oral tablets due to edema of the gastrointestinal tract associated with central venous pressure elevation caused by heart failure (gastrointestinal oedema), oxygen therapy, or decreased swallowing function in elderly patients. Tolvaptan is not readily soluble in water and not suitable for development as an injection. Otsuka Pharmaceutical therefore synthesized the new intravenous aquaretic OPC-61815. OPC-61815 is a compound with improved water solubility of tolvaptan, an AVP V_2-receptor antagonist, by the phosphorylation of the hydroxy group in the benzazepine ring, and it is readily metabolized to tolvaptan in the body through the hydrolysis of the phosphate ester site by an alkaline or acid phosphatase. OPC-61815 is being developed with an expectation to be effective for the treatment of volume overload in heart failure when adequate response is not obtained with other diuretics (eg, loop diuretics).

To date, the following trials of OPC-61815 has been completed: three phase 1 trials in healthy males: a single intravenous dose trial (263-08-001), repeated intravenous dose trial (263-09-001), and trial investigating the rate of intravenous administration (263-10-005), as well as one phase 2 clinical pharmacology trial in CHF patients (263-102-00001). Based on the results of these trials, this trial will be conducted 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 CHF patients.

1.1 Nonclinical Data

In a receptor binding study using ^{3}H-AVP as a labeled ligand, OPC-61815 showed affinity for human AVP V_2 receptor with an inhibition constant (K_i) value of 6.13 ± 1.34 nM that was approximately 1/14 that of the main active metabolite tolvaptan (K_i, 0.43 ± 0.06 nM). OPC-61815 showed low affinity for human AVP V_{1a} receptor with a K_i value of 54.2 ± 16.8 nM that was approximately 1/4 that of tolvaptan (K_i, 12.3 ± 0.80 nM). Neither OPC-61815 nor tolvaptan had affinity for human AVP V_{1b} receptor. OPC-61815 and tolvaptan inhibited AVP-induced cyclic adenosine 3',5'-monophosphate

(cAMP) production in a human endocervical carcinoma cell line expressing human AVP V_2 receptors, indicating that both drugs have an AVP V_2 receptor antagonistic activity. However, neither OPC-61815 nor tolvaptan alone increased cAMP production, suggesting that they possess no V_2 receptor agonistic activity.

In conscious rats given a single intravenous administration of OPC-61815 at 0.1275 to 12.75 mg/kg, dose dependent increase in urine volume and decreased urine osmolality were observed and neither of these effects were attenuated with a 7-day repeated intravenous administration of OPC-61815. In beagle dogs given a single intravenous administration of OPC-61815 at 0.1275 to 3.825 mg/kg, dose-dependent increase in urine volume and decrease in urine osmolality were observed accompanied by a dose-dependent increase in free water clearance, indicating that OPC-61815 is an aquaretic agent which increases free water excretion. In dogs, plasma AVP concentration increased after a single intravenous administration of OPC-61815, which was accompanied by no increase in plasma renin activity, and unlike furosemide, no activation of the renin-angiotensin system.

In a rat model of histamine-induced increased vascular permeability, a single intravenous administration of OPC-61815 (0.3825 to 3.825 mg/kg administered 2 hours before histamine injection) resulted in dose-dependently increased urine volume and decreased urine osmolality, as well as a dose-dependent reduction in the area of dye leakage at the histamine injection site. In a rat model of carrageenin-induced paw edema, a single intravenous administration of OPC-61815 (1.275 to 12.75 mg/kg administered 1 hour before carrageenin injection) inhibited the development of paw edema in a dose-dependent manner.

In a rat model of hyponatremia, 5-day repeated ascending intravenous administration of OPC-61815 at 0.255 to 5.1 mg/kg resulted in a dose-dependent increase in plasma sodium concentration, and improved the hyponatremia-associated increased water contents in the brain and heart.

The above non-clinical results have demonstrated the aquaretic effect of OPC-61815 administered intravenously, suggesting that OPC-61815 can be expected to provide clinical benefit in the treatment of various disorders associated with fluid retention due to abnormal water metabolism (eg, hyponatremia and edematous diseases).

For detailed nonclinical data, see the Investigator’s Brochure (IB).

1.2 Clinical Data

1.2.1 Phase 1 Trials of OPC-61815 Injection in Healthy Male Subjects (Trials 263-08-001, 263-09-001, and 263-10-005; Japan)

In a single intravenous dose trial (Trial 263-08-001[3]), OPC-61815 at 0.3, 1, 3, 7.5, 15, or 30 mg, or placebo was intravenously administered over 5 minutes in 54 healthy male subjects. All of the adverse events (AEs) reported in the OPC 61815 groups were mild in severity and resolved without treatments or with symptomatic treatments.

In a repeated intravenous dose trial (Trial 263-09-001[4]), OPC-61815 at 1.25, 5, or 20 mg, or placebo was intravenously administered over 1 minute as a single dose followed by once daily dosing for 7 consecutive days after 1-day dose intermission from the initial dose in 36 healthy male subjects. Adverse events, including feeling abnormal, pruritus, and erythema were frequently reported during the administration or immediately after the end of the administration. Most of these events were considered to be related to the IMP and had not been reported with the oral administration of tolvaptan. All of the AEs were mild or moderate in severity and resolved without treatments.

To investigate an infusion time that lessened the occurrence of the adverse drug reactions that had not been reported with oral tolvaptan but were observed with intravenous OPC-61815 in the repeated intravenous dose trial (Trial 263-09-001), and to explore the causes of these adverse drug reactions, a trial investigating the rate of intravenous administration (Trial 263-10-005[5]) was conducted. A single dose of OPC-61815 at 7.5 or 15 mg, or placebo was intravenously administered over 2 hours, 5 minutes, or 1 minute in 18 healthy male subjects, and AEs categorized as “feeling abnormal, pruritus, and erythema,” which were frequently reported in the repeated intravenous dose trial (Trial 263-09-001) were extracted as adverse events of special interest (AESI). The incidences of the AESI with a 2-hour infusion were 1 of 12 subjects in the OPC-61815 group and 3 of 6 subjects in the placebo group; a causal relationship to the investigational medicinal product (IMP) was ruled out for rash in the OPC-61815 group. The incidences of the AESI with a 5-minute infusion were 9 of 12 subjects in the OPC- 61815 group and 2 of 6 subjects in the placebo group, and those with a 1-minute infusion were 10 of 11 subjects in the OPC-61815 group and 4 of 6 subjects in the placebo group. With the exception of 1 occurrence of erythema at the 1-minute administration, all occurrences in the OPC-61815 group were concluded to be related to the IMP. All of the related AEs occurred during or immediately after the end of administration, and most of the events were transient and

resolved without treatments. There were no clinically relevant changes from baseline in the plasma histamine concentration.

For the detailed results of these trials, see the IB.

1.2.2 Phase 2 Clinical Pharmacology Trial of OPC-61815 Injection in Congestive Heart Failure Patients With Volume Overload (Trial 263-102-00001; Japan)

OPC-61815 at 2, 4, 8, or 16 mg was intravenously administered over 1 hour once daily for 5 consecutive days or tolvaptan 15-mg tablet was orally administered once daily for 5 days in 60 patients with CHF who have volume overload despite having received diuretics other than vasopressin antagonists. A phase 2 trial was conducted with the primary objective to investigate the dose of OPC-61815 injection formulation achieving exposure equivalent to that for tolvaptan 15-mg tablet. The detailed results for the primary endpoint are described in Section 2.2.

1) Pharmacokinetics and Pharmacodynamics

Following a single intravenous administration of OPC-61815 at 2, 4, 8, or 16 mg, the mean C_{max}, AUC_{24h}, AUC_t, and AUC_∞ values of OPC-61815 free form and tolvaptan increased in a dose-dependent manner. The median t_{max} values of OPC-61815 free form and tolvaptan were from 1.03 to 1.04 and 1.48 to 1.76 hours, respectively, and the mean $t_{1/2,z}$ values were from 1.8 to 3.8 hours and 7.4 to 8.6 hours. The mean CL and V_z values of OPC-61815 free form were from 4.29 to 5.50 L/h and 10.5 to 24.7 L, respectively. The mean ratios of AUC_{24h}, AUC_t, and AUC_∞ for tolvaptan to OPC-61815 free form were from 0.846 to 1.42, 0.847 to 1.45, and 0.989 to 1.77, respectively. Repeated intravenous administration of OPC-61815 at 2, 4, 8, or 16 mg once daily for 5 consecutive days resulted in no accumulation of OPC-61815 free form but an approximately 1.2- to 1.4-fold accumulation of tolvaptan. Tolvaptan exposure (C_{max} and AUC_{24h}) on Day 1, which was the primary variable, following single intravenous administration of OPC-61815 at 16 mg was the closest and similar to that following single administration of tolvaptan 15 mg tablet. Tolvaptan accumulated approximately 1.3-fold by repeated administration of tolvaptan 15 mg tablet once daily for 5 consecutive days, which was similar to the accumulation following repeated intravenous administration of OPC-61815 at 16 mg once daily for 5 consecutive days. The pharmacokinetic parameters of metabolites DM-4103 and DM-4107 after a single intravenous administration and repeated intravenous administration of OPC-61815 at 16 mg were similar to those after a

single oral administration and repeated oral administration of tolvaptan 15-mg tablet, respectively.

When OPC-61815 was intravenously administered at 2, 4, 8, or 16 mg once daily for 5 days, the daily urine volume increased from baseline in all dose groups on the day after start of IMP administration and onward.

2) Efficacy and Safety

The changes (mean ± standard deviation [SD]) in body weight from baseline at time of final IMP administration were −0.6 ± 0.6 kg in the OPC-61815 2-mg group, −1.1 ± 0.8 kg in the OPC-61815 4-mg group, −1.5 ± 1.1 kg in the OPC-61815 8-mg group, −2.1 ± 1.8 kg in the OPC-61815 16-mg group, and −1.7 ± 1.2 kg in the tolvaptan 15-mg tablet group; body weight decreased from baseline in all treatment groups.

The AEs reported in ≥2 subjects in the OPC-61815 group (all dose groups combined) were blood urea increased (4.2% [2 of 48 subjects] in the OPC-61815 group, 8.3% [1 of 12 subjects] in the tolvaptan 15-mg tablet group), and pyrexia, thirst, vessel puncture site reaction, blood creatinine increased, and headache (4.2% [2 of 48 subjects] each in the OPC-61815 group and 0.0% [0 of 12 subjects] in the tolvaptan 15-mg group). No deaths were reported. Two occurrences of serious adverse events (SAEs) (atrial fibrillation, endocarditis) were reported in 1 subject in the OPC-61815 4-mg group. Two subjects in the OPC-61815 4-mg group (atrial fibrillation, renal impairment) and 3 subjects in the tolvaptan 15-mg tablet group (liver disorder, hepatic congestion, renal impairment) discontinued IMP administration due to AEs. No subjects reported any of the AESI (eg, feeling abnormal, feeling hot, pruritus, rash, urticaria, erythema, hyperhidrosis, nausea, epigastric discomfort, or dyspnoea) that occurred frequently following bolus (in 1- or 5-minute) infusion of OPC-61815 and were considered to be due to IMP in the phase 1 trials.

For the detailed results of these trials, see the IB.

1.2.3 Phase 3, Double-blind, Placebo-controlled Trial of Tolvaptan Tablet in Congestive Heart Failure Patients With Volume Overload (Trial 156-06-002, Japan)

In a phase 3 trial of tolvaptan tablet (Trial 156-06-002[6]), tolvaptan at 15 mg/day or placebo was administered for 7 days to 110 adult heart failure patients with volume overload despite having received conventional diuretics.

The changes (mean ± SD) in body weight from baseline at the time of final IMP administration were −1.54 ± 1.61 kg in the tolvaptan 15-mg group and −0.45 ± 0.93 kg in

the placebo group. The decrease in body weight in the tolvaptan 15-mg group was significantly greater than that in the placebo group ($p < 0.0001$, t-test), with a difference (the tolvaptan 15-mg tablet group − the placebo group) of −1.09 kg (95% confidence interval [CI], −1.58 to −0.60 kg).

The AEs for which the incidence in the tolvaptan 15-mg group was ≥3%, and ≥3% higher than that in the placebo group were thirst (17.0% [9 of 53 subjects] in the tolvaptan 15-mg group and 1.8% [1 of 57 subjects] in the placebo group), constipation (17.0% [9 of 53 subjects] in the tolvaptan group and 5.3% [3 of 57 subjects] in the placebo group), pollakiuria (9.4% [5 of 53 subjects] in the tolvaptan group and 0.0% in the placebo group), nausea and malaise (5.7% [3 of 53 subjects] each in the tolvaptan group and 0.0% in the placebo group), and dizziness and headache (3.8% [2 of 53 subjects] each in the tolvaptan group and 0.0% in the placebo group). All of these AEs were mild to moderate in severity. The thirst, constipation, and pollakiuria were considered to be attributable to the diuretic effect of tolvaptan.

Serious adverse events were reported in 2 subjects in the tolvaptan 15-mg group and 7 subjects in the placebo group; one of the 2 subjects in the tolvaptan 15-mg group experienced renal failure chronic and (fatal) heart failure, and the other subject experienced atrial fibrillation.

1.3 Known and Potential Risks and Benefits

In completed clinical trials of OPC-61815 in healthy male subjects (Trials 263-08-001, 263-09-001, and 263-10-005), no deaths occurred and no other SAEs were reported. When OPC-61815 was administered to healthy subjects as bolus (1- or 5-minute) infusion (Trials 263-09-001 and 263-10-005), feeling abnormal, feeling hot, pruritus, rash, urticaria, erythema, hyperhidrosis, nausea, epigastric discomfort, and dyspnoea were reported as AESI. In a trial investigating the rate of intravenous administration (Trial 263-10-005), on the other hand, a 2-hour infusion of OPC-61815 induced such AESI only in 1 of 12 subjects in the OPC-61815 group and 3 of 6 subjects in the placebo group. These results suggest that a longer infusion period may lessen the occurrence of the AESI. In a phase 2 clinical pharmacology trial in which OPC-61815 was administered to patients with CHF as a 1-hour infusion (Trial 263-102-00001), no subjects reported the AESI that were considered to be caused by the IMP.

OPC-61815 is metabolized to tolvaptan in the body through hydrolysis of the phosphate ester site by an alkaline or acid phosphatase, and the tolvaptan acts as an aquaretic. Therefore, OPC-61815 is expected to bring benefits comparable to those of tolvaptan.

Tolvaptan, when administered to patients with cardiac edema, is known to be effective in body weight reduction and improvement of other findings (jugular venous distension, hepatomegaly, and lower limb edema) associated with the disease.[7]

The expected adverse drug reactions of tolvaptan are important information for predicting the adverse drug reactions of OPC-61815. In clinical trials involving patients with cardiac edema (Trials 156-03-001, 156-06-002, 156-06-004, 156-06-006, 156-10-005, 156-12-809-01, and 156-TWA-1101), the frequently reported AEs (with a ≥2% incidence, and higher than that in the placebo group) in 437 subjects treated with tolvaptan tablet were ventricular tachycardia, constipation, dry mouth, diarrhoea, vomiting, thirst, malaise, blood urea increased, blood uric acid increased, blood creatinine increased, blood potassium increased, blood sodium increased, blood glucose increased, blood urine present, platelet count decreased, blood pressure decreased, dehydration, hyperkalaemia, dizziness, headache, dizziness postural, pollakiuria, renal impairment, and epistaxis. For details regarding the AEs related to tolvaptan that have been reported in clinical trials, see the IB.

2 Trial Rationale and Objectives

2.1 Trial Rationale

Tolvaptan is approved in 2010 for the treatment of volume overload in heart failure when adequate response is not obtained with other diuretics (eg, loop diuretics), and has been administered to heart failure patients with volume overload despite have been received loop diuretics or other diuretics as an useful treatment option in the clinical setting. In clinical practice, however, intravenously-injectable aquaretics with the similar effects as tolvaptan has been needed for treating patients who have difficulty ingesting an oral drug due to decreased consciousness levels, those in whom the absorption of an oral drug is decreased due to gastrointestinal edema (intestinal edema) resulting from increased central venous pressure induced by heart failure, those in whom the administration of an oral drug is difficult due to the concurrent use of oxygen inhalation, and elderly patients with decreased swallowing function. Otsuka Pharmaceutical synthesized OPC-61815 as a novel intravenously injectable aquaretic since tolvaptan is difficult to be developed as an injectable formulation for its low solubility.

OPC-61815 is being developed for an intended approval in the same indication and target population as that of tolvaptan; therefore, OPC-61815 needs to be evaluated for efficacy

in a patient population similar to the patients who were enrolled in the phase 3 trial of tolvaptan. Since tolvaptan is currently positioned as a standard therapy for patients with heart failure with persistent fluid retention despite treatment with loop diuretics or other diuretics, it is ethically inappropriate to employ placebo as a comparator in a phase 3 trial to evaluate the efficacy of OPC-61815.

OPC-61815 has been evaluated in the following three completed phase 1 trials in healthy male subjects: a single intravenous dose trial (Trial 263-08-001), a repeated intravenous dose trial (Trial 263-09-001), and a trial investigating the rate of intravenous administration (Trial 263-10-005). Based on the results of the phase 1 trials, a phase 2 clinical pharmacology trial in CHF patients (Trial 263-102-00001) was conducted to determine the dose of OPC-61815 injection achieving the tolvaptan (OPC-41061) exposure equivalent to that for tolvaptan 15-mg tablet after intravenous administration of OPC-61815. The results indicated that OPC-61815 injection at 16 mg was equivalent to tolvaptan 15-mg tablet, and that OPC-61815 injection caused no significant safety concern in the dose range from 2 to 16 mg in CHF patients.

Based on the above, it is considered to be scientifically and ethically appropriate to conduct a phase 3 trial to confirm the non-inferiority of OPC-61815 to tolvaptan 15-mg tablet in patients with CHF using an OPC-61815 16-mg injection formulation, which has been demonstrated to be equivalent to tolvaptan 15-mg tablet.

2.2 Dosing Rationale

The dosage regimen of OPC-61815 planned in this trial is based on the results of a phase 2 clinical pharmacology trial in patients with CHF conducted to investigate the dose of OPC-61815 injection formulation achieving exposure equivalent to that for tolvaptan 15-mg tablet (Trial 263-102-00001).

Table 2.2-1 shows the tolvaptan exposure (C_{max} and AUC_{24h}) on Day 1, the primary endpoint of the phase 2 trial (Trial 263-102-00001). Table 2.2-2 shows the mean differences and their 95% CIs in log-transformed tolvaptan exposure (C_{max} and AUC_{24h}) on Day 1 between the oral administration of tolvaptan 15 mg and the intravenous administration of OPC-61815.

When OPC-61815 was intravenously administered over 1 hour at a dose of 2, 4, 8, or 16 mg once daily, the OPC-41061 exposure at 16 mg injection was closest and similar to that for tolvaptan 15-mg tablet. For safety, the incidences of AEs were 53.8% (7 of 13 subjects) in the OPC-61815 2-mg group, 58.3% (7 of 12 subjects) in the OPC-61815 4-mg group, 33.3% (4 of 12 subjects) in the OPC-61815 8-mg group, 72.7% (8 of 11

subjects) in the OPC-61815 16-mg group, and 83.3% (10 of 12 subjects) in the tolvaptan 15-mg tablet group. All events were reported only in 1 or 2 subjects. No deaths occurred in the trial. Two occurrences of SAEs were reported in 1 subject in the OPC-61815 4-mg group. There were no reports of the AESI, which occurred frequently with bolus (1- or 5-minute) infusion of OPC-61815 in phase 1 trials in healthy adult subjects and were considered to be related to IMP.

Based on the above, the dosage regimen of OPC-61815 is set to be a 1-hour infusion of 16 mg once daily in this trial.

The dosage regimen of tolvaptan planned for this trial is based on the results of a phase 3 trial of tolvaptan tablet (Trial 156-06-002).

Table 2.2-1 Tolvaptan Exposures (Cmax and AUC24h) on Day 1 After Intravenous Administration of OPC-61815 and After Oral Administration of Tolvaptan 15 mg (Mean ± SD)

Route of administration	**Intravenous**				**Oral**
Dose	OPC-61815 2 mg	OPC-61815 4 mg	OPC-61815 8 mg	OPC-61815 16 mg	Tolvaptan 15 mg
n	11	12	12	11	12
C_{max} (ng/mL)	41.4 ± 11.4	98.6 ± 43.7	149 ± 61.7	282 ± 96.0	325 ± 194
AUC_{24h} (ng·h/mL)	356 ± 157	983 ± 563	1340 ± 522	2400 ± 1030	2850 ± 1580

Trial 263-102-00001

Table 2.2-2 Mean Differences and 95% Confidence Intervals in Log-transformed Tolvaptan Exposure (Cmax and AUC24h) on Day 1 Between the Intravenous Administration of OPC-61815 and Oral Administration of Tolvaptan 15 mg

Dose	OPC-61815 2 mg	OPC-61815 4 mg	OPC-61815 8 mg	OPC-61815 16 mg
n	11	12	12	11
C_{max} (ng/mL)	−1.940 (−2.281, −1.598)	−1.114 (−1.447, −0.780)	−0.691 (−1.025, −0.357)	−0.050 (−0.392, 0.291)
AUC_{24h} (ng·h/mL)	−2.003 (−2.408, −1.597)	−1.035 (−1.432, −0.639)	−0.664 (−1.060, −0.267)	−0.125 (−0.530, 0.281)

Trial 263-102-00001

Using transformed-values, the differences in tolvaptan exposure between each OPC-61815 injection group and the tolvaptan 15-mg tablet group were calculated by an analysis of variance with dose as a factor.

2.3 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 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. An overview of the trial design is shown in Figure 3.1-1.

The 3 days before start of 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) (see Table 3.4.2-2) 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).

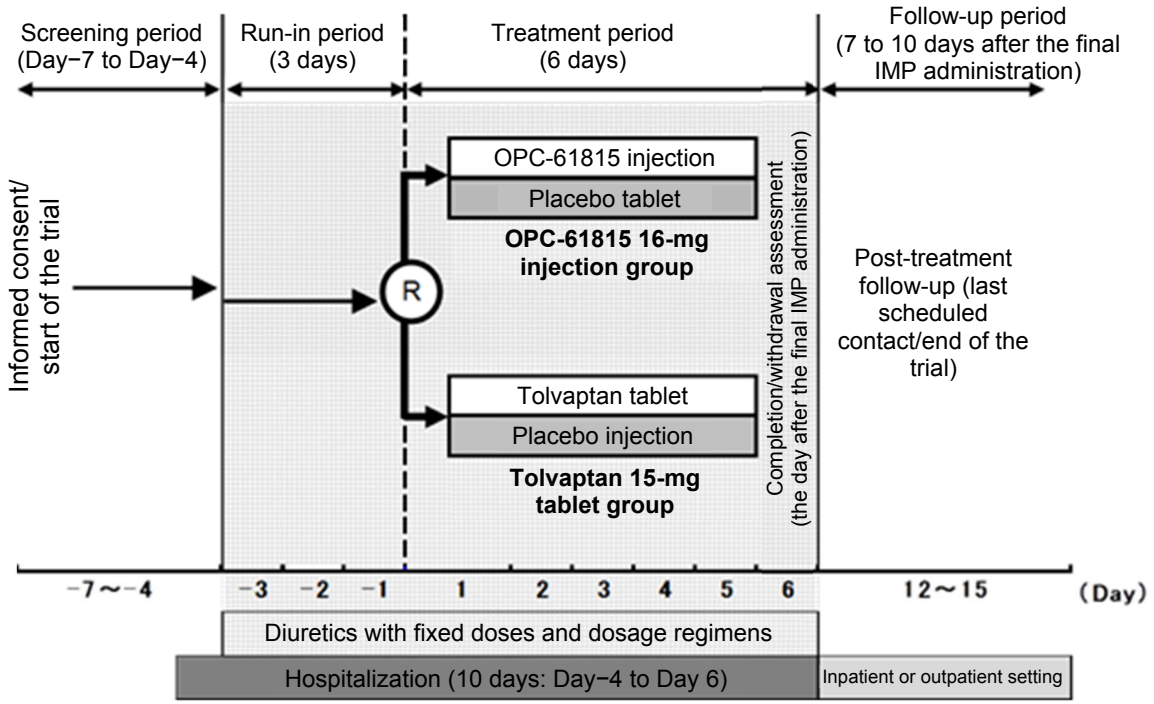

Figure 3.1-1 Trial Design Schematic

R: Randomization

Note) If IMP treatment is discontinued for any reason before Day 5, the same assessment as the completion assessment scheduled for Day 6 should be conducted on the day after the final IMP administration, whenever possible, and the follow-up should be conducted at any time between 7 and 10 days after the final IMP administration.

3.2 Trial Treatments

3.2.1 Dosage Regimen and Treatment Duration

The IMPs to be administered to subjects in each treatment group are shown in Table 3.2-1. 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.

Table 3.2-1 Investigational Medicinal Products Used in Each Treatment Group

Treatment group	IMPs (per day)
Tolvaptan 15-mg tablet	One vial of placebo injection + one tolvaptan 15-mg tablet
OPC-61815 16-mg injection	One vial of OPC-61815 16-mg injection + one placebo tablet

[Rationale for the treatment duration]

The results of a phase 2 trial (Trial 156-03-001) and a phase 3 trial (Trial 156-06-002) of tolvaptan tablet in patients with CHF revealed that the significant decrease in body weight in the tolvaptan group was greater than that in the placebo group throughout the treatment period in both trials, although the difference in the change in body weight between the groups was almost constant from Day 4 onward in the phase 2 trial (Trial 156-03-001) and peaked on Day 6 in the phase 3 trial (Trial 156-06-002).

Based on these results, a treatment duration of 5 days is sufficient to evaluate the change in body weight.

3.2.2 Preparation of Investigational Medicinal Products

The IMPs will be prepared just before use according to instructions to be specified separately.

3.3 Trial Population

3.3.1 Number of Subjects and Description of 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.

3.3.2 Subject Selection and Numbering

All subjects will be given a unique subject identifier (ID; site number [3 digits] + subject number ['S' + 5 digits]) upon providing consent. The site number will be designated by the sponsor. The subject number will be given in the order of informed consent from S00001 as the serial numbers in the trial sites. The trial site will prepare a list connecting all subjects consenting to participation in the trial and their subject identifiers, and retain the list.

3.4 Eligibility Criteria

3.4.1 Informed Consent

Informed consent will be freely obtained from all subjects. Informed consent will be documented by signing the consent form. DNA storage is optional. Subjects who do not consent to DNA storage may participate in the trial. The informed consent form (ICF) will be approved by the same institutional review board (IRB) that approves this protocol.

Each written information and ICF will comply with the ICH (International Conference on Harmonisation) Good Clinical Practice (GCP) Guideline[9] and local regulatory requirements.

Investigators or subinvestigators may discuss trial availability and the possibility for entry with a potential subject without first obtaining consent. However, informed consent must be obtained and documented prior to initiation of any procedures that are performed

solely for the purpose of determining eligibility for research, including withdrawal from current medication(s).

Potential subjects are free to refuse entry into the trial, or withdraw from the trial at any time, without justification, and there will be no consequences to their further care.

Once appropriate essential information has been provided and fully explained in layman's language to the subject by the investigator or subinvestigator, the IRB-approved written ICF will be signed and dated by both the subject and the person obtaining consent (investigator or subinvestigator), as well as by the trial coordinator, if he/she provides supplemental explanation. The subject will receive a copy of the signed ICF; the original shall be kept on file by the investigator or subinvestigator.

Subjects may be asked to sign additional ICFs if the protocol is amended and the changes to the protocol result in additional information that needs to be provided to the subjects, so that they can make a knowledgeable and voluntary decision on trial participation.

3.4.2 Inclusion Criteria

3.4.2.1 Screening Period

Subjects are required to meet all of the inclusion criteria (screening period) presented in Table 3.4.2-1.

Table 3.4.2-1 Inclusion Criteria (Screening Period)

1	Patients receiving any of the following oral diuretics (including patients planning to initiate treatment during the run-in period) • Loop diuretics equivalent to furosemide tablet or fine granules at a dose of 40 mg/day or higher • Concomitant use of a loop diuretic and a thiazide diuretic (including thiazide analogs) at any dose • Concomitant use of a loop diuretic and an aldosterone antagonist or potassium-sparing diuretic agent at any dose Note: The types and doses of concomitant diuretics are specified as follow: a) Loop diuretics equivalent to furosemide tablet or fine granules at a dose of 40 mg/day or higher Bumetanide tablet 1 mg, azosemide tablet 60 mg, and torasemide tablet 8 mg b) Thiazide diuretics (including similar drugs) Hydrochlorothiazide tablet, trichlormethiazide tablet, benzylhydrochlorothiazid tablet, and mefruside tablet c) Aldosterone antagonists or potassium-sparing diuretics Spironolactone tablet/fine granules and triamterene capsules
2	Patients with CHF in whom lower limb edema, pulmonary congestion, or jugular venous distension due to volume overload is present. Patients with pulmonary congestion may be enrolled if pulmonary congestion is confirmed by chest x-ray performed within 14 days prior to informed consent.
3	Male and female patients age of 20 to 85, inclusive, at the time of informed consent
4	Patients who are currently hospitalized or who are able to be hospitalized from the day before the run-in period (on Day −4) until the end of the treatment period

Table 3.4.2-1	Inclusion Criteria (Screening Period)
5	Patients who are capable of taking oral tablets
6	Patients who are capable of giving consent

(Rationale for the inclusion criteria [screening period])

1) This criterion is set to enroll patients who have volume overload despite having received diuretics other than vasopressin antagonists.
2) Volume overload may be manifested by lower limb edema, pulmonary congestion, jugular venous distension, hepatomegaly, and cardiac third sound. Among these manifestations, lower limb edema, pulmonary congestion, and jugular venous distension are selected as the inclusion criterion, because these symptoms are hardly affected by other factors and were reported by many subjects in a late phase 2 trial (Trial 156-03-001) and a phase 3 trial (Trial 156-06-002) of tolvaptan in patients with CHF.
3) Subjects participating in the trial should be adults who are capable of being responsible for their own consent. The upper limit of age is set at 85 years because many patients with CHF are elderly and also based on safety considerations.
4) Only patients who are able to be hospitalized will be enrolled to ensure accurate assessments and in view of the safety of subjects.
5) This criterion is set because tolvaptan tablet will be used as a comparator.
6) This criterion is set to ensure the implantation of an ethically appropriate trial.

3.4.2.2 Run-in Period

To appropriately evaluate the efficacy of the IMPs, only subjects who meet all of the inclusion criteria (run-in period) shown in Table 3.4.2-2 and are judged by the investigator or subinvestigator to be appropriate for an advancement to the treatment period will enter into the treatment period.

Table 3.4.2-2	Inclusion Criteria (Run-in Period)
7	Patients with lower limb edema, jugular venous distension (on Day −1 of the run-in period), or pulmonary congestion (confirmed by chest x-ray during the run-in period)
8	Patients who have received diuretics with no change in dose or regimen during the run-in period
9	Patients with no more than 1.0 kg change in body weight over the 2 days (Day −2 and −1 of the run-in period) prior to initial administration of the IMP

(Rationale for the inclusion criteria [run-in period])

7) These symptoms are often seen in association with volume overload and therefore selected as a criterion for enrolling patients with volume overload.
8) This criterion is set to enroll patients who still have volume overload despite having received diuretics other than vasopressin antagonists.
9) This criterion is set because having stable volume overload is necessary for appropriately evaluating the efficacy of OPC-61815.

3.4.3 Exclusion Criteria

Subjects will be excluded if they meet any of the exclusion criteria in Table 3.4.3-1.

Table 3.4.3-1 Exclusion Criteria

1	Patients with acute heart failure
2	Patients with mainly noncardiogenic congestive symptoms
3	Patients who are on a ventricular assist device
4	Patients who have any of the following diseases, complications, or conditions: • Suspected hypovolemia • Hypertrophic cardiomyopathy (excluding dilated phase) • Valvular disease with significant valvular stenosis • Hepatic encephalopathy with difficulty in adequate fluid intake
5	Patients who have experienced acute myocardial infarction within 30 days prior to the screening examination
6	Patients with a definite diagnosis of active myocarditis or amyloid cardiomyopathy
7	Patients who have any of the following diseases, complications, or conditions: • Poorly controlled diabetes mellitus • Anuria • Dysuria associated with urinary tract obstruction, calculus, or tumor
8	Patients who have any of the following medical histories: • History of sustained ventricular tachycardia or ventricular fibrillation within 30 days prior to the screening examination (for patients without an implantable cardioverter defibrillator) • History of cerebrovascular disease (excluding asymptomatic cerebral infarction) within 6 months prior to the screening examination • History of hypersensitivity or idiosyncratic reaction to benzazepines or benzazepine derivatives such as the ingredients of OPC-61815, tolvaptan, mozavaptan hydrochloride, and benazepril hydrochloride
9	Patients who are severely obese (body mass index [BMI] = body weight [kg]/height [m] ^{2} exceeding 35 kg/m^2)
10	Patients with supine systolic blood pressure of <90 mmHg
11	Patients with any of the following abnormalities in laboratory test results: Total bilirubin >3.0 mg/dL, serum creatinine > 3.0 mg/dL, serum Na <125 mEq/L and >147 mEq/L, and serum K >5.5 mEq/L

Table 3.4.3-1 Exclusion Criteria	
12	Patients with current symptoms or a history of hepatic impairment (including patients with aspartate aminotransferase [AST] or alanine aminotransferase [ALT] exceeding 3 times the upper limit of the reference range at the screening examination)
13	Patients who are unable to sense thirst or who have difficulty with fluid intake
14	Female patients who are breast-feeding or who have a positive pregnancy test result prior to receiving IMP
15	Sexually active males or women of childbearing potential (WOCBP) who do not agree to practice birth control or remain abstinent during the trial and for 30 days after the final IMP administration.
16	Patients who have received tolvaptan within 28 days prior to the screening examination
17	Patients who have participated in a clinical trial in which they received OPC-61815
18	Patients who have participated in another clinical trial and received another IMP within 30 days prior to the screening examination
19	Patients who are otherwise judged to be ineligible by the investigator or subinvestigator

Nonchildbearing potential is defined as male and female subjects who are surgically sterile (ie, male subjects who have undergone bilateral orchidectomy and female subjects who have undergone bilateral oophorectomy and/or hysterectomy) and female subjects who have been postmenopausal for at least 12 consecutive months.

Subjects must agree to the restrictions to concomitant medications as described in Section 4.

Subjects who sign an ICF but are not assigned to IMP are permitted to be re-screened one more time. In the event that the screening assessment is repeated, a new ICF signed by the subject must be obtained and a new subject identifier will be assigned to the subject.

[Rationale for the exclusion criteria]

1	This criterion is set because the rapid onset or worsening of the symptoms may hinder the conduct of the trial.
2	The criterion is set because the proposed target patient population of OPC-61815 is patients who have volume overload associated with CHF.
3	The use of a ventricular assist device may affect the efficacy or safety assessment of the IMPs.
4	Excessive diuretic treatment may adversely affect these symptoms.
5, 6	These criteria are based on safety considerations.
7	This criterion is based on safety considerations and set to exclude patients ineligible for participation in the trial.
8	These criteria are based on safety considerations.
9	This condition may hinder the efficacy assessment of the IMPs.
10	Blood pressure may decrease due to diuresis.

11 to 13	These criteria are based on safety considerations.
14 and 15	These criteria are based on general safety and ethical considerations.
16 and 17	The use of the IMPs may affect the efficacy or safety assessment of the IMPs.
18 and 19	These criteria are based on general safety and ethical considerations.

3.5 Endpoints

3.5.1 Primary Endpoint

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

[Rationale for the primary endpoint]

Since volume overload occurs at various body sites in CHF patients, body weight (change from baseline) is the most appropriate measure that objectively reflects the diuretic effect of the IMPs on the general state of volume overload. Therefore, the change from baseline in body weight is selected as the primary endpoint as in a phase 3 trial of tolvaptan in patients with CHF (Trial 156-06-002).

3.5.2 Secondary Endpoints

- 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

[Rationale for the secondary endpoints]

Congestive symptoms are measures that reflect volume overload resulting from CHF and therefore selected as a secondary endpoint for evaluating the efficacy of OPC-61815 using tolvaptan tablet as a comparator.

In addition to congestive symptoms, the NYHA classification, which assesses the severity of heart failure based on subjective symptoms is selected as a secondary endpoint to evaluate the efficacy of OPC-61815 using tolvaptan tablet as a comparator.

3.5.3 Pharmacokinetic Endpoint

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

3.5.4 Pharmacodynamic Endpoints

Daily urine volume, daily fluid intake, daily fluid balance, serum sodium concentration, serum potassium concentration, serum osmolality, biomarker measurements (plasma concentrations of AVP and brain natriuretic peptide [BNP], plasma renin activity, and serum concentrations of N-terminal pro-brain natriuretic peptide [NT proBNP] and troponin I), daily urine sodium excretion, daily urine potassium excretion, and urine osmolality

3.5.5 Safety Endpoints

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

3.6 Measures to Minimize/Avoid Bias

3.6.1 Randomization

Subjects who meet the criteria for a shift to the treatment period will be randomized at a 1:1 ratio to either of the OPC-61815 16-mg injection group or the tolvaptan 15-mg tablet group according to the interactive web response system (IWRS). A randomization confirmation form will be prepared separately to document the detail of the assignment method of treatments to subjects. The date of randomization and the IMP number will be recorded in the eCRF.

3.6.2 Blinding

Prior to start of the trial, the IMP allocation manager and the IMP packer will ensure that the IMPs are indistinguishable from each other. The allocation table will be kept under lock and key until the unblinding to be performed after finalization of all of the eCRFs and the database.

3.7 Trial Procedures

Trial assessment time points are summarized in Table 3.7-1.

Table 3.7-1 Schedule of Assessments

Item \ Day	Screening		Run-in Period			Treatment Period						Follow-up
	−7 to −4	−4	−3	−2	−1	1	2	3	4	5	Day 6/At Withdrawal (The Day After Final IMP Administration)	Day 12 to 15 /7 to 10 Days After Final IMP Administration
Informed consent	◇											
Informed consent for DNA storage	○(Optional Participation)											
Subject background	◇											
Inclusion/exclusion criteria	◇				◇							
Confirmation of concomitant medication/therapy	←											→
Subject registration, randomization[a]	◇					●					◇	
Hospitalization		←										→
IMP administration						♦	♦	♦	♦	♦		
Confirmation of IMP compliance						←				→		
Plasma drug concentrations						■	●				(◇)[b]	
Daily urine volume, daily fluid intake, urine sodium and potassium concentrations, urine osmolality			←	←	←	←	←	←	←	→		
Serum sodium[c] and potassium concentrations[c]	◇					●■	●	●	●	●	●	◇
Serum osmolality, biomarkers[d]						●					●	
Body weight	◇		●	●	●	●	●	●	●	●	●	◇
Congestive symptoms[e]	◇		◇	◇	◇	◇	◇	◇	◇	◇	◇	◇

Table 3.7-1 Schedule of Assessments

Item \ Day	Screening		Run-in Period			Treatment Period						Follow-up
	−7 to −4	−4	−3	−2	−1	1	2	3	4	5	Day 6/At Withdrawal (The Day After Final IMP Administration)	Day 12 to 15 /7 to 10 Days After Final IMP Administration
Chest x-ray (cardiothoracic ratio, pulmonary congestion)[f]	◇		◇ Once during run-in period								◇	
NYHA classification			◇ Once during run-in period								◇	
Adverse events	◄											►
Laboratory tests	◇					●					●	◇
Physical examination	◇		◇	◇	◇	◇	◇	◇	◇	◇	◇	◇
Vital signs (Blood pressure, pulse rate, body temperature)	◇		●	●	●	●	●	●	●	●	●	◇
12-Lead ECG[g]	◇					●■		◇			◇	
Urine pregnancy test (WOCBP only)	◇											◇
DNA storage[h]						○						

●= Before breakfast; ♦ = After breakfast; ■ = Predetermined time after IMP administration (see Table 3.7-2); ◇= Feasible time;
○= Optional (subjects at sites with a DNA storage agreement who gave informed consent for DNA storage before start of the trial)

[a]Subject registration and randomization: Subject registration and randomization will be performed using IWRS at screening and on Day 1, respectively. Subjects who meet all of the inclusion criteria and do not fall under any of the exclusion criteria will be assigned to receive IMP administration. In principle, randomization will be performed on Day 1 (if not feasible, randomization on Day −1 is acceptable, but eligibility regarding concomitant diuretics should still be reconfirmed on Day 1). Information on IMP administration and completion or discontinuation (early termination/withdrawal) will be recorded in the IWRS.

[b]Plasma drug concentrations will be measured at a feasible time only for early termination/withdrawal.

[c]Measurement of serum sodium and potassium concentrations during the treatment period will be performed at both the central laboratory and the trial site. If it is difficult to perform serum sodium and potassium concentration measurement at the trial site, plasma sodium and potassium concentrations may be

measured. Either serum or plasma should be used consistently for measurement of sodium and potassium concentrations in a given subject. However, even if plasma sodium and potassium concentrations are measured at the trial site, serum sodium and potassium concentrations will be measured at the central laboratory.

[d]Biomarkers: Plasma concentrations of AVP, BNP, plasma renin activity, and serum concentrations of NT-proBNP and troponin I

[e]Congestive symptoms: Lower limb edema, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound

[f]Chest x-ray: cardiothoracic ratio and pulmonary congestion

If chest x-ray has been performed at a regular visit prior to participation in the present trial (within 14 days before informed consent), assessment of cardiothoracic ratio and pulmonary congestion at screening may be performed based on that previous chest x-ray without having to perform a new chest x-ray.

[g]Timing of 12-lead ECG: Before breakfast and at 1 to 2 hours postdose on Day 1 and at a feasible time at other time points. If the serum potassium concentration at the trial site or the central laboratory is confirmed to exceed 5.5 mEq/L at any time point with no scheduled 12-lead ECG during the treatment period, an additional 12-lead ECG will be performed as an unscheduled examination.

[h]DNA storage: In principle, blood sampling for DNA storage will be performed on the day of initial IMP administration (Day 1). Informed consent to DNA storage should be obtained before blood sampling for DNA storage. If blood sample cannot be collected or re-collection is required, blood sampling will be repeated at a feasible time during the trial period.

Table 3.7-2 Allowable Time Window for Examinations/Tests and Blood Sampling After IMP Administration on Day 1	
Item	**Timing**
Plasma drug concentrations	60 to 75 minutes after start of IMP administration
	4 to 6 hours after start of IMP administration
	8 to 12 hours after start of IMP administration
Serum sodium concentration, serum potassium concentration	4 to 6 hours after start of IMP administration
	8 to 12 hours after start of IMP administration
12-Lead ECG	1 to 2 hours after start of IMP administration
Congestive symptoms	At a feasible time
Adverse events, physical examination	At a feasible time

3.7.1 Schedule of Assessments

3.7.1.1 Screening

After informed consent has been obtained, the investigator or subinvestigator will assign a subject identifier to the subject according to Section 3.3.2, record the date of acquisition of informed consent and the assigned subject identifier in the source documents and the eCRF, and enroll the subject in the IWRS. The operation of the IWRS will be specified by the procedures prepared separately as a subject management system.

Within 4 to 7 days before start of IMP administration (Day −7 to Day −4), the following examinations and tests will be conducted to assess the eligibility of the subject for participation in the trial. The result of eligibility assessment will be recorded in the source documents and the eCRF.

[Examinations and tests]

Subject characteristics (birth date, sex, height, country, race, ethnicity, underlying disease, type of heart failure, presence and type of arrhythmias, presence of a pacemaker, presence of an implantable cardioverter defibrillator, complications, medical history), serum sodium concentration, serum potassium concentration, body weight, congestive symptoms (lower limb edema, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound), chest x-ray[Note] (cardiothoracic ratio and pulmonary congestion), clinical laboratory tests, physical examination, vital signs (blood pressure, pulse rate, and body temperature), 12-lead ECG, concomitant medications and therapies, and urine pregnancy test (WOCBP only)

Note: If chest x-ray has been performed at a regular visit prior to participation in the present trial (within 14 days before informed consent), assessment of cardiothoracic ratio

and pulmonary congestion at screening may be performed based on that previous chest x-ray without having to perform a new chest x-ray.

3.7.1.2 Run-in Period (Day −3, Day −2, and Day −1)

The investigator or subinvestigator will conduct the following examinations and tests to assess the eligibility for a shift to the treatment period. Diuretics that have been used since start of the run-in period (Day −3) will be continued to be used with the same doses and dosage regimens until the completion (withdrawal) assessment, regardless of the previous use or method of use before run-in period.

Subjects must be hospitalized from the day before start of the run-in period through the completion (withdrawal) assessment.

1) Each day during the run-in period
   a) Before breakfast
   - Body weight
   - Vital signs (blood pressure, pulse rate, and body temperature)

   b) After breakfast

   Subject are required to urinate completely immediately after breakfast, and then urine collection and fluid intake measurement will start to assess the following items.
   - Daily urine volume
   - Daily fluid intake
   - Daily fluid balance (difference between daily fluid intake and daily urine volume)
   - Daily urine sodium excretion and daily urine potassium excretion (calculated from urine sodium concentration, urine potassium concentration, and daily urine volume)
   - Urine osmolality

   c) At a feasible time
   - Congestive symptoms (lower limb edema, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound)
   - Adverse events, physical examination
   - Concomitant medications and therapies

2) Any single day during the run-in period

The following examinations will be conducted once at a feasible time.

- Chest x-ray (cardiothoracic ratio and pulmonary congestion)
- NYHA classification

3.7.1.3 Randomization and Shift to the Treatment Period

1) Judgment of eligibility for a shift to the treatment period

Compliance with diuretic therapy during the run-in period, body weight, and congestive symptoms during the run-in period will be assessed to confirm that all of the inclusion criteria (run-in period) are met and the result of confirmation will be entered into the IWRS.

2) Treatment allocation

Subjects who have met all of the inclusion criteria (run-in period) will be randomly assigned to either of the treatment groups below to receive IMP in a double-blind manner. The investigator or subinvestigator will confirm the IMP number assigned by the IWRS.

- OPC-61815 16-mg injection group
- Tolvaptan 15-mg tablet group

3.7.1.4 Treatment Period (Day 1)

1) Before breakfast
   - Serum sodium concentration, serum potassium concentration, serum osmolality, and biomarkers
   - Body weight
   - Clinical laboratory tests
   - Vital signs (blood pressure, pulse rate, and body temperature)
   - 12-Lead ECG
   - Blood sampling for DNA storage (DNA storage is optional. Informed consent should be obtained before blood sampling for DNA storage.)
2) After breakfast

Subject are required to urinate completely immediately after breakfast, and urine collection and fluid intake measurement will start to assess the following items from the point at which urination immediately before IMP administration has been completed.

- Daily urine volume, daily fluid intake, and daily fluid balance
- Daily urine sodium excretion and daily urine potassium excretion
- Urine osmolality

3) IMP administration

The investigator or subinvestigator will confirm that the subject meets all of the inclusion criteria and falls under none of the exclusion criteria, administer the IMPs to the subject, and enter the status of IMP administration into the IWRS.

4) After IMP administration

The investigator or subinvestigator will conduct the following examinations.

- Blood sampling for measurement of the plasma drug concentrations: 60 to 75 minutes, 4 to 6 hours, and 8 to 12 hours after start of IMP administration
- Serum sodium concentration and serum potassium concentration: 4 to 6 hours and 8 to 12 hours after start of IMP administration
- 12-Lead ECG: 1 to 2 hours after start of IMP administration

5) At a feasible time

- Congestive symptoms (lower limb edema, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound)
- Adverse events, physical examination
- Concomitant medications and therapies
- Confirmation of IMP compliance

3.7.1.5 Treatment Period (Day 2)

1) Before breakfast
   - Blood sampling for measurement of the plasma drug concentrations (22 to 24 hours after start of IMP administration on Day 1)
   - Serum sodium concentration and sodium potassium concentration
   - Body weight
   - Vital signs (blood pressure, pulse rate, and body temperature)
2) After breakfast

Subject are required to urinate completely immediately after breakfast, and urine collection and fluid intake measurement will start to assess the following items from the point at which urination immediately before IMP administration has been completed.

- Daily urine volume, daily fluid intake, and daily fluid balance
- Daily urine sodium excretion and daily urine potassium excretion
- Urine osmolality

3) IMP administration

4) At a feasible time
    - Congestive symptoms (lower limb edema, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound)
    - Adverse events, physical examination
    - Concomitant medications and therapies
    - Confirmation of IMP compliance

3.7.1.6 Treatment Period (Day 3)

1) Before breakfast
    - Serum sodium concentration and sodium potassium concentration
    - Body weight
    - Vital signs (blood pressure, pulse rate, and body temperature)
2) After breakfast

Subject are required to urinate completely immediately after breakfast, and urine collection and fluid intake measurement will start to assess the following items from the point at which urination immediately before IMP administration has been completed.

- Daily urine volume, daily fluid intake, and daily fluid balance
- Daily urine sodium excretion and daily urine potassium excretion
- Urine osmolality

3) IMP administration
4) At a feasible time
    - Congestive symptoms (lower limb edema, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound)
    - Adverse events, physical examination
    - 12-Lead ECG
    - Concomitant medications and therapies
    - Confirmation of IMP compliance

3.7.1.7 Treatment Period (Days 4 and 5)

1) Before breakfast
    - Serum sodium concentration and sodium potassium concentration
    - Body weight
    - Vital signs (blood pressure, pulse rate, and body temperature)

2) After breakfast

Subject are required to urinate completely immediately after breakfast, and urine collection and fluid intake measurement will start to assess the following items from the point at which urination immediately before IMP administration has been completed.

- Daily urine volume, daily fluid intake, and daily fluid balance
- Daily urine sodium excretion and daily urine potassium excretion
- Urine osmolality

3) IMP administration
4) At a feasible time on each day
   - Congestive symptoms (lower limb edema, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound)
   - Adverse events, physical examination
   - Concomitant medications and therapies
   - Confirmation of IMP compliance

3.7.1.8 Treatment Period (Completion Assessment on Day 6 or Withdrawal Assessment on Day After the Final IMP Administration)

The investigator or subinvestigator will conduct the completion assessment on Day 6 as described below. If IMP treatment is discontinued before Day 6 for any reason, the same assessment as the completion assessment for Day 6 will be conducted at a feasible time as the withdrawal assessment on day after final IMP administration, whenever possible, and then follow-up will be made 7 to 10 days after the final IMP administration. During the withdrawal assessment, plasma drug concentrations will be measured (at a feasible time), whenever possible. Information on trial completion or trial withdrawal will be entered into the IWRS.

1) Before breakfast
   - Serum sodium concentration, serum potassium concentration, serum osmolality, and biomarkers
   - Body weight
   - Clinical laboratory tests and vital signs (blood pressure, pulse rate, and body temperature)
2) At a feasible time
   - Blood sampling for measurements of plasma drug concentrations (only at the withdrawal assessment)

- Congestive symptoms (lower limb edema, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound)
- Chest x-ray (cardiothoracic ratio and pulmonary congestion)
- NYHA classification
- Adverse events, physical examination
- 12-Lead ECG
- Concomitant medications and therapies

3.7.1.9 Follow-up After Completion of the Treatment Period (Day 12 to Day 15, 7 to 10 Days After the Final IMP Administration)

The investigator or subinvestigator will conduct the following examinations and tests at a feasible time within 7 to 10 days after the final IMP administration. If the subject has already been discharged from the trial site, the follow-up may be conducted on outpatient visit.

- Serum sodium concentration and sodium potassium concentration
- Body weight and congestive findings (lower limb edema, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound)
- Adverse events, clinical laboratory tests, physical examination, and vital signs (blood pressure, pulse rate, and body temperature)
- Urine pregnancy test (WOCBP only)
- Concomitant medications and therapies

3.7.1.10 Follow-up

Any AE that has not yet resolved by the completion assessment on Day 6 or the withdrawal assessment will be followed up according to Section 5.7.

3.7.2 Efficacy Assessments

3.7.2.1 Body Weight

The investigator or subinvestigator will instruct the subject to urinate at least once after waking up, minimizing the influences of defecation and clothing, and then measure the body weight before breakfast using a scale appropriately maintained. The date and time of measurement, and the measured body weight (in kg, to the first decimal place) will be recorded in the source document and the eCRF. The measurement result will be rounded to the first decimal place even if the measurement value is shown in the second decimal place or more.

3.7.2.2 Congestive Symptoms (Lower Limb Edema, Jugular Venous Distension, Hepatomegaly, Pulmonary Rales, and Cardiac Third Sound)

The investigator or subinvestigator will examine congestive symptoms including lower limb edema, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound, and assess the presence and severity of each symptom as described below. The date and the result of assessment will be recorded in the source document and the eCRF.

1) Lower limb edema

The tibial border or dorsum pedis, in principle, will be examined for the presence of edema with the subject seated, and the severity of edema will be assessed according to the criteria below.

Table 3.7.2.2-1 Criteria for Assessment of Lower Limb Edema

	Severity	Assessment criteria
0	Absent	No pitting is detectable.
1	Mild	Slight pitting is detected.
2	Moderate	Pitting is present.
3	Severe	Easily visible edema is present.

2) Jugular venous distension

The presence of jugular venous distension will be checked, and if present, the height (in cm) from the sternal angle to the highest point of pulsation in the internal jugular vein will be measured with the subject in a semi-upright position. The measurement result to the first decimal place will be recorded.

3) Hepatomegaly

The presence of a palpable liver will be checked, and if present, the width (distance from the right costal arch of the right chest, in cm) will be measured. The measurement result to the first decimal place will be recorded.

4) Pulmonary rales

The presence of pulmonary rales will be checked by auscultation.

5) Cardiac third sound

The presence of cardiac third sound will be checked by auscultation.

3.7.2.3 Chest X-ray (Cardiothoracic Ratio and Pulmonary Congestion)

The investigator or subinvestigator will take a chest x-ray, and the record the date of the examination in the source document and the eCRF. Cardiothoracic ratio and pulmonary congestion will be assessed as described below.

1) Cardiothoracic ratio

The investigator or subinvestigator will measure the cardiothoracic ratio and record the result in the source document and the eCRF. The result will be expressed to 1 decimal place rounded from 2 decimals, whenever possible.

2) Pulmonary congestion

The investigator or subinvestigator will assess the severity of pulmonary congestion according to the criteria below, and record the result of assessment in the source document and the eCRF.

Table 3.7.2.3-1 Criteria for Assessment of Pulmonary Congestion

	Severity	Assessment criteria
0	Absent	No congestion
1	Mild	Pulmonary venous congestion
2	Moderate	Interstitial pulmonary edema
3	Severe	Alveolar pulmonary edema

Adapted from Forrester JS, et al.[10]

3.7.2.4 NYHA Classification

The investigator or subinvestigator will assess the NYHA classification[11], and record the date and result of the assessment in the source document and the eCRF.

Table 3.7.2.4-1 NYHA Classification

Functional capacity	
Class I	Patients with cardiac disease, but without resulting in a limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Patients with cardiac disease resulting in a slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Patients with cardiac disease resulting in a marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Patients with cardiac disease resulting in the inability to carry on any physical activity without discomfort. Symptoms of heart failure or anginal syndrome may be present, even at rest. If any physical activity is undertaken, discomfort is increased.

3.7.3 Safety Assessments

3.7.3.1 Adverse Events

Refer to Section 5, Reporting of Adverse Events.

3.7.3.2 Clinical Laboratory Assessments

Venous blood and urine samples for clinical laboratory tests (Table 3.7.3.2-1) will be collected at the specified time points, and the date and time of blood sampling and the date of urine collection will be recorded in the source document. The samples will be shipped to the central laboratory for central measurements.

In order for the investigator or subinvestigator to be promptly aware of serum sodium and potassium concentrations, in consideration of subject safety, serum sodium and potassium concentrations will also be measured at the trial site. The status (collected/not collected), and the date and time of blood sampling, as well as the results of the serum sodium concentration measurement will be recorded in the source document and the eCRF, and those of the serum potassium concentration measurement will be recorded in the source document. If it is difficult to perform serum sodium and potassium concentration measurement at the trial site, plasma sodium and potassium concentrations may be measured. Either serum or plasma should be used consistently for measurement of sodium and potassium concentrations in a given subject. However, even if plasma sodium and potassium concentrations are measured at the trial site, serum sodium and potassium concentrations will be measured at the central laboratory. If the serum potassium concentration at the trial site or the central laboratory is confirmed to exceed 5.5 mEq/L, a 12-lead ECG will be performed as necessary in reference to Section 3.7.3.4.

The central laboratory will measure the following laboratory parameters according to the procedures specified by the laboratory and provide the results of the measurements to the sponsor and the investigator or subinvestigator. The status (collected/not collected), the date and time of blood sampling, and the date of urine collection will be recorded in the eCRF. The electronic file submitted to the sponsor by the central laboratory will be regarded as the source document; therefore, entry of the results in the eCRF will be unnecessary.

Table 3.7.3.2-1 Clinical Laboratory Assessments

Hematology: Red Blood Cell count Hemoglobin Hematocrit White Blood Cell count with differential (neutrophils, eosinophils, basophils, monocytes, and lymphocytes) Platelet count	**Serum Chemistry:** Total protein Albumin Total bilirubin AST ALT Alkaline phosphatase ϒ- Glutamyltransferase Lactic dehydrogenase Creatine kinase (creatine phosphokinase) Glucose Total cholesterol Triglycerides Urea nitrogen Creatinine Uric acid Serum electrolytes (sodium, potassium, chlorine, and calcium) PAP, TRACP-5b[b]
Urinalysis (qualitative): pH Protein Glucose Occult blood Ketone bodies Bilirubin Urobilinogen	
Additional Tests: Pregnancy test for WOCBP (hCG test)[a]	

hCG = human chorionic gonadotropin

aUrine pregnancy test will be conducted at screening and follow-up. If the urine pregnancy test is positive, a serum test will be conducted as specified in Section 5.5.

[b]PAP (prostatic acid phosphatase) and TRACP-5b (tartrate-resistant acid phosphatase 5b) will be measured only on Day 1.

If the subject is a WOCBP, a pregnancy test should be performed at screening examination and the result must be obtained before initial IMP administration. A diagnostic test kit provided by the sponsor will be used for the urine human chorionic gonadotropin (hCG) test. If the test result is unclear, the urine hCG test will be repeated. The investigator or subinvestigator will confirm the test result and record the status, the date, and the result (positive or negative) of the test in the source document and the eCRF.

3.7.3.3 Physical Examination and Vital Signs

1) Physical examination

The investigator or subinvestigator will check the physical conditions of the subject by interview and other methods at the prespecified time points. The physical examination includes the observation of the head, ears, eyes, nose and pharynx, chest, abdomen, genitourinary tract, extremities, nerves, and skin/mucosae. At the screening examination, the date and the results of assessment will be recorded in the source document and the eCRF. At subsequent assessments, only the date of assessment will be recorded in the source document and the eCRF. A clinically important physical

finding that is absent at the screening examination but observed at any post-treatment assessment will be recorded as an AE.

2) Vital signs (blood pressure, pulse rate, and body temperature)
At the prespecified time points, axillary temperature will be measured after the subject is kept rested according to the procedures specified by the trial site. Blood pressure (systolic and diastolic) and pulse rate will be measured after the subject is kept supine for at least 3 minutes. The measurement result of body temperature should be rounded to the first decimal place for recording, even if the measurement result is shown the second decimal place or more. The date and time, and the results of measurements will be recorded in the source document and the eCRF.

3.7.3.4 12-Lead Electrocardiogram Assessments

At the prespecified time points, a rest 12-lead electrocardiogram (ECG) will be recorded using the ECG monitor provided by the central ECG measurement facility and according to the procedure specified by the facility. However, if the serum potassium concentration at the trial site or the central laboratory is confirmed to exceed 5.5 mEq/L at any time point with no specified 12-lead ECG during the treatment period,, an additional 12-lead ECG will be performed as an unscheduled examination. The investigator or subinvestigator will interpret each ECG chart as normal or abnormal, and record the status (measured/ not measured), the date of recording, as well as the interpretation (normal or abnormal [details, if abnormal]) in the source document and the eCRF.

The ECG record will be sent to the central ECG measurement facility to measure the heart rate, RR interval, PR interval, QRS axis, QT interval, and QTc (QT corrected for heart rate) interval (QTcB, QTcF). The central ECG measurement facility will in turn send the 12-lead ECG analysis report to the investigator or subinvestigator.

The investigator or subinvestigator will reconfirm the interpretation of the 12-lead ECG referring to the analysis report, which will then be signed and retained.

The electronic file of the 12-lead ECG analysis report provided to the sponsor by the central ECG measurement facility will be used as the source document; therefore, entry of the heart rate, RR interval, PR interval, QRS axis, QT interval, and QTc interval (QTcB, QTcF) in the eCRF will be unnecessary.

3.7.4 Prior and Concomitant Medications

The investigator or subinvestigator will record all medications and therapies taken by the subject from signing of informed consent through Day 6 completion/withdrawal

assessment on the eCRF. The investigator or subinvestigator will record all medications and therapies taken by the subject for treatment of an AE or which caused an AE until the end of the trial (defined as the last scheduled contact) on the eCRF. For concomitant medications, the following will be recorded in the eCRF: medication, indication, dose, frequency, route, start date, and end date. For concomitant therapies, the following will be recorded in the eCRF: therapy, indication, start date, and end date.

3.7.5 Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic Assessments

3.7.5.1 Pharmacokinetic Assessments

3.7.5.1.1 Pharmacokinetic Blood Samples

1) Time points of blood sampling
   - Day 1 of the treatment period: 60 to 75 minutes, 4 to 6 hours, and 8 to 12 hours after start of IMP administration
   - Day 2 of the treatment period: 22 to 24 hours after start of IMP administration on Day 1 (before IMP administration on Day 2)

2) Procedures for blood sampling and measurements

The central laboratory will collect the blood samples, which will be shipped to the bioanalytical laboratory for analysis. For the handling and shipment of samples, see Appendix 1.

The bioanalytical laboratory will measure the plasma concentrations of OPC-61815 free form and tolvaptan (OPC-41061), report blinded measurement results to the sponsor, if necessary, and provide an electronic file containing unblinded drug concentration data to the sponsor after breaking the blind.

The status (collected/not collected), type (venous or arterial), and date and time of blood sampling will be recorded in the eCRF. The results of drug concentration measurements will be directly reported to the sponsor from the bioanalytical laboratory; therefore, entry in the eCRF will be unnecessary.

In the event that new information on the IMPs is obtained, metabolites that are not specified in this protocol may be analyzed. In addition, the collected plasma samples may be used for investigation of an analytical method, if necessary.

3) Rationale for the timing of blood sampling

In this trial, plasma drug concentration data will be collected to conduct a population pharmacokinetic (PPK) analysis in patients with CHF. The timing of blood sampling for drug concentration measurement is determined based on the results of a

simulation from a PPK model using the results of a phase 2 clinical pharmacology trial of OPC-61815 (Trial 263-102-00001), also considering feasibility. As a result, blood sampling for drug concentration measurements on Day 1 of the treatment period will be conducted at the following 4 time points: a point around which the plasma concentrations of OPC-61815 free form and tolvaptan are expected to reach a peak (60 to 75 minutes after start of IMP administration), and 3 points which are expected to be the elimination phase (4 to 6 hours, 8 to 12 hours, and 22 to 24 hours after start of IMP administration).

3.7.5.2 Pharmacodynamic Assessments

3.7.5.2.1 Daily Urine Volume

During the run-in period (until before IMP administration on Day 1 of the treatment period), daily urine volume will be measured for the time interval starting at immediately after complete urination after breakfast and ending at complete urination after breakfast on the following day.

During the treatment period (from IMP administration on Day 1 to the day after final IMP administration), daily urine volume will be measured for the each time interval from the point after complete urination immediately before the IMP administration to the point after complete urination immediately before the IMP administration on the following day. If the exact daily urine volume cannot be measured because part of the urine is discarded or for other reasons, the daily urine volume on that day will be handled as missing data.

The status (measured/not measured), start date and time, completion date and time of urine collection, as well as the daily urine volume will be recorded in the source document and the eCRF.

3.7.5.2.2 Daily Fluid Intake

Daily fluid intake (juice, milk, tea, water, transfusion, etc.) will be measured for the same intervals as the measurement of daily urine volume. The status (measured/not measured), start date and time, completion date and time of measurement, as well as the daily fluid intake will be recorded in the source document and the eCRF. Water that the subject drinks with the IMP will be included in the fluid intake after the IMP administration.

3.7.5.2.3 Daily Fluid Balance

The daily fluid balance will be calculated by deducting “the daily urine volume” from “the daily fluid intake.” Daily fluid balances will be calculated by the sponsor; therefore, entry in the eCRF will be unnecessary.

3.7.5.2.4 Pharmacodynamic Laboratory Tests (Serum Sodium Concentration, Serum Potassium Concentration, Serum Osmolality, Biomarkers, Daily Urine Sodium Excretion, Daily Urine Potassium Excretion, and Urine Osmolality)

The samples presented in Table 3.7.5.2.4-1 will be collected at the time points specified in Section 3.7.1, and the date and time of venous blood sampling will be recorded in the source document and the eCRF. Regarding the serum sodium and potassium concentrations for pharmacodynamic assessment, data obtained as part of the clinical laboratory tests for safety at the same blood sampling points specified in Section 3.7.3.2 will be used. For the procedures for sample collection, processing, and storage, see Appendix 1. If the exact daily urine volume cannot be measured because part of the urine is discarded or for other reasons, the incomplete urine sample will not be shipped to the central laboratory and the urine electrolyte concentrations and urine osmolality on that day will be handled as missing data.

Table 3.7.5.2.4-1 Pharmacodynamic Laboratory Tests

Serum: Serum sodium concentration Serum potassium concentration Serum osmolality Serum troponin I concentration Serum NT-proBNP concentration	Plasma: Plasma AVP concentration Plasma BNP concentration Plasma renin concentration
Urine: Urine sodium concentration Urine potassium concentration Urine osmolality	

All of the samples will be shipped to the central laboratory, which centrally measures the parameters according to the prespecified procedures and reports the results to the sponsor and the investigator or subinvestigator. An electronic file containing the measurement results will be provided to the sponsor from the central laboratory; therefore, entry in the eCRF will be unnecessary.

In order for the investigator or subinvestigator to be promptly aware of serum sodium and potassium concentrations, in consideration of subject safety, serum sodium and potassium concentrations will also be measured at the trial site. The status (collected/not collected), the date and time of blood sampling, as well as the result of the serum sodium concentration measurement will be recorded in the source document and the eCRF, and those of serum potassium concentration measurement will be recorded in the source document. If it is difficult to perform serum sodium and potassium concentration measurement at the trial site, plasma sodium and potassium concentrations may be

measured. Either serum or plasma should be used consistently for measurement of sodium and potassium concentrations in a given subject. However, even if plasma sodium and potassium concentrations are measured at the trial site, serum sodium and potassium concentrations will be measured at the central laboratory.

The daily urine sodium excretion and daily urine potassium excretion will be calculated by multiplying the urine sodium concentration and the urine potassium concentration, respectively, by the daily urine volume. Urine excretions will be calculated by the sponsor; therefore, entry in the eCRF will be unnecessary.

3.7.5.3 Pharmacogenomic Assessment

3.7.5.3.1 DNA Storage

1) Rationale for DNA storage

In this trial, DNA samples will be stored on a voluntary basis. DNA storage will be conducted on subjects who provide written consent only at trial sites that provide prior consent to DNA storage. In Q&A 1 in the "Clinical Trials using Pharmacogenomics" (PFSB/ELD Notification No. 0930007 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare [MHLW] dated 30 Sep 2008), the MHLW states that DNA samples for possible genomic/genetic analysis to evaluate the IMP (PK, efficacy, safety, etc.) may be collected from subjects during the clinical trial in either of the following cases: (1) the target and timing of the potential genomic/genetic analysis has been specifically identified at the time of the trial, or (2) the target or timing of the potential genomic/genetic analysis has not been specifically identified at the time of the trial, but it is planned to conduct analysis for the evaluation of the IMP in future. The MHLW also states in Q&A 2 in the same notification, that samples for possible genomic/genetic analysis with a purpose independent of the evaluation of the IMP may be collected from subjects during the trial. The ICH E18 Guidelines, "Genomic Sampling and Management of Genomic Data" (PSEHB/PED Notification No. 0118-1 dated 18 Jan 2018) states that genomic sample acquisition is strongly encouraged in all phases and studies of clinical development.

Based on the above, samples for DNA analysis will be collected from subjects, to enable the future exploratory investigation as to DNA variants relating to individual differences in responsiveness (eg, efficacy, safety, PK) to OPC-61815 and/or disease-associated DNA variants.

2) Purpose of DNA storage

To enable the future exploratory investigation as to DNA variants relating to individual differences in responsiveness (eg, efficacy, safety, PK) to OPC-61815 and/or disease-associated DNA variants

3) Target subject group

DNA storage will be conducted on subjects who provide written consent only at trial sites at which the IRB provides prior approval for blood sampling for DNA storage. Consent to DNA storage must be obtained from subjects before blood sampling for DNA storage. Withdrawal from participation in the trial will not result in withdrawal from participation in DNA storage.

4) Handling of DNA samples

a) Time points of blood sampling

A blood sample for DNA storage will be collected before IMP administration on Day 1. If blood sample cannot be collected or re-collection is required, blood sampling will be repeated at a feasible time during the trial period. The status (collected/not collected), and the date and time of blood sampling will be recorded in the source document and the eCRF.

b) Sample for DNA storage

For the detailed procedures for sample collection, handling, and shipment, see Appendix 1.

c) DNA storage period

The collected DNA samples will be stored until (1) possible genomic/genetic analysis is determined to be unnecessary, (2) 15 years has passed since informed consent has been obtained from the first subject (or the legally acceptable representative), or (3) the subject (or the legally acceptable representative) withdraws consent to DNA storage, whichever comes first.

3.7.5.3.2 Potential Genomic/Genetic Analysis

Genomic/genetic analysis will only be conducted if analysis is determined to be useful for the purposes described in Section 3.7.5.3.1 2). When it is determined to conduct genomic/genetic analysis, a pharmacogenomic research protocol will be prepared and approved by the sponsor's research review committee, and then the analysis will be conducted according to the local regulations. The results of the genomic/genetic analysis will not be included in the final study report, but documented separately as a research report.

The target of possible genomic/genetic analysis has not been identified. Genome-wide association analysis using DNA chips, DNA microarrays, or next-generation DNA sequencers may be conducted, however, the results of the analysis will not be used for purposes other than those described in Section 3.7.5.3.1 2).

DNA samples for possible genomic/genetic analysis will be double-coded by the DNA biorepository and shipped to the genomic/genetic analysis laboratory (not yet designated). The genomic/genetic analysis laboratory will conduct the genomic/genetic analysis using the double-coded samples and report the double-coded results to the sponsor.

Even if the subject is withdrawn from the trial at his/her request, the results of genomic/genetic analysis that have been already obtained will not be discarded.

1) Disclosure of the results of genomic/genetic analysis to subjects
Even if some information is obtained from the genomic/genetic analysis, the analysis results will be only exploratory and at the early stage of research, and their scientific reliability such as precision or certainty will not have been adequately demonstrated. Disclosure of information without established scientific reliability will not be beneficial to subjects. Therefore, the sponsor will not disclose the results of genomic/genetic analysis to subjects, in principle.

2) Informed consent for participation in DNA storage and withdrawal of consent
Written information regarding DNA storage and possible genomic/genetic analysis using DNA samples will be prepared separately from written information for the trial, and the informed consent signed by the subject will be obtained. The date of the informed consent obtained from the subject will be recorded in the source document and the eCRF.

If a subject withdraws the consent for DNA storage during the storage period, the sponsor will request the biorepository to discard the sample of the subject, and the biorepository will discard the samples in such a way that the subject cannot be identified. If individual samples cannot be identified because information connecting samples and subjects identifiers (eg, code list) is destroyed or for other reasons, the sample of a subject who withdraws consent may not be consequently discarded.

Withdrawal from participation in the trial will not result in withdrawal from participation in DNA storage. If the results of a genomic/genetic analysis have been obtained at the time of consent withdrawal, the results will not be discarded.

3.7.6 End of Trial

The end of trial date is defined as the last date of visit/contact or the date of final contact attempt from the post-treatment follow-up eCRF page for the last subject completing or withdrawing from the trial.

3.8 Stopping Rules, Withdrawal Criteria, and Procedures

3.8.1 Entire Trial or Treatment Arm(s)

If the sponsor terminates or suspends the trial for any reason, prompt notification will be given to the head of the trial site and regulatory authorities in accordance with regulatory requirements.

3.8.2 Individual Site

Individual trial site participation may be discontinued by the sponsor, the investigator, or the IRB if judged to be necessary for medical, safety, regulatory, ethical or other reasons consistent with applicable laws, regulations, and GCP. The head of the trial site will notify the sponsor promptly if the trial is terminated by the investigator or the IRB at the site.

3.8.3 Individual Subject Discontinuation

3.8.3.1 Treatment Discontinuation

After randomization, a subject may stop treatment permanently for a variety of reasons. Treatment discontinuations may be initiated by a subject who is not satisfied with treatment or may become medically necessary due to AEs, required treatment with a disallowed medication or therapy, or other issues, as determined by the investigator or subinvestigator. However, each investigator or subinvestigator must comprehensively review the circumstances and offer the subject options for continued treatment to the degree possible as described in Section 3.8.3.4.

A subject who initiates treatment and then discontinues the treatment will be encouraged to undergo all of the examinations and tests specified for the withdrawal assessment. The withdrawal assessment will be conducted according to Section 3.7.1.8.

3.8.3.2 Documenting the Reasons for Treatment Discontinuation

A subject may discontinue participation in the trial at any time, and the investigator or subinvestigator may discontinue a subject's participation in the trial if medically necessary. Subjects who fall under any of the following must be withdrawn from the trial.

If a subject discontinues treatment, a single reason for the discontinuation (the main reason) will be recorded in the eCRF.

1) Reasons related to AE:
   - Subject decides to discontinue because of annoyance or discomfort due to a non-serious AE which is not otherwise determined to be an undue hazard
   - AST or ALT value obtained at the trial site or the central laboratory is ≥3 times the upper limit of normal (ULN).
   - Serum or plasma sodium concentration measured at the trial site or the central laboratory increases by ≥12 mEq/L from immediately predose within 24 hours after start of the IMP administration.
   - Serum or plasma sodium concentration measured at the trial site or the central laboratory is ≥155 mEq/L during the treatment period.
   - The onset of drug-induced hypersensitivity is suspected.
   - Any severe AESI (feeling abnormal, feeling hot, erythema, hyperhidrosis, pruritus, rash, urticaria, nausea, epigastric discomfort, or dyspnoea) occurs.
   - Continuing IMP places the subject at undue risk as determined by the investigator or subinvestigator (eg, a safety concern that is possibly, probably, or likely related to IMP).
     – Serious adverse event
     – Other potentially IMP-related safety concerns or AEs
2) Withdrawal of informed consent by the subject (when it is confirmed to be unrelated to AEs)
3) Protocol deviations (other than poor compliance with the IMP administration rules)
   - Deviations related to the inclusion or exclusion criteria
   - Deviations related to prohibited or restricted concomitant medications
4) Judgment by the investigator or subinvestigator (for the reasons other than an AE)
5) Death
6) Lost to follow-up
7) Pregnancy (see Section 5.5)
8) Technical problems (eg, malfunctions of medical devices)
9) Premature termination of the entire or part of the trial by the sponsor

If the subject discontinues IMP due to an AE, the investigator, subinvestigator, or other trial personnel, will make every effort to follow the event until it has resolved or stabilized, or until the subject is lost to follow-up or has died. The procedures in Section 3.8.3.1 must be followed.

3.8.3.3 Withdrawal of Consent

All subjects have the right to withdraw their consent from further participation in the trial at any time without prejudice. Subjects cannot withdraw consent for use of data already collected as part of the trial, but only for future participation. The investigator or subinvestigator can also discontinue a subject's participation in the trial at any time if medically necessary. Unless the subject provides their written withdrawal of consent or there is other written documentation by the investigator or subinvestigator confirming the subject's verbal intent to completely withdraw from the trial, subjects should be followed for all protocol-specified evaluations and assessments, if possible.

Complete withdrawal of consent requires a subject's refusal of ALL of the following methods of follow up (these methods of follow up will also be noted in the trial ICF):

- Participation in all follow-up procedures specified in the protocol (whether at trial site, by telephone, or by an in-home visit).
- Participation in a subset of protocol specified follow-up procedures (by a frequency schedule and method, as agreed by subject and staff).
- Contact of the subject by trial personnel, even if only by telephone, to assess current medical condition, and obtain necessary medical or laboratory reports relevant to the trial's objectives.
- Contact of alternative person(s) who have been designated in source records as being available to discuss the subject's medical condition, even if only by telephone, mail, or e-mail (eg, family, spouse, partner, legal representative, friend, neighbor, or physician).
- Access to medical information from alternative sources (eg, hospital/clinic medical records, referring doctor's notes, public records, dialysis, transplantation or vital registries, or social media sources).

Withdrawal of consent is a critical trial event and therefore should be approached with the same degree of importance and care as is used in initially obtaining informed consent. The reasons for a subject's intended withdrawal need to be completely understood, documented, and managed to protect the rights of the subject and the integrity of the trial. A subject may initially express their desire to discontinue IMP administration, which is not equivalent to a complete withdrawal of consent for further participation (see Section 3.8.3.1). A subject may, however, indicate that further trial participation is creating a burden on their work or social schedule. Therefore, the investigator or subinvestigator should follow the procedures outlined in Section 3.8.3.4 to determine if the subject can continue participation in the trial if modifications to his/her treatment and/or schedule of assessments can be accommodated. Only subjects who withdraw their

permission for all of the above degrees of follow-up are considered to have completely withdrawn their consent to participate in the trial.

3.8.3.4 Procedures to Encourage Continued Trial Participation

In all cases of impending IMP discontinuation or consent withdrawal, investigators or subinvestigators will be given instructions to meet and discuss with the subject their options of continuing in the trial, preferably on therapy. The investigator should ensure understanding and documentation of the reasons for the subject's desire to withdraw consent.

3.9 Screen Failures

A screen failure subject is one from whom informed consent is obtained and is documented in writing (ie, subject signs an ICF), but who is not assigned to trial treatment.

Subjects who sign an ICF but are not assigned to IMP are permitted to be re-screened once. In the event that the screening assessment is repeated, a new ICF signed by the subject must be obtained and a new subject identifier will be assigned to the subject.

If the subject meets the definition of a screen failure, the following information will be recorded in the eCRF:

- Subject identifier
- Date of informed consent
- Visit date (on which the screening examination is conducted)
- Date of data collection
- Sex
- Birth date
- Race
- Ethnicity
- Country
- Whether the subject meets all of the inclusion criteria (the criterion number(s) the subject does not meet, if any)
- Whether the subject falls under any of the exclusion criteria (the criterion number(s) the subject falls under, if any)
- Screen failure date
- Reason for screen failure

3.10 Definition of Completed Subjects

The treatment period is defined as the time period during which subjects are evaluated for primary and/or secondary objectives of the trial irrespective of whether or not the subject was administered all doses of the IMP. Subjects who are evaluated at the last scheduled visit during the treatment period will be defined as trial completers. For purposes of this trial, subjects who undergo the completion assessment on Day 6 will be defined as trial completers.

3.11 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted on or before the last scheduled contact, who do not have a known reason for discontinuation (eg, withdrew consent or AE), and for whom a survival status at the end of the trial cannot be determined will be classified as "lost to follow-up." Survival status can be determined from a variety of sources, either by obtaining acceptable documentation for death (ie, death certificate, medical records, public records, statement by a family member or primary care physician) or acceptable documentation for life (ie, direct contact with the subject, medical records, successful telephone contact with the subject, statement by a family member or primary care physician, or public records).

The investigator, subinvestigator, or designee will make 3 documented attempts to contact the subject by telephone and in the event they are unable to reach the subject by telephone, they will attempt to contact the subject via certified mail or an alternative similar method, where appropriate, before assigning a "lost to follow-up" status. If the subject is classified as "lost to follow-up," the status (contacted/not contacted), date of contact, and attempted contact method will be recorded in the eCRF.

3.12 Subject Compliance

Subjects will remain under the control of the investigator or subinvestigator throughout the trial period. The investigator or subinvestigator will direct the subjects to comply with the matters described below.

- Subjects must receive the IMPs and concomitant diuretics according to the specified dosage regimens.
- Subjects must follow the prespecified trial schedule.
- Subjects must not use the prohibited concomitant medications (see Section 4.1).
- Subjects must not change the dosage regimens of the restricted concomitant medications (see Section 4.2).

- Subjects must not disclose the information obtained by participating in the trial to third parties.

3.13 Protocol Deviations

In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent process, IMP dispensing or subject dosing error, treatment assignment error, subject enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator, subinvestigator, or designee will contact the sponsor at the earliest possible time by telephone. The investigator or subinvestigator and sponsor will come as quickly as possible to a joint decision regarding the subject's continuation in the trial. This decision will be documented by the investigator or subinvestigator and the sponsor, and reviewed by the site monitor.

If a major deviation occurs, the onset date and the details of the deviation will be recorded in the source document and the eCRF.

4 Restrictions

4.1 Prohibited Medications

During the period from the specified time point through the completion assessment on Day 6 or the withdrawal assessment, use of the medications listed in Table 4.1-1 will be prohibited.

Table 4.1-1 List of Prohibited Concomitant Medications and Foods

No.	Medications and foods prohibited	Timing
1	Vasopressin antagonists	From 28 days before the screening examination
2	The following drugs for heart failure (injections): a) Human atrial natriretic peptide products b) Phosphodiesterase III inhibitors c) Catecholamine products d) Colforsin products	From start of the run-in period
3	Diuretics (injections)	
4	Medications and foods which may inhibit or induce the CYP 3A4 activity (see Table 4.1-2)	
5	Medications including investigational drugs other than OPC-61815 that are unapproved in Japan	

CYP = cytochrome P450

Table 4.1-2 Medications and Foods Which May Inhibit or Induce CYP3A4 Activity

Therapeutic category	Drugs
(1) CYP3A4 inhibitors (except external use agents)	
Antimicrobial drugs	Clarithromycin, erythromycin, fluconazole, itraconazole, miconazole, norfloxacin, chloramphenicol, voriconazole, and ciprofloxacin
Anti-HIV drugs	Atazanavir, indinavir, nelfinavir, ritonavir, saquinavir, lopinavir, telaprevir, fosamprenavir, cobicistat, darunavir, and elvitegravir
Drugs for viral liver diseases	Ombitasvir/paritaprevir/ritonavir
Calcium channel blockers	Diltiazem and verapamil
Antidepressants	Fluvoxamine
Antiulcer drugs	Cimetidine
Anticancer drugs	Imatinib and crizotinib
Immunosuppressants	Cyclosporine
Antiemetics	Aprepitants
Other medications	Tofisopam, istradefylline, and clotrimazole
Foods	Grapefruit, star fruit, Seville orange, and their processed products
(2) CYP3A4 inducers (except external use agents)	
Barbiturates	Phenobarbital, amobarbital, pentobarbital, barbital, secobarbital, and primidone
Adrenal corticosteroids	Cortisone, hydrocortisone, prednisolone, methylprednisolone, triamcinolone, dexamethasone, betamethasone, paramethasone, and fludrocortisone
Antihypertensive drugs	Bosentan
Anti-HIV drugs	Efavirenz, etravirine, and nevirapine
Antiepileptics	Carbamazepine, phenytoin, and oxcarbazepine
Antitubercular drugs	Rifampicin and rifabutin
Anticancer drugs	Enzalutamide and mitotane
Other medications	Modafinil
Foods	Products containing St John's Wort

HIV = human immunodeficiency virus

[Rationale for the prohibited concomitant medications and foods]

Nos. 1 to 3 These medications may confound the efficacy evaluation of the IMPs.

4 These medications may confound the pharmacokinetic, safety, or efficacy evaluation of the IMPs.

5 The safety of these drugs has not been established in Japanese patients.

4.2 Restricted Concomitant Medications

Some medications and therapies other than OPC-61815 and tolvaptan may be used under the conditions stated below during the period from start of the run-in period through the completion (withdrawal) assessment.

1) The doses and dosage regimens of diuretics other than vasopressin antagonists and SGLT2 inhibitors must not be changed from start of the run-in period through the completion (withdrawal) assessment.
2) The doses and dosage regimens of medications that may affect volume overload status and the underlying disease, as listed in Table 4.2-1, must not be changed.
3) In subjects who are on a diet therapy (salt restriction), the limit for salt in a meal should be retained.

Table 4.2-1 Restricted Concomitant Medications/Therapies

1	Transfusion (except when used as a solvent for other drugs)
2	Medications to supplement potassium
3	Xanthines
4	Nonsteroidal antiinflammatory drugs (except those used on an as-needed basis or for local effects)
5	Antihypertensives
6	Heart failure drugs other than the prohibited concomitant medications

[Rationale for the restricted concomitant medications/therapies]

1) to 3): The use of these medications/therapies will be restricted to stabilize the effects of concomitant medications (other than the IMPs) or concomitant diet therapy (salt restriction) on diuresis and fluid electrolyte concentrations.

5 Reporting of Adverse Events

5.1 Definitions

An AE is defined as any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. Adverse events would not include information recorded as medical history at screening for pre planned procedures for which the underlying condition was known and no worsening occurred. An adverse reaction is any untoward and unintended response to an IMP related to any dose administered.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the IMP caused the AE.

An SAE includes any event that results in any of the following outcomes:

- Death
- Life-threatening; ie, the subject was, in the opinion of the investigator or subinvestigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity/disability or substantial disruption of the ability to conduct normal life functions.
- Requires in-patient hospitalization or prolongs hospitalization.
  - Hospitalization itself should not be reported as an SAE; whenever possible the reason for the hospitalization should be reported.
  - Hospitalizations or prolonged hospitalizations for social admissions (ie, those required for reasons of convenience or other non-medical need) are not considered SAEs.
- Congenital anomaly/birth defect.
- Other medically significant events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above; eg, allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

Nonserious adverse events are all AEs that do not meet the criteria for a "serious" AE.

Immediately Reportable Event (IRE):

- Any SAE.
- Any AE related to occupational exposure.
- Potential serious hepatotoxicity (see Section 5.4).
- Pregnancies are also defined as IREs. Although normal pregnancy is not an AE, it will mandate IMP discontinuation and must be reported on an IRE form to the sponsor. Pregnancy will only be documented on the AE eCRF if there is an abnormality or complication.

Clinical Laboratory Test Value Changes: It is the investigator or subinvestigator's responsibility to review the results of all laboratory tests as they become available. This review will be documented by the investigator or subinvestigator's dated signature on the laboratory report. For each abnormal laboratory test result, the investigator needs to ascertain if this is an abnormal (ie, clinically significant) change from baseline for that individual subject. This determination, however, does not necessarily need to be made the first time an abnormal value is observed. The investigator or subinvestigator may repeat

the laboratory test or request additional tests to verify the results of the original laboratory tests. If this laboratory value is considered medically relevant by the investigator or subinvestigator (subject is symptomatic, requiring corrective treatment or further evaluation), or if the laboratory value leads to discontinuation, and/or fulfills a seriousness criterion, this is considered an AE.

Severity: Adverse events will be graded on a 3-point scale. The intensity of an adverse experience is defined as follows:

1 = Mild: Discomfort noticed, but no disruption to daily activity.

2 = Moderate: Discomfort sufficient to reduce or affect normal daily activity.

3 = Severe: Inability to work or perform normal daily activity.

IMP Causality: Assessment of causal relationship of an AE to the use of the IMP is defined as follows:

Related: There is a reasonable possibility of a temporal and causal relationship between the IMP and the AE.

Not Related: There is no temporal or causal relationship between the IMP and the AE.

5.2 Eliciting and Reporting Adverse Events

The investigator or subinvestigator will periodically assess subjects for the occurrence of AEs. To avoid bias in eliciting AEs, subjects should be asked the non-leading question: "How have you felt since your last visit?" All AEs (serious and nonserious) reported by the subject must be recorded on the source documents and eCRFs provided by the sponsor. The AE, onset date, resolution date, seriousness, severity, causal relationship to the IMP (IMP Causality), action taken with IMP treatment, and outcome will be recorded in the source document and the eCRF. Adverse event and SAE collection will begin after the subject has signed the ICF.

Use medical terminology in AE reporting. Adverse events should be reported as a single unifying diagnosis whenever possible or, in the absence of a unifying diagnosis, as individual signs or symptoms. Exacerbation or disease progression should be reported as an AE only if there are unusual or severe clinical features that were not present, or experienced earlier, or not expected based on the course of the condition. If an AE that has been previously reported worsens and its severity or seriousness changes, it will be recorded as a new AE in the eCRF.

In addition, the sponsor must be notified immediately by e-mail of any IRE according to the procedure outlined in Section 5.3. Special attention should be paid to recording hospitalization and concomitant medications.

The information below will be recorded in the eCRF according to the eCRF entry instructions provided by the sponsor.

- Adverse event
- Onset date (also the time, for AEs occurring during stay at the trial site or for vomiting) and resolution date

  For AEs occurring while the subject is hospitalized, the onset time will be recorded whenever possible. If the exact onset time of vomiting is unknown (the onset time cannot be identified to the minute), the time will be recorded to the hour.
- Severity
- Seriousness (If serious, specify the category of seriousness)
- IMP causality
- Measures taken with IMP administration
- Outcome

5.3 Immediately Reportable Events

The investigator must immediately report after either the investigator, subinvestigator, or site personnel become aware of any SAE, potential serious hepatotoxicity, or confirmed pregnancy, by e-mail to the sponsor using the contact information on the cover page of this protocol. An IRE form must be completed and sent by e-mail, in principle, to the sponsor.

Subjects experiencing SAEs or IREs should be followed clinically until the event has resolved or stabilized, or until the subject is lost to follow-up or has died. Resolution means that the subject has returned to the baseline state of health and stabilized means that the investigator or subinvestigator does not expect any further improvement or worsening of the subject's condition. It is expected that the investigator or subinvestigator will provide or arrange appropriate supportive care for the subject and will provide prompt updates on the subject's status to the sponsor.

5.4 Potential Serious Hepatotoxicity

For a subject who experiences an elevation in AST or ALT that is ≥3 times the ULN, a total bilirubin level should also be evaluated. If the total bilirubin is ≥2 times the ULN, complete an IRE form with all values listed and also report as an AE on the eCRF.

5.5 Pregnancy

Women of child-bearing potential are defined as female subjects for whom menstruation has started and who are not documented as sterile (ie, have had a bilateral oophorectomy and/or hysterectomy or who have been postmenopausal for at least 12 months).

For WOCBP and for men who are sexually active, there must be a documented agreement that the subject and/or their partner will take effective measures (ie, double barrier method) to prevent pregnancy during the course of the trial and for 30 days after the last dose of IMP. Unless the subject is sterile (ie, women who have had a bilateral oophorectomy and/or hysterectomy or who have been postmenopausal for at least 12 consecutive months; or men who have had a bilateral orchidectomy) or remains abstinent, at least one of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pills, or condom with spermicide.

Before enrolling WOCBP in this clinical trial, investigators must review the below guidelines about trial participation with all WOCBP. The topics should generally include:

- General information
- Informed consent form
- Pregnancy prevention information
- Drug interactions with hormonal contraceptives
- Contraceptives in current use
- Guidelines for the follow-up of a reported pregnancy

Before trial enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form stating that the above mentioned risk factors and the consequences were discussed with her.

A urine and/or serum pregnancy test for hCG will be performed at screening on all WOCBP. If a urine test is performed and is positive, the investigator will follow up with a confirmatory serum test.

During the trial, all WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual cycle).

If a subject is suspected to be pregnant before she receives IMP, the IMP administration must be withheld until the results of serum pregnancy tests are available. If the pregnancy is confirmed, the subject must not receive the IMP and must not be enrolled in the trial. If

pregnancy is suspected while the subject is taking IMP, the IMP must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of the pregnancy test is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety) and the subject will be withdrawn from the trial.

The investigator or subinvestigator must immediately notify the sponsor of any pregnancy associated with IMP exposure during the trial and for 30 days after the last dose of IMP, and record the event on the IRE form and forward it to the sponsor. The sponsor will forward Pregnancy Surveillance Form(s) for monitoring the outcome of the pregnancy.

Protocol-required procedures for trial discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered, if indicated. In addition, the investigator or subinvestigator must report to the sponsor, on appropriate Pregnancy Surveillance Form(s), follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for a minimum of 6 months from the date of birth.

5.6 Procedure for Breaking the Blind

The investigator or subinvestigator will be able to obtain the emergency key from the IWRS only if a medical emergency occurs, and opening of the treatment assignment code is considered to be important for treating the subject. The opening of the emergency key will be automatically provided to the sponsor from the IWRS by e-mail. If the blind is broken, the Pharmacovigilance department must be notified immediately (see the cover page of this protocol for contact information). Documentation of breaking the blind should be recorded in the subject's medical record with the date and time the blind was broken and the names of the personnel involved. Once the blind is broken for a subject, that subject may not reinitiate treatment with the IMP.

5.7 Follow-up of Adverse Events

5.7.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified at any time during the trial must be recorded on the AE eCRF with the current status (ongoing or resolved/recovered) noted. All nonserious events (that are not IREs) that are ongoing at the last scheduled contact will be recorded as ongoing on the eCRF. For any AE having been identified throughout the trial, during

analysis, additional relevant medical history information may be requested by the sponsor to further ascertain causality (including, but not limited to, information such as risk related behavior, family history, and occupation). Follow-up information after the end of the trial date (the date of the last scheduled contact) will be recorded in the subject's medical record.

5.7.2 Follow-up of Serious Adverse Events and Immediately Reportable Events

This trial requires that subjects be actively monitored for SAEs and IREs for 7 to 10 days after the final IMP administration (up to the date of the trial end [the last scheduled contact]).

Serious AEs and IREs that are identified or ongoing on the date of the trial end must be recorded as such on the AE eCRF page. If updated information (eg, resolved status) on SAE or IRE status becomes available after a subject's last scheduled contact up to the last visit of the last subject for the entire trial, this must be reported to the sponsor and recorded on the AE eCRF page, according to the appropriate reporting procedures. The investigator or subinvestigator will follow SAEs and IREs until the event has resolved or stabilized, or the subject is lost to follow-up or has died, and continue to report any significant follow-up information on an IRE form to the sponsor.

5.7.3 Follow-up and Reporting of Serious Adverse Events Occurring After the Date of Trial End (Last Scheduled Contact)

Any new SAEs or IREs reported to the investigator or subinvestigator, which occur after the end of trial (last scheduled contact) and are determined by the investigator or subinvestigator to be reasonably associated with the use of the IMP, should be reported to the sponsor. This may include SAEs or IREs that are captured on follow-up telephone contact or at any other timepoint after the defined trial period. The investigator or subinvestigator should follow SAEs or IREs identified after the defined trial period, and continue to report any significant follow-up information on an IRE form to the sponsor until the events are resolved or stabilized, or the subject is lost to follow-up or has died.

6 Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic Analyses

6.1 Pharmacokinetics

6.1.1 Datasets for Pharmacokinetic Analysis

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

6.1.2 Pharmacokinetic Analysis

6.1.2.1 Endpoints

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

6.1.2.2 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), arithmetic mean, SD, coefficient of variation, minimum, median, and maximum.

6.2 Population Pharmacokinetic Analysis

A population pharmacokinetic analysis (PPK) analysis will be conducted using the plasma drug concentration data and a report will be prepared separately.

6.3 Pharmacodynamics

A pharmacodynamic analysis will be conducted on the pharmacodynamic analysis set (see Section 7.2).

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 valance 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 will be calculated.

- Daily urine volume
- Daily fluid intake

- Daily fluid balance
- Serum sodium concentration and sodium potassium concentration
- Serum osmolality
- Biomarkers (plasma AVP concentration, plasma BNP concentration, plasma renin activity, serum NT-proBNP concentration, and serum troponin I concentration)
- Daily urine sodium excretion
- Daily urine potassium excretion
- Urine osmolality

6.4 Pharmacokinetics/Pharmacodynamics

No pharmacokinetic/pharmacodynamic analysis is planned.

6.5 Pharmacogenomics

For the pharmacogenomic analysis, see Section 3.7.5.3.2.

7 Statistical Analysis

7.1 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).

7.2 Datasets for Analysis

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

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

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

7.3 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.

7.4 Primary and Secondary Endpoint Analyses

The analyses described below will be conducted on the full analysis set.

7.4.1 Primary Endpoint Analysis

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 non-inferiority margin of 0.48.

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 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.

7.4.2 Secondary Endpoint Analysis

7.4.2.1 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 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 7.4.2.1-1). The resolution rate is defined as the proportion of subjects in whom the symptom is present at baseline and it resolved after IMP administration.

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 7.4.2.1-1 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 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.

7.4.2.2 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 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 the presence 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.

7.4.2.3 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 95% CI 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.

7.4.2.4 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.

7.5 Analysis of Demographic and Baseline Characteristics

In the FAS and the safety analysis set, the frequency distribution and descriptive statistics of the subject characteristics will be calculated.

7.6 Safety Analysis

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

7.6.1 Adverse Events

All AEs will be coded by system organ class and Medical Dictionary for Regulatory Activities preferred term. The incidence of the following events will be summarized:

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

IMP-related TEAEs will be summarized in the same manner as shown above.

7.6.2 Clinical Laboratory Data

Clinical laboratory data obtained from central measurements will be used. 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.

The numbers and percentages of subjects who have a visit with serum total bilirubin value of ≥2 times the ULN and an AST or ALT value of ≥3 times the ULN at any post-treatment time point will be calculated.

7.6.3 Vital Signs 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.

7.6.4 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.

8 Management of Investigational Medicinal Product

For full details on IMP management, see the OPC-61815 IB and the clinical operation manual.

8.1 Packaging and Labeling

The IMPs will be provided to the IMP storage manager by the sponsor or designated agent. The IMPs for each subject will be supplied as a packaged set composed of 6 vials containing either of OPC-61815 16-mg injection or placebo injection, and 1 small box containing 10 tolvaptan 15-mg tablets or 10 placebo tablets in a PTP sheet. Each vial and each small box will be labeled to clearly state "For clinical trial use only," and disclose the protocol number, name of the IMP, quantity, batch number, expiration date, storage method, and sponsor's name and address. The packaged set for each subject will be labeled to clearly state "For clinical trial use only," and disclose the protocol number, IMP numbers, name of the IMPs, quantities, batch numbers, expiration dates, storage methods, subject identifier, and sponsor's name and address.

8.2 Storage

The IMP will be stored in a securely locked cabinet or enclosure. Access will be limited to the IMP storage manager. The IMP storage manager may not provide IMP to any subject not participating in this protocol.

The IMPs will be stored at room temperature.

The trial site staff will maintain a temperature log in the IMP storage area recording the temperature at least once each working day.

8.3 Accountability

The IMP storage manager must maintain an inventory record of IMP (including investigational, active control, or placebo) received, dispensed, administered, and returned.

8.4 Returns and Destruction

Upon completion or termination of the trial, all unused IMPs and partially used IMPs must be returned to the sponsor or a designated agent.

All IMP returned to the sponsor must be accompanied by appropriate documentation and be identified by protocol number and trial site number on the outermost shipping

container. Returned supplies should be in the original containers. The assigned trial monitor will facilitate the return of unused IMP and partially used IMP.

8.5 Reporting of Product Quality Complaints

A Product Quality Complaint (PQC) is any written, electronic, or verbal communication by a healthcare professional, consumer, subject, medical representative, Competent Authority, regulatory agency, partner, affiliate or other third party that alleges deficiencies or dissatisfaction related to identity, quality, labeling, packaging, reliability, safety, durability, tampering, counterfeiting, theft, effectiveness or performance of a drug product or medical device after it is released for distribution. Examples include, but are not limited to, communications involving:

- Failure/malfunction of a product to meet any of its specifications
- Incorrect or missing labeling
- Packaging issues (eg, damaged, dirty, crushed, missing product)
- Blister defects (eg, missing, empty blisters)
- Bottle defects (eg, under/over-fill, no safety seal)
- Vial defects
- Product defect (eg, odor, chipped, broken, embossing illegible)
- Loss or theft of product

8.5.1 Eliciting and Reporting Product Quality Complaints

The investigator, subinvestigator, or designee must record all PQCs identified through any means from the receipt of the IMP from the sponsor or sponsor's designee, through and including reconciliation and up to destruction, including subject dosing. The investigator, subinvestigator, or designee must notify the sponsor or sponsor's designee (contact information: PQC_263-102-00003@otsuka.jp) of the information listed in Section 8.5.2 by e-mail, immediately after becoming aware of the PQC.

Identification of a PQC by the subject should be reported to the investigator or subinvestigator, who should then follow one of the reporting mechanisms above.

8.5.2 Information Required for Reporting Purposes

- Description of compliant
- Reporter identification (eg, subject, investigator, subinvestigator, trial site, person preparing the IMP, etc.)
- Reporter contact information (eg, address, phone number, e-mail address)

- ID of material (product/compound name, coding)
- Clinical protocol reference (number and/or trial name)
- Dosage form/strength (if known)
- Pictures (if available)
- Availability for return

8.5.3 Return Process

Indicate during the report of the PQC if the complaint sample is available for return. As needed, the sponsor may provide the procedure for returning the sample.

It must be documented in the site accountability record that a complaint sample for a dispensed kit has been forwarded to the sponsor for complaint investigation.

8.5.4 Assessment/Evaluation

Assessment and evaluation of PQCs will be handled by the sponsor.

9 Records Management

9.1 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include but are not limited to progress notes, electronic data, screening logs, and recorded data from automated instruments. Source documents concerning plasma drug concentration data will retained by the bioanalytical laboratory. The sponsor will retain the electronic file of the plasma drug concentration data provided from the bioanalytical laboratory, as a copy.

All source documents other than plasma drug concentration data pertaining to this trial will be maintained by the trial site and made available for direct inspection by authorized persons. The investigator or the trial site will permit trial-related monitoring, audits, IRB review, and regulatory inspection(s) by providing direct access to source data/documents by authorized persons as defined in the ICF. In all cases, subject confidentiality must be maintained in accordance with local regulatory requirements.

9.2 Data Collection

During each subject's visit to the trial site, the investigator or subinvestigator will record progress notes to document all significant observations. At a minimum, these notes will contain:

- Documentation of the informed consent process, including any revised consents;
- Documentation of the investigator or subinvestigator's decision to enroll the subject into the trial, the review of all inclusion/exclusion criteria prior to IMP administration, and confirmation of the subject's actual participation in the trial;
- The date of the visit and the corresponding Visit or Day in the trial schedule;
- General subject status remarks, including any significant medical findings. The severity, frequency, duration, action taken, and outcome of any AEs and the investigator's assessment of relationship to IMP must also be recorded;
- Any changes in concomitant medications or dosages;
- A general reference to the procedures completed;
- The signature (or initials) and date of investigator or subinvestigator (or designee) who made an entry in the progress notes.

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the progress notes as described above. Any changes to information in paper source documents will be initialed and dated on the day the change is made by a trial site staff member authorized to make the change. Changes will be made by striking a single line through erroneous data (so as not to obliterate the original data), and clearly entering the correct data (eg, ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the investigator or subinvestigator. When using an electronic trial data system, full audit trail of the change should be maintained.

The information recorded in the medical record or other source documents should be directly entered in the sponsor's electronic data capture system by an authorized trial site staff. Changes to the data will be captured by an automatic audit trail.

9.3 File Management at the Trial Site

The head of the trial site will ensure that the trial site file is maintained in accordance with Section 8 of the ICH GCP Guideline E6 and as required by applicable local regulations. The trial site will take measures to prevent accidental or premature destruction of these documents.

9.4 Records Retention at the Trial Site

The trial sites should maintain all documents and records relevant to the trial for the longest of the following 2 periods and the date on which DNA storage is determined to be terminated. If the sponsor requires longer maintenance, the storage period and method will be discussed with the trial site.

- A period of at least 2 years after the date on which approval to market the drug is obtained, or a period of at least 3 years after the date on which the sponsor notifies the trial site that development of the IMP is discontinued or that the final report of this trial will not be submitted with the approval application for the IMP
- A period of at least 3 years after the trial is terminated or completed

The trial site must not dispose of any records relevant to this trial without either (1) written permission from the sponsor or (2) provision of an opportunity for the sponsor to collect such records. The trial site will be responsible for maintaining adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial. Such documentation is subject to inspection by the sponsor and the relevant regulatory authorities.

10 Quality Control and Quality Assurance

10.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, the ICH E6 GCP: Consolidated Guidance, and applicable regulatory requirements and local laws. As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the progress of the trial), the sponsor's monitors will visit the site during the trial, as well as communicate frequently via telephone, e-mail, and written communications. In addition, all investigators, subinvestigators, and trial site personnel will undergo initial and ongoing training for this particular trial, and this training will be clearly documented.

10.2 Auditing

The sponsor's Quality Assurance Unit (or representative) may conduct trial site audits. Audits will include, but are not limited to, IMP supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. The investigator agrees to participate with audits.

Regulatory authorities may inspect the trial site during or after the trial. The investigator will cooperate with such inspections and will contact the sponsor immediately if such an inspection occurs.

11 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, ICH GCP Guideline (E6), international ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Science guidelines, and applicable local laws and regulations.

Each trial site will seek approval by an IRB according to regional requirements, and the trial site will provide that documentation to the sponsor. The IRB will evaluate the ethical, scientific, and medical appropriateness of the trial. Further, in preparing and handling the eCRF, the investigator or subinvestigator and his/her staff will take measures to ensure adequate care in protecting subject confidentiality. To this end, a subject number or subject identifier will be used to identify each subject. Financial aspects, subject insurance, and the publication policy for the trial will be documented in the agreement between the sponsor and the trial site.

12 Confidentiality

All information generated in this trial will be considered confidential and will not be disclosed to anyone not directly concerned with the trial without the sponsor's prior written permission. Subject confidentiality requirements of the region(s) where the trial is conducted will be met. However, authorized regulatory officials and sponsor personnel (or their representatives) may be allowed full access to inspect and copy the records, consistent with local requirements. All IMPs, subject bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the sponsor.

Subjects will be identified only by unique subject numbers in eCRFs. If further subject identification is required, subjects' full names may be made known to a regulatory agency or other authorized officials if necessary, subject to local regulations.

13 Amendment Policy

The investigator will not make any changes to this protocol without the sponsor's prior written consent and subsequent approval/favorable opinion by the IRB. Any permanent change to the protocol, whether an overall change or a change for specific trial site(s), must be handled as a protocol amendment. Any amendment will be written by the sponsor. Each amendment will be submitted to the IRB, as required by local regulations. Except for "administrative" or "nonsubstantial" amendments, investigators or subinvestigators will wait for IRB approval/favorable opinion of the amended protocol, before implementing the change(s). Administrative amendments are defined as having no effect on the safety of subjects, conduct or management of the trial, trial design, or the quality or safety of IMP(s) used in the trial. A protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately followed by IRB notification within local applicable timelines. The sponsor will submit protocol amendments to the applicable regulatory agencies within local applicable timelines.

When the IRB, investigators, and/or the sponsor conclude that the protocol amendment substantially alters the trial design and/or increases the potential risk to the subject, the currently approved written information and ICF will require similar modification. In such cases, after approval/favorable opinion of the new written information and ICF by the IRB, repeat informed consent will be obtained from subjects enrolled in the trial before expecting continued participation and before the amendment-specified changes in the trial are implemented.

14 Publication Authorship Requirements

Authorship for any Otsuka-sponsored publications resulting from the conduct of this trial will be based on International Committee of Medical Journal Editors (ICMJE) authorship criteria (http://www.icmje.org/recommendations). According to ICMJE guidelines, one may be considered an author only if the following criteria are met:

1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All authors must meet the above criteria, and all who qualify for authorship based on the above criteria should be listed as authors.

Investigators or other trial participants who do not qualify for authorship may be acknowledged in publications resulting from the trial. By agreeing to participate in the trial, investigators or other trial participants consent to such acknowledgement in any publications resulting from its conduct.

15 References

1 McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. N Engl J Med. 1971;285:1441-6.

2 Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (The Japanese Circulation Society 2017/The Japanese Heart Failure Society 2017). 2018.

3 Machikawa F. A phase 1, placebo-controlled, double-blind, single intravenous dose trial of OPC-61815 in healthy male subjects. Clinical study report (Protocol 263-08-001) issued 30 Aug 2010.

4 Hasunuma T. A phase 1, placebo-controlled, double-blind, repeated intravenous dose trial to evaluate the safety, pharmacokinetics, and pharmacodynamics of OPC-61815 at 1.25, 5, and 20 mg in healthy male subjects. Clinical study report (Protocol 263-09-001) issued 26 Oct 2010.

5 Hasunuma T. A phase 1, single-center, placebo-controlled, double-blind trial to evaluate the safety, pharmacokinetics, and pharmacodynamics of OPC-61815 by dosage regimen. Clinical study report (Protocol 263-10-005), issued 29 Feb 2012.

6 Saito K. A placebo-controlled, double-blind, comparative trial of OPC-41061 for the treatment of cardiac edema (congestive heart failure). Clinical study report (Protocol 156-06-002) issued 22 Jan 2009.

7 Matsuzaki M, Hori M, Fukunami M. Efficacy and Safety of Tolvaptan in Heart Failure Patients with Volume Overload Despite the Standard Treatment with Conventional Diuretics: A Phase III, Randomized, Double-blind, Placebo-controlled Study (QUEST Study). 2011;25:33-45

9 International Council for Harmonisation (ICH) [homepage on the Internet]. E6: Good Clinical Practice: Consolidated Guideline [finalized 1996 May, corrected 1996 Jun 1996; cited 2014 Dec 5]. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf.

10 Forrester JS, Diamond G, Chatterjee K, Swan HJ. Medical therapy of acute myocardial infarction by application of hemodynamic subsets (First of two parts). N Engl J Med. 1976;295(24):1356-62.

[11] The Criteria Committee of the New York Heart Association, Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Editioned, 1994.

Appendix 1 Handling and Shipment of Bioanalytical Samples

1) Handling of samples

Storage tubes and other all tubes to be used will be labeled individually to disclose the protocol No., subject No., test parameter, sampling time point, etc.

2) Blood samples for pharmacokinetic assessment

Approximately 2 mL of blood will be taken in an EDTA-containing test tube. In principle, venous blood sampling by direct venipuncture or catheterization will be conducted, except in cases where the investigator or subinvestigator considers arterial blood sampling by catheterization to be preferable. The collected blood will be mixed by slowly turning upside-down several times, placed in ice bath, and then (within 45 minutes after sampling) centrifuged at approximately 1500 g for 10 minutes at 4°C to separate plasma. The plasma will be divided almost equally, and placed in 2 sample stock tubes (primary sample and backup sample) that are appropriately labeled. The plasma samples will be stored in a freezer set at below −20°C. The exact time at which the blood sample was actually taken (not the scheduled sampling time) will be recorded in the eCRF. The central laboratory will collect plasma samples from each trial site and ship them to the bioanalytical laboratory according to the shipment schedule prepared in consultation with the sponsor. The plasma samples will be placed with an adequate amount of dry ice in an adiabatic container while being shipped. The central laboratory and the bioanalytical laboratory will store the plasma samples in a freezer set at below −70°C. The remainder of the plasma samples after measurements will be stored at the bioanalytical laboratory and discarded after the issue of the clinical study report.

3) Samples for pharmacodynamic laboratory tests

The trial site will collect, process, and store samples for pharmacodynamic laboratory tests according to procedures provided separately by the sponsor.

- Serum sodium concentration, serum potassium concentration, and serum osmolality

  Blood will be taken using a serum separation tube, mixed by slowly turning upside-down several times, allowed to stand for at least 30 minutes at room temperature, and then centrifuged to obtain serum. The serum will be taken in a sample stock tube and stored refrigerated.
- Plasma AVP concentration

  Blood will be taken using an EDTA-containing tube, mixed by slowly turning upside-down several times, and centrifuged at a refrigerated temperature to obtain plasma. The plasma will be taken in a sample stock tube and stored frozen.

- Plasma BNP concentration and plasma renin activity

  Blood will be taken in an EDTA-containing tube from a subject who has remained at rest in a supine position, mixed by slowly turning upside-down several times, and centrifuged at a refrigerated temperature to obtain plasma. The plasma will be taken in a sample stock tube and stored frozen.
- Serum NT-proBNP concentration

  Blood will be taken using a serum separation tube, mixed by slowly turning upside-down several times, allowed to stand for at least 30 minutes at room temperature, and then centrifuged to obtain serum. The serum will be taken in a sample stock tube and stored frozen.
- Serum troponin I concentration

  Blood will be taken using a serum separation tube, mixed by slowly turning upside-down several times, allowed to stand for at least 30 minutes at room temperature, and then centrifuged to obtain serum. The serum will be taken in a sample stock tube and stored frozen.
- Urine sodium concentration, urine potassium concentration, and urine osmolality

  The collected urine will be aliquoted into sample stock tubes and stored refrigerated. Before transferring to sample stock tubes, the urine volume will be measured.

4) Blood sample for DNA storage

Approximately 2 mL of blood will be taken in an EDTA-containing test tube. In principle, venous blood sampling by direct venipuncture or catheterization will be conducted, except in cases where the investigator or subinvestigator considers arterial blood sampling by catheterization to be preferable. The collected blood sample will be mixed by slowly turning upside-down several times, transferred to a sample stock tube that is appropriately labeled, and then stored in a freezer set at below −20°C within 60 minutes after sampling. The status (collected/not collected), and the date and time of blood sampling will be recorded in the source document and the eCRF. The central laboratory will collect blood samples for DNA storage from each trial site and ship the samples to the DNA repository. The plasma samples will be placed with an adequate amount of dry ice in an adiabatic container, while being shipped. The DNA repository will store the blood samples in a freezer set at −70°C. After double coding the samples by assigning a new unique code to each sample, the DNA repository will extract the DNA and store the obtained DNA sample in a freezer set at −70°C. Upon the request of the sponsor, the DNA repository will discard the sample in such a state that the subject cannot be identified.

Appendix 2 Protocol Amendments/Administrative Changes

Amendment Number: 1

Issue Date: 14 Mar 2019

PURPOSE:

Changing the trial procedures and editing the descriptions of the protocol including correcting writing errors

BACKGROUND:

The trial procedures were corrected with a view toward feasibility. In addition, the descriptions of the protocol were edited (including corrections of writing errors.)

MODIFICATIONS TO PROTOCOL:

- Table 3.7-1, Note b, 3.7.3.2, and 3.7.5.2.4:
  The following statement was added with a view toward feasibility: "If it is difficult to perform serum sodium concentration measurement at the trial site, plasma sodium concentration may be measured. Either serum or plasma should be used consistently for measurement of sodium concentration in a given subject. However, even if plasma sodium concentration is measured at the trial site, serum sodium concentration will be measured at the central laboratory."

- 3.7.1.5, 2) After breakfast; 3.7.1.6, 2) After breakfast; and 3.7.1.7, 2) After breakfast:
  The description "... and urine collection and fluid intake measurement will start to assess the following items." was changed as follows for more clarification: "... and urine collection and fluid intake measurement will start to assess the following items <u>from the point at which urination immediately before IMP administration has been completed.</u>"

- 3.7.1.5, 3) IMP administration; 3.7.1.6, 3) IMP administration; and 3.7.1.7, 3) IMP administration:
  The statement "The fact of IMP treatment will be entered into the IWRS" was deleted (writing error).

- 3.8.3.2, 1) Reasons related to AEs:
  The statement "Serum sodium concentration measured at the trial site or the central laboratory increases by ≥12 mEq/L from immediately predose within 24 hours after start of IMP administration." was changed into the following statement with a view to the feasibility: "Serum <u>or plasma</u> sodium concentration measured at the trial site or the central laboratory increases by ≥12 mEq/L from immediately predose within 24 hours after start of IMP administration."

The statement “Serum sodium concentration measured at the trial site or the central laboratory is ≥155 mEq/L during the treatment period.” was changed into the following statement with a view to the feasibility: “Serum or plasma sodium concentration measured at the trial site or the central laboratory is ≥155 mEq/L during the treatment period.”

Amendment Number: 2

Issue Date: 27 Mar 2020

PURPOSE:

Addition of trial procedures and editing of descriptions in the protocol including the correction of errors

BACKGROUND:

Trial procedures were added in consideration of ensuring the safety of subjects. The descriptions in the protocol were also edited (including the correction of errors.)

MODIFICATIONS TO PROTOCOL:

- Table 3.7-1
  - Item:

    "Serum sodium[c] and potassium concentrations" was changed into "Serum sodium[c] and potassium concentrations[c]" in consideration of ensuring the safety of subjects.
  - Note c:

    The statement, "Measurement of serum sodium concentration during the treatment period will be performed at both the central laboratory and the trial site. If it is difficult to perform serum sodium concentration measurement at the trial site, plasma sodium concentration may be measured. Either serum or plasma should be used consistently for measurement of sodium concentration in a given subject. However, even if plasma sodium concentration is measured at the trial site, serum sodium concentration will be measured at the central laboratory." was changed into the following statement in consideration of ensuring the safety of subjects: "Measurement of serum sodium and potassium concentrations during the treatment period will be performed at both the central laboratory and the trial site. If it is difficult to perform serum sodium and potassium concentration measurement at the trial site, plasma sodium and potassium concentrations may be measured. Either serum or plasma should be used consistently for measurement of sodium and potassium concentrations in a given subject. However, even if plasma sodium and potassium concentrations are measured at the trial site, serum sodium and potassium concentrations will be measured at the central laboratory."
  - Note g:

    The following statement was added in consideration of ensuring the safety of subjects: "If the serum potassium concentration at the trial site or the central laboratory is confirmed to exceed 5.5 mEq/L at any time point with no specified 12-lead ECG during the treatment period,, an additional 12-lead ECG will be performed as an unscheduled examination."

- Table 3.7-2:
  "(Note symbol) a" was deleted (a typographical error).

- 3.7.3.2:
  The statement "In order for the investigator or subinvestigator to be promptly aware of serum sodium concentrations, in consideration of subject safety, serum sodium concentrations will also be measured at the trial site. The status (collected/not collected), and the date and time of blood sampling, as well as the results of measurement will be recorded in the source document and the eCRF. If it is difficult to perform serum sodium concentration measurement at the trial site, plasma sodium concentration may be measured. Either serum or plasma should be used consistently for measurement of sodium concentration in a given subject. However, even if plasma sodium concentration is measured at the trial site, serum sodium concentration will be measured at the central laboratory." was changed into the following statement in consideration of ensuring the safety of subjects: "In order for the investigator or subinvestigator to be promptly aware of serum sodium and potassium concentrations, in consideration of subject safety, serum sodium and potassium concentrations will also be measured at the trial site. The status (collected/not collected), and the date and time of blood sampling, as well as the results of the serum sodium concentration measurement will be recorded in the source document and the eCRF, and those of the serum potassium concentration measurement will be recorded in the source document. If it is difficult to perform serum sodium and potassium concentration measurement at the trial site, plasma sodium and potassium concentrations may be measured. Either serum or plasma should be used consistently for measurement of sodium and potassium concentrations in a given subject. However, even if plasma sodium and potassium concentrations are measured at the trial site, serum sodium and potassium concentrations will be measured at the central laboratory. If the serum potassium concentration at the trial site or the central laboratory is confirmed to exceed 5.5 mEq/L, a 12-lead ECG will be performed as necessary in reference to Section 3.7.3.4."

- 3.7.3.4:
  The following statement was added in consideration of ensuring the safety of subjects: "However, if the serum potassium concentration at the trial site or the central laboratory is confirmed to exceed 5.5 mEq/L at any time point with no specified 12-lead ECG during the treatment period,, an additional 12-lead ECG will be performed as an unscheduled examination."

- 3.7.5.2.4:
  The statement "In order for the investigator or subinvestigator to be promptly aware of serum sodium concentrations, in consideration of subject safety, serum sodium concentrations will also be measured at the trial site. The status (collected/not collected), the date and time of blood sampling, as well as the result of measurement will be recorded in the source document and the eCRF. If it is difficult to perform

serum sodium concentration measurement at the trial site, plasma sodium concentration may be measured. Either serum or plasma should be used consistently for measurement of sodium concentration in a given subject. However, even if plasma sodium concentration is measured at the trial site, serum sodium concentration will be measured at the central laboratory." was changed into the following statement in consideration of ensuring the safety of subjects: "In order for the investigator or subinvestigator to be promptly aware of serum sodium and potassium concentrations, in consideration of subject safety, serum sodium and potassium concentrations will also be measured at the trial site. The status (collected/not collected), the date and time of blood sampling, as well as the result of the serum sodium concentration measurement will be recorded in the source document and the eCRF, and those of the serum potassium concentration measurement will be recorded in the source document. If it is difficult to perform serum sodium and potassium concentration measurement at the trial site, plasma sodium and potassium concentrations may be measured. Either serum or plasma should be used consistently for measurement of sodium and potassium concentrations in a given subject. However, even if plasma sodium and potassium concentrations are measured at the trial site, serum sodium and potassium concentrations will be measured at the central laboratory."

- 7.3:

  "Missing data at the time of final IMP administration will be imputed using the last available data obtained by the day after final IMP administration." was changed into the following statement due to a error: "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."

Agreement

I, the undersigned principal investigator, have read and understand the protocol (including the Investigator's Brochure) and agree that it contains all the ethical, legal, and scientific information necessary to conduct this trial in accordance with the principles of Good Clinical Practices and as described herein and in the sponsor's (or designee's) Clinical Trial Agreement.

I will provide copies of the protocol to all physicians, nurses, and other professional personnel to whom I delegate trial responsibilities. I will discuss the protocol with these persons to ensure that they are sufficiently informed regarding the investigational new drug, OPC-61815, the concurrent medications, the efficacy and safety parameters, and the conduct of the trial in general. I am aware that this protocol must be approved by the Institutional Review Board (IRB) responsible for such matters in the clinical trial facility where OPC-61815 will be tested prior to commencement of this trial. I agree to adhere strictly to the attached protocol (unless amended in the manner set forth in the sponsor's Clinical Trial Agreement, at which time I agree to adhere strictly to the protocol, as amended).

I understand that this IRB-approved protocol will be submitted to the appropriate regulatory authority/ies by the sponsor. I agree that clinical data entered on eCRF by me and my staff will be utilized by the sponsor in various ways, such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow sponsor and designee monitors and auditors full access to all medical records at the research facility for subjects screened or enrolled in the trial.

I agree to await IRB approval before implementation of any substantial amendments to this protocol. If, however, there is an immediate hazard to subjects, I will implement the amendment immediately, and provide the information to the IRB within the required local applicable timelines. Administrative changes to the protocol will be transmitted to the IRB for informational purposes only, if required by local regulations.

I agree to provide all subjects with informed consent forms, as required by the applicable regulations and by ICH guidelines. I agree to report to the sponsor any adverse experiences in accordance with the terms of the sponsor's Clinical Trial Agreement and the relevant regional regulation(s) and guideline(s). I further agree to provide all required information regarding financial certification or disclosure to the sponsor for all investigators and subinvestigators in accordance with the terms of the relevant regional regulation(s). I understand that participation in the protocol involves a commitment to publish the data from this trial in a cooperative publication before publication of efficacy and safety results on an individual basis may occur, and I consent to be acknowledged in any such cooperative publications that result.

Principal Investigator Print Name	Trial Site
Signature	Signature Date

The signature on this agreement is digitally signed. The electronic signature page is attached to the agreement.