CLINICAL STUDY PROTOCOL

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

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Otsuka Pharmaceutical Co., Ltd

Investigational Medicinal Product

OPC-61815

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Protocol No. 263-102-00001

CONFIDENTIAL – PROPRIETARY INFORMATION

Clinical Development Phase:	2
Sponsor:	Otsuka Pharmaceutical Co., Ltd
Immediately Reportable Event:	Department of Pharmacovigilance Otsuka Pharmaceutical Co., Ltd Email: IRE_263-102-00001@otsuka.jp
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Protocol Synopsis

Name of Sponsor: Otsuka Pharmaceutical Co., Ltd Name of Investigational Medicinal Product: OPC-61815		Protocol No.: 263-102-00001
Protocol Title:	A Multicenter, Double-blind, Randomized, Active-controlled, Parallel-group Comparison Clinical Pharmacology Trial to Investigate the Dose of OPC-61815 Injection Equivalent to Tolvaptan 15-mg Tablet in Patients With Congestive Heart Failure (CHF)	
Clinical Phase/Trial Type:	2 / Clinical pharmacology	
Treatment Indication:	CHF patients with volume overload despite having received diuretics other than vasopressin antagonists	
Objective(s):	Primary: To investigate the dose of OPC-61815 injection formulation achieving exposure equivalent to that for tolvaptan 15-mg tablet by 1-hour intravenous administration of OPC-61815 at 2, 4, 8, or 16 mg once daily or oral administration of tolvaptan tablet at 15 mg once daily for 5 days in CHF patients with volume overload despite having received diuretics other than vasopressin antagonists Secondary: To investigate the efficacy, pharmacokinetics, pharmacodynamics, and safety of OPC-61815 in comparison with tolvaptan tablet by 1-hour intravenous administration of OPC-61815 at 2, 4, 8, or 16 mg once daily or oral administration of tolvaptan tablet at 15 mg once daily for 5 days in CHF patients with volume overload despite having received diuretics other than vasopressin antagonists.	
Trial Design:	A multicenter, randomized, double-blind, active controlled (with tolvaptan tablet), double-dummy, parallel group comparison trial	
Subject Population:	Japanese male and female CHF patients with volume overload despite having received diuretics other than vasopressin antagonists, age 20 to 85 years, inclusive (Sample size: A total of 50 subjects, comprising 10 subjects in each group[Note)] Note: Subject enrollment will be conducted to ensure that there are ≥10 subjects per group who complete blood sampling for measurement of plasma drug concentrations up until 24 hours postdose on Day 1.	

Inclusion/Exclusion Criteria:	Main criteria for inclusion: • Subjects who are currently on treatment with any of the following diuretics – 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 • Subjects with CHF in whom lower limb edema, pulmonary congestion, and/or jugular venous distension due to volume overload is present • Male or female subjects at age 20 to 85 years, inclusive, at time of informed consent • Subjects who are currently hospitalized or who are able to be hospitalized during the trial • Subjects who are capable of taking oral tablets • Subjects who are given diuretic agents with no change in dose or regimen during the run-in period • Subjects with no more than 1.0 kg change in body weight over the 2 days (Day −2 to Day −1 of the run-in period) prior to investigational medicinal product (IMP) administration Main criteria for exclusion: • Subjects with acute heart failure • Subjects with mainly noncardiogenic congestive symptoms • Subjects who are on an ventricular assist device • Subjects who are suspected of having hypovolemia, hypertrophic cardiomyopathy (excluding dilated phase), valvular disease with significant valvular stenosis, or hepatic encephalopathy with difficulty in adequate fluid intake

	• Subjects who have experienced acute myocardial infarction within 30 days prior to the screening examination • Subjects with definite diagnosis of active myocarditis or amyloid cardiomyopathy • Subjects with poorly controlled diabetes mellitus, anuria, or dysuria associated with urinary tract obstruction, calculus, or tumor • Subjects with a history of hypersensitivity to any of ingredients of OPC-61815 or tolvaptan • Subjects with a history of hypersensitivity or idiosyncratic reaction to benzazepine or benzazepine derivatives such as mozavaptan hydrochloride and benazepril hydrochloride • Subjects who are severely obese (body mass index [BMI], body weight [kg]/height $[m]^2$ exceeding 35 kg/m^2) • Subjects with supine systolic blood pressure of <90 mmHg • Subjects with any of the following laboratory test abnormalities: Total bilirubin, >3.0 mg/dL; serum creatinine, >3.0 mg/dL; serum sodium >147 mEq/L; serum potassium, >5.5 mEq/L • Subjects with concurrent symptoms or history of hepatic impairment • Subjects who are unable to sense thirst or who have difficulty with fluid intake
Trial Site(s):	Approximately 40 trial sites in Japan

Investigational Medicinal Product(s), Dose, Dosage regimen, Treatment period, Formulation, Mode of Administration:	Lyophilized formulation containing 2, 4, 8, or 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 for 5 days either tolvaptan 15-mg tablet or placebo tablet will be orally administered, followed immediately by 1-hour intravenous administration of either OPC-61815 at 2, 4, 8, or 16 mg or placebo. As there will be a difference in appearance between the OPC-61815 solution and the placebo solution at the time of preparation, the person responsible for IMP preparation at the trial site (non-blinded staff) will prepare the double-blinded IMP, which will then be administered by the investigator or subinvestigators, etc.
Trial Assessments:	**Pharmacokinetics:** Blood sampling for measurement of plasma concentrations of parent drugs and metabolites **Pharmacodynamics:** Blood sampling for serum concentrations of sodium and potassium, serum osmolality, and biomarker measurements; and urine sampling or cumulative urine volume collection for daily urine volume, daily fluid balance, daily urine sodium excretion, daily urine potassium excretion, urine osmolality, and daily fluid intake **Efficacy:** Body weight, congestive symptoms (lower limb edema, other edema, jugular venous distension, pulmonary congestion confirmed by chest X-ray, pulmonary rales, third cardiac sound, and hepatomegaly), cardiothoracic ratio, and NYHA classification **Safety:** Adverse event reporting, clinical laboratory tests, physical examination, vital signs (blood pressure, pulse rate, and body temperature), and 12-lead electrocardiogram **Screening:** Medical and medication history, physical examination, clinical laboratory tests, vital signs, body weight, and urine pregnancy test, etc.

Criteria for Evaluation:	**Primary Endpoint:** • Tolvaptan exposure (maximum [peak] plasma drug concentration [Cmax] and area under the concentration-time curve from time zero to 24 hours [AUC24h] on Day 1 of the treatment period) **Secondary Endpoint(s):** • Pharmacokinetics: Plasma concentrations and pharmacokinetic parameters of OPC-61815, tolvaptan, DM-4103, and DM-4107 • Pharmacodynamics: Serum concentrations of sodium and potassium, serum osmolality, biomarkers (plasma concentrations of arginine vasopressin and brain natriuretic peptide, plasma renin activity, and serum concentrations of NT-proBNP and troponin), daily urine volume, daily fluid intake, daily fluid balance, daily urine sodium excretion, daily urine potassium excretion, and urine osmolality • Efficacy: Body weight, congestive symptoms (lower limb edema, other edema, jugular venous distension, pulmonary congestion confirmed by chest X-ray, pulmonary rales, third cardiac sound, and hepatomegaly), cardiothoracic ratio, and NYHA classification • Safety: Adverse event reporting, clinical laboratory tests (including pregnancy test), physical examination, vital signs (blood pressure, pulse rate, and body temperature), and 12-lead electrocardiogram

Statistical Methods:	**Statistical Methods for Primary Endpoint:** For each parameter for tolvaptan exposure (C_{max} and AUC_{24h} on Day 1 of the treatment period), descriptive statistics will be calculated for each group. The descriptive statistics calculated will include number of subjects, arithmetic mean, standard deviation, coefficient of variation, geometric mean, minimum, median, and maximum values. For each parameter, the differences (each OPC-61815 group − tolvaptan 15-mg tablet group) in the mean value and its 95% confidence interval will be calculated using logarithmic transformation (natural logarithm). **Rationale for Sample Size:** The primary objective of this clinical trial is to compare tolvaptan exposure in order to investigate the dose of OPC-61815 injection required to achieve exposure equivalent to tolvaptan 15-mg tablet for use in conducting phase 3 confirmatory clinical trials of OPC-61815. The number of subjects required for this purpose was determined to be at least 10 subjects per group (50 subjects in total) who complete blood sampling for measurement of plasma drug concentrations up until 24 hours postdose on Day 1. In consideration of the possibility of some subjects withdrawing from the trial prior to 24 hours postdose on Day 1, the approximate target number of subjects for the start of IMP administration is set at 11 subjects per group (55 subjects in total).
Trial Duration:	Planned duration of the clinical trial: Jul 2017 to May 2018 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 Day 7 to Day 10 after the final IMP administration)

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List of Abbreviations

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AVP	Arginine vasopressin
BMI	Body mass index
BNP	Brain natriuretic peptide
cAMP	Cyclic adenosine 3',5'-monophosphate
CIOMS	Council for International Organizations of Medical Science
CRF	Case report form
CK (CPK)	Creatine kinase
CYP	Cytochrome P450
DILI	Drug Induced Liver Injury
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EDC	Electronic data capture
EU	European Union
GCP	Good Clinical Practice
γ-GTP	γ-Glutamyltransferase
hCG	Human chorionic gonadotropin
HIV	Human Immunodeficiency Virus
IB	Investigator's brochure
ICF	Informed consent form
ICD	Implantable Cardioverter Defibrillator
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
LDH	Lactic dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
NYHA	New York Heart Association
OPC	Otsuka Pharmaceutical Co.
PAP	Prostatic acid phosphatase
PQC	Product quality complaint
SAE	Serious adverse event
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

WOCBP Women of childbearing potential

List of Pharmacokinetic Parameters

Abbreviation/ Term	Unit	Spelled-out Form or 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
AUC_%Extrap	%	Percentage of AUC due to extrapolation from t_{last} to infinity [$(AUC_{\infty} - AUC_t)/AUC_{\infty} \times 100$]
C_{24h}	ng/mL	Concentration of drug in the plasma at 24 hours
CL	L/h	Total body clearance of drug from the plasma
CL/BW	L/h/kg	CL/normalized in body weight
CL/F	L/h	Apparent clearance of drug from plasma after extravascular administration
CL/F/BW	L/h/kg	CL/F normalized for body weight
C_{max}	ng/mL	Maximum (peak) plasma concentration of the drug
λ_z	h^{-1}	Apparent terminal-phase disposition rate constant (first-order)
$R_{5,ac}(C_{24h})$		Accumulation ratio of 5th dose to first dose at regular administration for C_{24h}
$t_{1/2,z}$	h	Terminal-phase elimination half-life
t_{last}	h	Time of last measurable (positive) concentration
t_{max}	h	Time to maximum (peak) plasma concentration

1 Introduction

Tolvaptan is an arginine vasopressin V_2 receptor antagonist synthesized by Otsuka Pharmaceutical Co., Ltd. (Hereinafter Otsuka Pharmaceutical). It specifically inhibits the binding of arginine vasopressin (AVP) to the V_2 receptor in the distal nephron to increase water excretion without affecting electrolyte excretion (aquaretic effect). For typical symptoms of congestive heart failure (CHF) include dyspnea, orthopnea, and jugular venous distension,[1] diuretics are widely used in the treatment of these symptoms.[2,3] 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, dose increase is not always an option even when adequate response is not obtained. In contrast, a greater diuretic effect can be expected with tolvaptan because of its different mechanism of action compared with other conventional diuretics. Moreover, tolvaptan does not lower serum electrolyte levels and has little effect on renal function, making it an option for patients who are not suitable for dose increase or prolonged treatment with conventional diuretics.

In Japan, tolvaptan was approved in 2010 under the trade name of Samsca® tablets for the indication of "volume overload in heart failure when adequate response is not obtained with other diuretics (eg, loop diuretics)." In 2013, a new indication of "body fluid retention in hepatic cirrhosis when adequate response is not obtained with other diuretics (eg, loop diuretics)" was approved. In 2014, another indication of "control of the progression of autosomal dominant polycystic kidney disease with increased renal volume and rapid renal volume growth" was granted for the drug. Outside Japan, in 2009, tolvaptan was approved in the United States for "treatment of hyponatremia with normal fluid volume or clinically significant volume overload in patients with heart failure or syndrome of inappropriate antidiuretic hormone secretion (SIADH)" and in Europe for "hyponatremia secondary to SIADH." In 2015, an additional indication of "control of the progression of rapidly progressive autosomal dominant polycystic kidney disease with stage 1 to 3 chronic renal failure" was granted in Europe. Tolvaptan has been approved in over 40 countries/regions.

Tolvaptan is administered to patients in clinical settings as an oral aquaretic and provides a useful treatment option for heart failure patients who have persistent fluid retention despite treatment with other conventional diuretics. However, 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 an impaired swallowing reflex in elderly patients. Tolvaptan is not readily soluble in water and not suited for development as an injection. Otsuka Pharmaceutical therefore synthesized the new intravenous aquaretic OPC-61815. OPC-61815 is a compound with improved water solubility achieved by phosphorylation of the hydroxyl group in the benzazepine ring of tolvaptan, AVP V_2 receptor antagonist. When administered, the phosphate ester of OPC-61815 is hydrolyzed by alkali and acid phosphatase in the body and tolvaptan forms. OPC-61815 is under development with the expectation that the compound will be effective in the treatment of "volume overload in heart failure when adequate response is not obtained with other diuretics (eg, loop diuretics)."

So far, the following three phase 1 trials of OPC-61815 have been completed in healthy adult male subjects: 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). Based on the results of these trials, the present trial has been planned to investigate the dose of OPC-61815 intravenous injection achieving exposure equivalent to that with tolvaptan 15-mg oral tablet.

1.1 Nonclinical Data

In a receptor-binding study using [^{3}H]-AVP as a labeled ligand, OPC-61815 exhibited affinity for the human AVP V_2 receptor (K_i value: 6.13 ± 1.34 nM), but that affinity was about 1/14 that of the primary active metabolite tolvaptan (K_i value: 0.43 ± 0.06 nM). OPC-61815 also showed weak affinity for human AVP V_{1a} receptor (K_i value: 54.2 ± 16.8 nM), only 1/4 that of tolvaptan (K_i value: 12.3 ± 0.80 nM). Like tolvaptan, OPC-61815 does not show affinity for human AVP V_{1b} receptor. OPC-61815 and tolvaptan showed an antagonistic action against V_2 receptor in HeLa cells expressing human AVP V_2 receptor by inhibiting the production of cyclic adenosine 3',5'-monophosphate (cAMP) by AVP. However, neither OPC-61815 nor tolvaptan induced any increase in cAMP production by itself, indicating that they possess no intrinsic V_2 receptor agonistic activity.

Conscious rats given a single intravenous administration of OPC-61815 (0.1275 to 12.75 mg/kg) showed a dose-dependent increase in urine volume and decrease in urine osmolality. These changes were not attenuated with 7-day repeated dosing. Beagle dogs given single intravenous administration of OPC-61815 (0.1275 to 3.825 mg/kg) showed a dose-dependent increase in urine volume and decrease in urine osmolality. Free water clearance was dose-dependently increased in the dogs, indicating OPC-61815 is an aquaretic agent which increases free water excretion. Dogs given a single intravenous administration of OPC-61815 showed an increase in plasma AVP concentration without increase in plasma renin activity. This showed that, unlike furosemide, OPC-61815 does not activate the renin-angiotensin system.

Histamine-induced vascular hyperpermeability model rats showed a dose-dependent increase in urine volume and decrease in urine osmolality after a single intravenous administration of OPC-61815 (0.3825 to 3.825 mg/kg, 2 hours before histamine dosing), with a dose-dependent suppression of the area of pigment leakage at the histamine administration site. In a carrageenin-induced paw edema model, development of paw edema was dose-dependently inhibited after a single intravenous administration of OPC-61815 (1.275 to 12.75 mg/kg, 1 hour before carrageenin dosing).

In hyponatremia model rats, plasma concentration which was once lowered increased as the intravenous administration dose of OPC-61815 was increased (0.255 to 5.1 mg/kg). Water content in the brain and heart was increased due to hyponatremia, but it was improved after OPC-61815 administration.

These results show that intravenous administration of OPC-61815 demonstrated the aquaretic actions, suggesting that OPC-61815 can be expected to provide clinical efficacy in the treatment of various diseases associated with volume expansion due to abnormal water metabolism such as hyponatremia and edematous disorders.

Please refer to the Investigator's Brochure (IB) for more detailed information.

1.2 Clinical Data

(1) Single Intravenous Dose Trial in Healthy Adult Males (Phase 1) (263-08-001)

In the phase 1 single intravenous dose trial (263-08-001), 54 healthy adult male subjects were given a single intravenous administration (over 5 minutes) of OPC-61815 injection 0.3, 1, 3, 7.5, 15, or 30 mg or placebo. The plasma concentration of OPC-61815 free form reached a peak between the completion of injection and 0.020 hour after injection [median time to maximum (peak) plasma concentration (t_{max})] and quickly decreased to

below the lower limit of quantitation (46.2 ng/mL) by 8 hours postdose in every dose group. The peak plasma concentration (C_{max}), area under the concentration-time curve from time zero to infinity (AUC_{∞}), and area under the concentration-time curve calculated to the last observable concentration at time t (AUC_t) increased with the dose increase. The mean terminal-phase elimination half-life ($t_{1/2,z}$) was 0.63 to 1.7 hours. Tolvaptan rapidly appeared in the plasma following intravenous administration of OPC-61815, with the plasma concentration peaking between 0.5 and 1.0 hour postdose and then decreasing to below the lower limit of quantitation (2.00 ng/mL) by 72 hours postdose in every dose group. The C_{max}, AUC_{∞}, and AUC_t all increased dose-dependently, and the mean $t_{1/2,z}$ was between 2.2 and 5.7 hours. A dose-dependent increase in urine volume was observed following a single intravenous administration of OPC-61815 injection 3 to 30 mg. There was little change in urine electrolyte excretion. Serum sodium concentration and serum osmolality increased, but there were no changes in serum potassium concentration. In terms of safety, all adverse events (AEs) reported in subjects treated with OPC-61815 were mild and resolved without treatment or with palliative treatment.

(2) Repeated Intravenous Dose Trial in Healthy Adult Males (Phase 1) (263-09-001)

In the phase 1 repeated intravenous dose trial (263-09-001), 36 healthy adult male subjects were given a single intravenous administration of OPC-61815 injection 1.25, 5, or 20 mg or placebo, followed by repeated intravenous doses (over 1 minute) for 7 days after a 1-day washout. No accumulation of OPC-61815 free form or its main active metabolite (tolvaptan) was seen. The area under the concentration-time curve (AUC) and C_{max} of both OPC-61815 free form and tolvaptan increased dose-dependently. During once-daily 7-day repeated intravenous administration of OPC-61815 injection 5 mg and 20 mg, an increase in urine volume was observed. However, the rate of increase did not accelerate during repeated administration. In terms of safety, AEs including feeling abnormal, pruritus, and erythema were reported frequently during and immediately after administration of OPC-61815. All the AEs were mild or moderate and subsequently resolved without treatment. However, because many of these events were judged to be potentially causally related to the investigational medicinal product (IMP) and were not reported in subjects treated with oral tolvaptan, it is suspected that OPC-61815 solution could be related to the occurrence of these events.

(3) Intravenous Dose Trial on Rate of Injection in Healthy Adult Males (Phase 1) (263-10-005)

The intravenous dose trial on rate of injection (263-10-005) was conducted to investigate the duration of administration that can avoid the potentially drug-related adverse events reported in the phase 1 repeated intravenous dose trial and not reported in subjects treated with oral tolvaptan. The trial was also aimed at exploring the cause of those potentially drug-related adverse events. Eighteen healthy adult male subjects were given a single intravenous administration of OPC-61815 injection 7.5 mg or 15 mg or placebo at different administration durations (2 hours, 5 minutes, and 1 minute). The median t_{max} of OPC-61815 free form was 1.8 to 2.0 hours after a 2-hour single intravenous administration of OPC-61815. The mean C_{max} of OPC-61815 free form after 2-hour administration was approximately 70% lower than that after both 5-minute and 1-minute administration. The median t_{max} of tolvaptan after 2-hour administration was 2.3 hours. The mean C_{max} of tolvaptan was similar across the durations of administration. The rate of increase in mean urine volume until 4 hours after a 2-hour single intravenous administration of OPC-61815 was lower than that after both 5-minute and 1-minute administration.

In terms of safety, the AEs similar to feeling abnormal, pruritus, and erythema, etc. that were frequently reported in the repeated intravenous dose trial (263-09-001) were selected as notable AEs. Those notable AEs occurred in 1 out of 12 subjects in the OPC-61815 groups and in 3 out of 6 subjects in the placebo group after 2-hour administration. Any causal relationship between the events and the IMP was ruled out except for the pruritus reported in 1 subject of the placebo group. The notable events occurred in 9 out of 12 subjects in the OPC-61815 groups and 2 out of 6 subjects in the placebo group after 5-minute administration. All the events were judged to be related to the IMP. The notable events were reported in 10 out of 11 subjects in the OPC-61815 groups and in 4 out of 6 subjects in the placebo group after 1-minute administration. All the events excluding erythema reported once in 1 subject treated with OPC-61815 were judged to be related to the IMP. All the AEs potentially causally related to the IMP occurred during or immediately after intravenous administration. Most of those events resolved without treatment within 10 minutes after the start of IMP administration. Because there were no clinically significant changes from baseline in plasma histamine concentration, the cause of the notable AEs is unclear.

Please refer to the IB for more detailed information.

1.3 Known and Potential Risks and Benefits

OPC-61815 has never been administered to patients with heart failure. No deaths or other serious adverse events (SAEs) were reported in the phase 1 trials in healthy adult male subjects (263-08-001, 263-09-001, and 263-10-005). Feeling abnormal, feeling hot, pruritus, erythema, hyperhidrosis, nausea, epigastric discomfort, and dyspnea were the significant AEs reported following bolus intravenous administration (over 1 or 5 minutes) of OPC-61815 in Trial 263-09-001 or 263-10-005. Significant AEs were defined as those similar to feeling abnormal, pruritus, and erythema, etc. that were reported frequently in the repeated intravenous dose trial (263-09-001).

As noted earlier, OPC-61815 has not previously been administered to patients with heart failure. Nevertheless, OPC-61815 should have similar benefits to tolvaptan because, when the phosphate ester of OPC-61815 is hydrolyzed by alkali and acid phosphatase in the body, tolvaptan forms and acts as an aquaretic agent. Tolvaptan has been shown to relieve weight increase and other signs commonly observed in patients with cardiac edema (jugular venous distension, hepatomegaly, and lower limb edema).

In a clinical trial in patients with cardiac edema, the following AEs were frequently reported among 437 patients given tolvaptan (in ≥ 2% incidence among tolvaptan-treated patients and at a higher frequency than in placebo-treated patients): ventricular tachycardia, constipation, dry mouth, diarrhoea, vomiting, thirst, 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, dehydration, hyperkalaemia, dizziness, pollakiuria, renal impairment, and epistaxis.

Please refer to the IB for more detailed information.

2 Trial Rationale and Objectives

2.1 Trial Rationale

Tolvaptan is approved for oral administration at 15 mg once daily in the treatment of "volume overload in heart failure when adequate response is not obtained with other diuretics (eg, loop diuretics)."

OPC-61815 is a compound based on tolvaptan of which the lower water solubility has been improved by phosphorylation of the hydroxide of the benzazepine ring. In the body, OPC-61815 is considered to be metabolized to tolvaptan via hydrolysis of the phosphate ester by alkaline and acid phosphatase, and the formed tolvaptan acts as an aquaretic agent. OPC-61815 provides an aquaretic intravenous treatment option for "congestive

heart failure patients with excessive fluid retention despite treatment with other diuretics" and should prove useful. We started clinical development of OPC-61815 in heart failure patients with persistent fluid retention despite treatment with conventional diuretics for the intended indication of "volume overload in heart failure when adequate response is not obtained with other diuretics (eg, loop diuretics)." The aquaretic effect of OPC-61815 is thought to be produced by the active metabolite tolvaptan. Because tolvaptan is widely used in heart failure patients who have fluid retention despite treatment with conventional diuretics, treating patients with placebo in a clinical trial of OPC-61815 is considered unethical. A phase 3 trial of OPC-61815 will therefore investigate the noninferiority of OPC-61815 to tolvaptan 15-mg tablet instead of using placebo as control.

Data in healthy adults show intravenous OPC-61815 at doses of 3 to 30 mg (about half the dose levels of tolvaptan tablets) achieves equivalent exposure of tolvaptan and daily urine volume to those achieved with oral tolvaptan tablets at doses of 5 to 60 mg. However, because OPC-61815 has not previously been administered to heart failure patients, the dose-exposure relationships of intravenous OPC-61815 and oral tolvaptan in heart failure patients are not yet clear. This phase 2 pharmacology trial has been planned to determine the dose of OPC-61815 injection equivalent to tolvaptan 15-mg tablet, which is used in clinical setting in heart failure patients with fluid retention despite treatment with conventional diuretics.

Based on the above, we consider the conduct of this trial is scientifically and ethically justified.

2.2 Justification for DNA storage

This trial will store deoxyribonucleic acid (DNA) samples on a voluntary basis. Sampling for DNA storage will take place only at the trial sites that have agreed to perform sampling for DNA storage prior to the trial. DNA samples will be collected only from subjects who have given consent to DNA storage in writing. In the questions and answers section of the "Clinical trials based on pharmacogenomics" (Notification No. 0930007 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau issued on 30 Sep 2008), the Ministry of Health, Labour and Welfare states that collection of DNA samples from trial subjects and retention of the samples for genomic/genetic analysis related to evaluation of IMPs used in a trial (pharmacokinetics, efficacy, safety, etc.) are acceptable provided (1) the target and schedule of analysis are established at the conduct of the trial or (2) genomic/genetic analysis is planned although neither its target nor schedule has been established at the conduct of the trial.

We therefore think storing DNA samples for future analysis of the relationships between interindividual differences in the efficacy, safety, or pharmacokinetics of OPC-61815 and variations of DNA characteristics (eg, genetic polymorphism) is justified.

2.3 Dosing Rationale

(1) Dose

Tolvaptan exposure and daily urine volume reported in the single intravenous dose trial of OPC-61815 (263-08-001[4]) and single oral dose trials of tolvaptan (156-95-302[5] and 156-00-001[6]) in healthy adults are summarized respectively in Table 2.3-1 and Table 2.3-2.

At the dose ranges tested (OPC-61815 injection 3, 7.5, 15, and 30 mg and tolvaptan tablets 5, 15, 30, and 60 mg), OPC-61815 injection at about half the dose of tolvaptan tablets achieved tolvaptan exposure and daily urine volume equivalent to those achieved with tolvaptan tablets.

Table 2.3-1 Pharmacokinetic Parameters (Mean ± Standard Deviation) of Plasma Tolvaptan Concentration in Healthy Adults After Administration of Intravenous OPC-61815 and Oral Tolvaptan

Intravenous OPC-61815[a]				Oral Tolvaptan			
Dose (mg)	C_{max} (ng/mL)	AUC_t (ng·h/mL)	t_{max}[b] (h)	Dose (mg)	C_{max} (ng/mL)	AUC_t (ng·h/mL)	t_{max}[b] (h)
3 (N = 6)	34.58± 5.420	155.0 ± 29.76	1.0	5[c] (N = 6)	48.3 ± 16.0	203.43± 80.47	1.5[e]
7.5 (N = 6)	116.7 ± 30.23	527.5 ± 134.2	0.5	15[d] (N = 6)	135.27 ± 52.58	645.4 ± 367.0	2.0
15 (N = 6)	268.8 ± 52.66	1598 ± 586.6	1.0	30[d] (N = 12)	213.37 ± 75.75	1301.5 ± 552.6	2.0
30 (N = 6)	442.5 ± 64.87	1980 ± 535.8	0.5	60[d] (N = 6)	315.22 ± 104.89	2321.4 ± 633.5	3.0

[a]Trial 263-08-001, [b]Median, [c]Trial 156-95-302, [d]Trial 156-00-001, [e]Median calculated from individual values (only the mean is provided in the clinical study report of Trial 156-95-302)

Table 2.3-2 Daily Urine Volume (Mean ± Standard Deviation) of Healthy Adults After Administration of Intravenous OPC-61815 and Oral Tolvaptan

Intravenous OPC-61815[a]		Oral Tolvaptan	
Dose (mg)	**Daily Urine Volume (mL/24h)**	**Dose (mg)**	**Daily Urine Volume (mL/24h)**
Placebo (N = 16)	2687.8 ± 1519.7	Placebo[c] (N = 14)	2584.5 ± 1298.4
3 (N = 6)	3752.3 ± 465.2	5[b] (N = 6)	2710.8± 363.3[d]
7.5 (N = 5)	4240.0 ± 756.2	15[c] (N =6)	3018.5 ± 729.9
15 (N = 6)	5810.2 ± 1213.4	30[c] (N = 12)	5722.9 ± 643.2
30 (N = 6)	7173.7 ± 1582.4	60[c] (N = 6)	8751.5 ± 1280.6

[a]Trial 263-08-001, [b]Trial 156-95-302, [c]Trial 156-00-001, [d]Daily urine volume was calculated from individual values (only the measurements of individual collection periods are provided in the clinical study report of Trial 156-95-302)

In Japan, the approved dose and regimen of Samsca tablets, of which active ingredient is tolvaptan, is "The usual adult dosage of Tolvaptan is 15 mg once a day orally." The recommended initial dose is 7.5 mg for patients with a serum sodium concentration of less than 125 mEq/L and patients in whom a rapid decrease in plasma volume should be avoided. Because intravenous administration of OPC-61815 at about half the dose of tolvaptan tablets achieved tolvaptan exposure equivalent to tolvaptan tablets in healthy adults, this trial will administer OPC-61815 injection at 4 mg, 8 mg (respectively about half the tolvaptan tablets 7.5 mg and 15 mg), and 16 mg (double dose of 8 mg), as the doses expected to achieve effects equivalent to tolvaptan tablets.

Liver metabolism of tolvaptan is expected to be decreased in heart failure patients due to blood flow in organs and especially in the liver, compared with healthy adults. Also, the first-pass metabolism (in the gastrointestinal tract and liver) of tolvaptan tablets may differ in healthy adults and heart failure patients. Because of these matters, in heart failure patients, OPC-61815 injection at a dose about half that of tolvaptan tablets may not reproduce equivalent tolvaptan exposure to tolvaptan tablets as indicated in healthy adults.

Considering that OPC-61815 injection has not previously been administered to heart failure patients and also that OPC-61815 injection at a lower dose than indicated in

healthy adults may achieve equivalent tolvaptan exposure to that with tolvaptan 15-mg tablet, we decided to administer OPC-61815 injection at 2 mg in addition to at 4 mg, 8 mg, and 16 mg.

(2) Regimen

The once-daily administration of OPC-61815 is selected for this trial because a sufficient plasma tolvaptan exposure and daily urine volume had been achieved with the same regimen in phase 1 trials in healthy adults (263-08-001, 263-09-001, and 263-10-005[7]). In the repeated dose trial administering OPC-61815 injection intravenously for 1 minute (263-09-001), the following AEs not reported in the single dose trial that administered the injection for 5 minutes (263-08-001) were reported: feeling abnormal in 9 of 27 subjects, pruritus in 5 of 27 subjects, pruritus generalised in 3 of 27 subjects, and erythema in 3 of 27 subjects. The trial investigating the rate of intravenous injection of OPC-61815 (263-10-005) administered the drug over 2 hours, 5 minutes, and 1 minute to explore the cause of the above AEs and also to investigate the relationships between the events and the rate of administration. None of these potentially drug-related adverse events occurred when OPC-61815 injection 7.5 mg and 15 mg were administered over 2 hours.

The results of the trial indicate the risk of the above potentially drug-related adverse events may be reduced by administering OPC-61815 with longer administration duration.

The daily urine volume (mean ± standard deviation) in the trial investigating the rate of administration is summarized in Table 2.3-3.

Daily urine volume was generally consistent regardless of the rate of administration. This suggests the diuretic effect 24 hours after administration is not likely to be affected by the rate of administration.

Table 2.3-3	**Daily Urine Volume (Mean ± Standard Deviation) of Healthy Adults Following Intravenous Administration of OPC-61815 at a Dose of 7.5 mg and 15 mg Over 1 Minute, 5 Minutes, and 2 Hours**	
Dose (mg)	**Duration of Administration**	**Daily Urine Volume (mL/24 h)**
Placebo	1 minute (N = 6)	2576.7 ± 1412.2
	5 minutes (N = 6)	2418.4 ± 764.0
	2 hours (N = 6)	2272.3 ± 951.5
7.5	1 minute (N = 5)	3276.8 ± 614.1
	5 minutes (N = 6)	3647.5 ± 828.9
	2 hours (N = 6)	3353.0 ± 861.8
15	1 minute (N = 6)	5584.8 ± 953.0
	5 minutes (N = 6)	4818.3 ± 1358.6
	2 hours (N = 6)	4765.2 ± 1583.9

Figure 2.3-1 illustrates the time course of urine excretion rate by the rate of administration in the trial on the rate of intravenous administration. Table 2.3-4 summarizes the t_{max} of plasma tolvaptan by the rate of administration. The initial peak of urine excretion rate was observed between 0.75 and 1.25 hours with bolus injection (administered for 1 or 5 minutes). With 2-hour administration, it was 2.75 hours. The t_{max} of tolvaptan was 0.5 to 1 hour with bolus injection and 2.3 hours with 2-hour administration. The peak urine excretion rate was observed slightly after the t_{max}, but the above results indicate shortening the t_{max} should achieve an earlier onset of action.

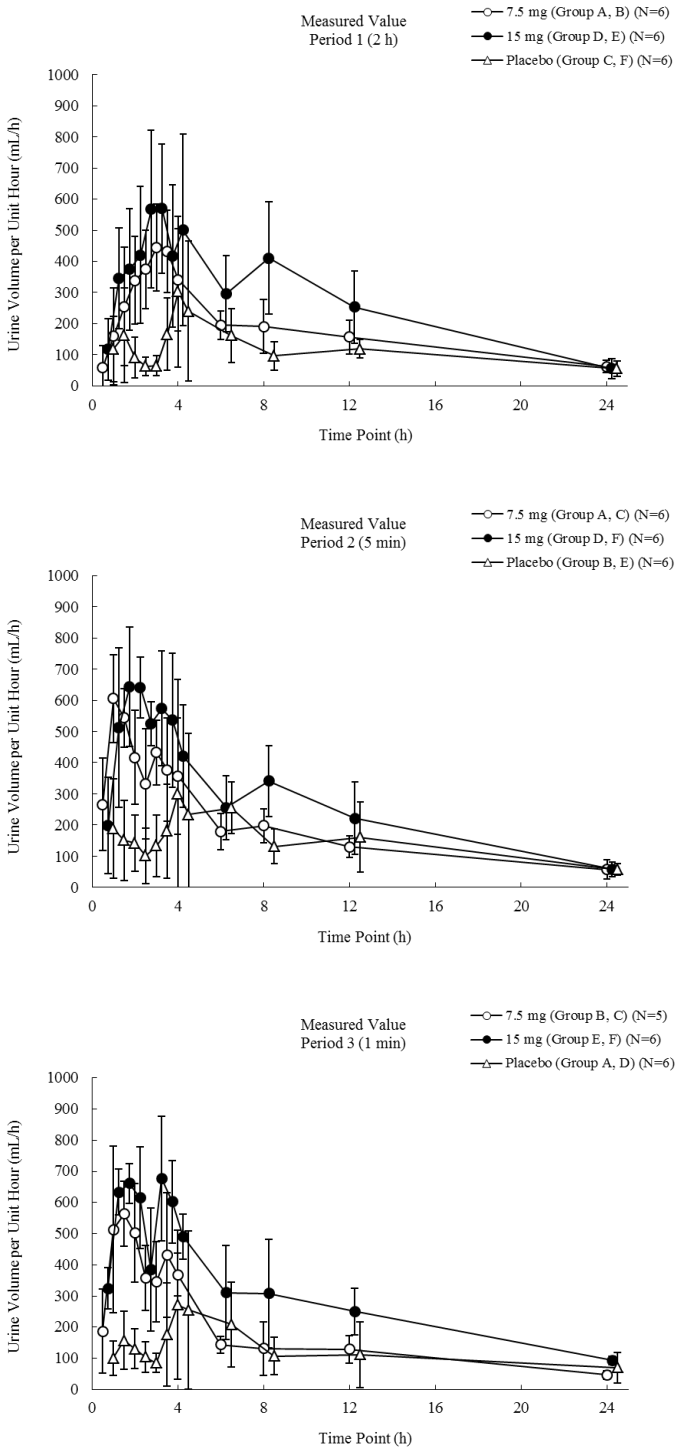

Figure 2.3-1 **Time Course of Urine Excretion Rate After Intravenous Administration of OPC-61815 at a Dose of 7.5 mg and 15 mg Over 1 Minute, 5 Minutes, and 2 Hours**

Table 2.3-4	**t_{max} of Tolvaptan Following Intravenous Administration of OPC-61815 at a Dose of 7.5 mg and 15 mg Over 1 Minute, 5 Minutes, and 2 Hours**		
	t_{max} (h) of Plasma Tolvaptan		
Dose \ **Duration of administration**	**1 minute**	**5 minutes**	**2 hours**
7.5 mg	0.50	1.00	2.30
15 mg	0.75	0.50	2.30

(Median)

PK models of plasma OPC-61815 and tolvaptan concentration were created using data from the prior phase 1 studies (263-08-001, 263-09-001, and 263-10-005) for simulation of change in pharmacokinetic parameters of OPC-61815 and tolvaptan by the rate of administration. The simulated pharmacokinetic parameters of tolvaptan following administration of OPC-61815 injection 8 mg are summarized in Table 2.3-5. The simulation showed no significant differences in the AUC_{24h} or C_{max} of tolvaptan across the duration of administration. This suggests similar effects regardless of the duration of administration. However, the observed differences in t_{max} indicate the duration of administration may affect the time to onset of action. The t_{max} of tolvaptan was 1, 1.5, and 2.25 hours after bolus (1 or 5 minutes), 1-hour, and 2-hour intravenous injection of OPC-61815, respectively. The difference in t_{max} between bolus injections, which was over 1 hour by 2-hour intravenous injection, was estimated to decrease to about 30 minutes by 1-hour intravenous injection. The t_{max} of tolvaptan after administration of tolvaptan 15-mg tablet is 2 hours. Therefore, these results suggest that, if OPC-61815 is administered intravenously over 1 hour, compared with tolvaptan tablets, an earlier t_{max} of tolvaptan and an earlier onset of action should be achieved.

Table 2.3-5	**Simulated Pharmacokinetic Parameters of Tolvaptan Following Intravenous Administration of OPC-61815 at a Dose of 8 mg for 1 Minute, 5 Minutes, 1 Hour, and 2 Hours**		
Duration of administration	**AUC_{24h} (h·ng/mL) (mean ± standard deviation)**	**C_{max} (ng/mL) (mean ± standard deviation)**	**t_{max} (h) (median)**
1 minute	521.5 ± 141.2	115.1 ± 24.12	1
5 minutes	531.5 ± 145.5	115.5 ± 23.86	1
1 hour	521.1 ± 142.6	109.6 ± 22.07	1.5
2 hours	522.5 ± 144.4	99.93 ± 20.11	2.25

Early onset of action (eg, for relief of dyspnea) is desired in some patients hospitalized with heart failure. This trial will intravenously administer OPC-61815 at 2 mg, 4 mg, 8 mg, and 16 mg over 1 hour in CHF patients to investigate the dose and regimen of OPC-61815 equivalent to once-daily tolvaptan 15-mg tablet.

2.4 Trial Objectives

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

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

3 Trial Design

3.1 Type/Design of Trial

This is a multicenter, randomized, double-blind, active-controlled (with tolvaptan tablet), double-dummy, parallel group comparison trial. Fifty CHF patients with volume overload despite having received diuretics other than vasopressin antagonists will be randomly assigned to OPC-61815 injection 2 mg, 4 mg, 8 mg, or 16 mg or tolvaptan tablet 15 mg group (10 per group) (see Table 3.1-1) to investigate the dose of OPC-61815 injection required to achieve exposure equivalent to tolvaptan 15-mg tablet. To account for withdrawals, 11 patients per group (total 55 patients) will start IMP administration.

Table 3.1-1 Treatment Groups and Sample Size

Group	OPC-61815 Dose	Tolvaptan Dose	Sample Size[a]
Tolvaptan 15-mg tablet	0 mg/day	15 mg/day	10
OPC-61815 injection 2 mg	2 mg/day	0 mg/day	10
OPC-61815 injection 4 mg	4 mg/day	0 mg/day	10
OPC-61815 injection 8 mg	8 mg/day	0 mg/day	10
OPC-61815 injection 16 mg	16 mg/day	0 mg/day	10

[a]At least 10 patients per group will complete blood sampling for plasma drug concentration measurement by 24 hours after administration on Day 1.

The trial schedule is summarized in Figure 3.1-1. The 3-day period prior to IMP administration constitutes the run-in period. The use of diuretics, body weight change, and congestive symptoms are evaluated during the run-in period. Only the patients who meet the criteria for enrollment in the treatment period (see Table 3.4.3-1) will be enrolled to undergo treatment. The patients will receive the IMP once a day for 5 days during the treatment period. No change of a diuretic dose or regimen will be allowed throughout the run-in period and until the end-of-trial examination on the day after final administration in the treatment period. End-of-trial examination will be performed on Day 6 (day after final administration) and post-treatment follow-up examination will be performed between Days 12 and 15.

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

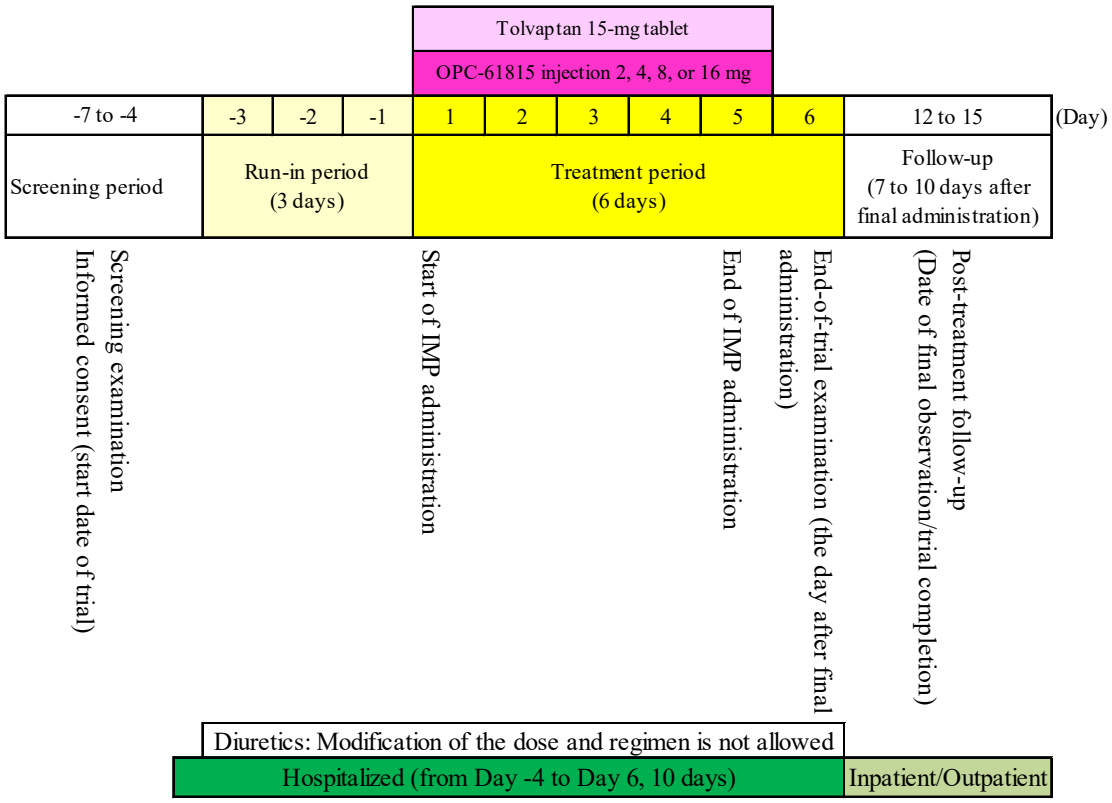

Figure 3.1-1 Trial Design Schematic

Note) Each patient who fails to complete 5-day IMP administration for any reason should be asked to undergo same tests/examination to those scheduled for the end-of-trial examination (the day after the final IMP administration), if possible, and be followed up between 7 and 10 days after the final IMP administration.

3.2 Trial Treatments

3.2.1 Dose and Regimen and Duration of Treatment

The dose levels and formulations for each group are summarized in Table 3.2-1. The investigator or subinvestigator will administer either one tolvaptan 15-mg tablet or placebo tablet once a day with water, immediately followed by intravenous administration of either OPC-61815 injection at 2 mg, 4 mg, 8 mg, or 16 mg or placebo for 1 hour (acceptable range: 55 to 65 minutes) according to a separate written procedure for IMP administration. Each dose should be administered promptly after the patient completes urine sampling (for daily urine volume measurement) after breakfast each day during the 5-day treatment period. The time of administration (start time of administration) on Day 2 and later should be not more than 20 minutes before or after the time of administration (start time of administration) on Day 1. After confirming each

dose has been administered, the investigator or subinvestigator documents the start and finish time of administration (for injection) or the date and time of administration (for tablet) in source documents and case report form (CRF). The IMP is to be administered even if the patient fails to eat breakfast that day.

Table 3.2-1 Dose Levels and Formulations per Group

Group	OPC-61815 Dose	Formulation(s) (per day)
Tolvaptan 15-mg tablet	0 mg/day	1 vial of placebo injection, 1 tolvaptan 15-mg tablet
OPC-61815 injection 2 mg	2 mg/day	1 vial of OPC-61815 injection 2 mg, 1 placebo tablet
OPC-61815 injection 4 mg	4 mg/day	1 vial of OPC-61815 injection 4 mg, 1 placebo tablet
OPC-61815 injection 8 mg	8 mg/day	1 vial of OPC-61815 injection 8 mg, 1 placebo tablet
OPC-61815 injection 16 mg	16 mg/day	1 vial of OPC-61815 injection 16 mg, 1 placebo tablet

[Rationale for duration of treatment]

The primary endpoint of this trial is tolvaptan exposure (C_{max} and AUC_{24h} on Day 1 of the treatment period). Tolvaptan does not accumulate and repeated administration of the drug is thought to demonstrate a blood concentration-time profile similar to that after single administration. Because of this, tolvaptan exposure can be evaluated based on a single day of treatment. Body weight is included in the efficacy secondary endpoints. The late phase 2 trial (156-03-001) and phase 3 trial (156-06-002) of tolvaptan in CHF patients administered the drug for 7 days. The difference in body weight change between the tolvaptan 15-mg tablet group and placebo group was almost consistent from the fourth day of treatment in the phase 2 trial (156-03-001) and largest after 6 days of treatment in the phase 3 trial (156-06-002). Throughout treatment, the body weight of patients in the tolvaptan 15-mg group was statistically significantly decreased compared with that in the placebo group. Effects of the IMP on body weight can therefore be evaluated based on treatment over a 5-day period. Based on the above, a 5-day treatment period should be appropriate for this trial.

3.2.2 IMP Preparation

The person responsible for IMP preparation (non-blinded staff) designated at the trial site will prepare the IMP before use according to a specified procedure. The person responsible for IMP preparation (non-blinded staff) is obliged to keep confidential all information acquired through IMP preparation.

3.3 Trial Population

3.3.1 Number of Subjects and Description of Population

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

3.3.2 Subject Selection and Numbering

A subject identifier (subject ID) (site number [3 digits] + 'S' + subject number [5 -digit in-site serial number]) will be assigned to each consented subject. The site number (3 digits) will be designated by the sponsor. The subject number (5-digit in-site serial number) will start from "00001" and be assigned to each subject in the order of consent per trial site. The trial site will create and keep a list of all consented subjects and their subject identifiers.

3.4 Eligibility Criteria

3.4.1 Informed Consent

Written informed consent will be freely obtained from all subjects. Consent will be documented on a written informed consent form (ICF). Any patient who has given consent to participate in the trial may still refuse to provide samples for DNA storage without having to withdraw from the trial. The ICF will be approved by the same institutional review board (IRB) that approves this protocol.

Each ICF will comply with the ICH (International Council for Harmonisation) Good Clinical Practice (GCP) Guideline[8] and local regulatory requirements.

Investigator or subinvestigator 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 before initiation of any procedures that are performed solely for the purpose of determining eligibility for this trial, 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). If a study collaborator has provided a supplemental explanation, the IRB approved written ICF will be signed and dated by the study collaborator. 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 to significantly add or change procedures.

3.4.2 Inclusion Criteria

Subjects are required to meet the inclusion criteria presented in Table 3.4.2-1.

Table 3.4.2-1 Inclusion Criteria

1	Subjects who are currently on treatment with any of the following oral diuretics (or are scheduled to start treatment with the drugs 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 permissible types and doses of diuretics are as follows: a) Loop diuretics equivalent to furosemide tablet or fine granules at a dose of 40 mg/day or higher Bumetanide tablet, 1 mg; azosemide, 60 mg; torasemide, 8 mg b) Thiazide diuretics (including thiazide analogs) Hydrochlorothiazide tablet, trichlormethiazide tablet, benzylhydrochlorothiazide tablet, mefruside tablet c) Aldosterone antagonist or potassium-sparing diuretic agent Spironolactone tablet/fine granules, triamterene capsule
2	Subjects with CHF in whom lower limb edema, pulmonary congestion, and/or jugular venous distension due to volume overload is present. When pulmonary congestion is confirmed by chest X-ray performed within 14 days before consent, the subject may be included in the trail
3	Male or female subjects age 20 to 85 years, inclusive, at the time of informed consent
4	Subjects who are currently hospitalized or who are able to be hospitalized from the day before the run-in period (Day −4) to the end of the treatment period
5	Subjects who are capable of taking oral tablets
6	Subjects capable of giving consent

	[Rationale for inclusion criteria]
1	This criterion is set to include patients who are using loop diuretics equivalent to furosemide at dose of 40 mg/day or higher, a combination of a loop diuretic(s) and thiazide diuretic(s), or a combination of a loop diuretic(s) and aldosterone antagonist(s) because these are commonly used for the treatment of cardiac edema.
2	Common signs of volume overload include jugular venous distension, hepatomegaly, and third cardiac sound, etc. in addition to lower limb edema and pulmonary congestion. Lower limb edema, pulmonary congestion, and jugular venous distension are included in the criterion because these are less likely to be caused by factors other than volume overload compared with other signs and also because they were observed in many patients in the late phase 2 trial (156-03-001) and phase 3 trial (156-06-002) of tolvaptan in CHF patients.
3	The lower limit is the age limit of adults who have capability to be responsible for consent. The upper limit of 85 is set because most CHF patients are elderly and also for safety reasons.
4	This criterion is set to include subjects who are able to be hospitalized to ensure accurate evaluation and for their own safety.
5	This criterion is set because tolvaptan tablets are used as control.
6	This criterion is set to ensure ethical conduct of the trial.

3.4.3 Criteria for Enrollment in the Treatment Period (Inclusion Criteria of Run-in Period)

Subjects who meet the criteria for enrollment in the treatment period (shown in Table 3.4.3-1) and are judged by the investigator or subinvestigator to be suitable for enrollment in the treatment period will be enrolled for appropriate efficacy evaluation.

Table 3.4.3-1 Criteria for Enrollment in the Treatment Period (Inclusion Criteria of Run-in Period)

7	Subjects with either lower limb edema, jugular venous distension (on Day −1 of the run-in period), or pulmonary congestion (confirmed by chest X-ray performed during the run-in period)
8	Subjects who are given diuretic agents with no change in dose or regimen during the run-in period
9	Subjects with no more than 1.0 kg change in body weight over the 2 days (Day −2 to Day −1 of the run-in period) prior to IMP administration

	[Rationale for inclusion criteria of run-in period]
7	This criterion is set as these signs of excessive volume overload are expected to be relieved by the aquaretic effect of OPC-61815.
8	This criterion is set to enroll subjects who have persistent volume overload despite having been treated with a common diuretic regimen other than vasopressin antagonists.
9	This criterion is set to ensure that subjects who have a constant volume overload are enrolled for efficacy evaluation of OPC-61815.

3.4.4 Exclusion Criteria

Subjects will be excluded if they meet any of the exclusion criteria in Table 3.4.4-1.

A subject excluded as a result of falling under any of the exclusion criteria may be rescreened if any changes in the condition resulting in falling under the exclusion criteria are observed. For rescreening, the subject will be asked to follow the procedure described in Section 3.9.

Table 3.4.4-1 Exclusion Criteria	
1	Subjects with acute heart failure
2	Subjects with mainly noncardiogenic congestive symptoms
3	Subjects who are on an ventricular assist device
4	Subjects who have the following diseases, complication, or conditions: • Subjects who are suspected of having hypovolemia • Hypertrophic cardiomyopathy (excluding dilated phase) • Valvular disease with significant valvular stenosis; or • Hepatic encephalopathy with difficulty in adequate fluid intake
5	Subjects who have experienced acute myocardial infarction within 30 days prior to the screening examination
6	Subjects with definite diagnosis of active myocarditis or amyloid cardiomyopathy
7	Subjects who have the following diseases, complication, or conditions: • Poorly controlled diabetes mellitus • Anuria • Dysuria associated with urinary tract obstruction, calculus, or tumor
8	Subjects who have the following history of disease: • History of sustained ventricular tachycardia or ventricular fibrillation within 30 days prior to the screening examination among subjects without an implantable cardioverter defibrillator • History of cerebrovascular disease (excluding asymptomatic cerebral infarction) within 6 months prior to the screening examination • Subjects with a history of hypersensitivity to any of ingredients of OPC-61815 or tolvaptan • History of hypersensitivity or idiosyncratic reaction to benzazepines or benzazepine derivatives such as mozavaptan hydrochloride and benazepril hydrochloride
9	Subjects who are severely obese (body mass index [BMI], body weight [kg]/height [m]^2 exceeding 35 kg/m^2)
10	Subjects with supine systolic blood pressure of <90 mmHg
11	Subjects with any of the following laboratory test abnormalities: Total bilirubin, >3.0 mg/dL; serum creatinine, >3.0 mg/dL; serum sodium >147 mEq/L; serum potassium, >5.5 mEq/L
12	Subjects with concurrent symptoms or history of hepatic impairment (including subjects with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) at the screening examination exceeding 3 times the upper limit of normal)
13	Subjects who are unable to sense thirst or who have difficulty with fluid intake
14	Females who are breast-feeding and/or who have a positive pregnancy test result prior to receiving investigational medicinal 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 last administration of IMP
16	Subjects treated with another IMP within 30 days prior to the screening examination
17	Subjects 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 restrictions as described in Section 4.

[Rationale for exclusion criteria]	
1	This criterion is set because subjects must be able to swallow the tolvaptan tablet (control) and because acute onset or worsening of symptoms can make trial continuation difficult.
2	This criterion is set because OPC-61815 is intended for patients with volume overload due to CHF.
3	This criterion is set to avoid potential influence on efficacy and safety evaluation in the trial.
4	This criterion is set because excessive diuretic therapy is undesirable.
5, 6	These criteria are set for safety reasons.
7	This criterion is set for safety reasons and because such subjects are considered ineligible for participation in the trial.
8	This criterion is set for safety reasons.
9	This criterion is set because efficacy evaluation will be difficult in such subjects.
10	This criterion is set because diuresis may decrease blood pressure.
11 to 13	These criteria are set for safety reasons.
14 to 17	These criteria are set for general safety and ethical considerations.

3.5 Endpoints

3.5.1 Primary Endpoint

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

3.5.2 Secondary Endpoints

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

3.5.3 Safety Endpoints

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

3.5.4 Rationale for Endpoints

Table 3.5.4-1 summarizes the rationale for the endpoints

Table 3.5.4-1 Rationale for Endpoints

Endpoints	Rationale
Primary Endpoint	This is necessary to determine the dose of OPC-61815 that achieves tolvaptan exposure equivalent to tolvaptan 15-mg tablet in patients with heart failure. Tolvaptan does not accumulate and repeated administration of the drug is thought to demonstrate a blood concentration-time profile similar to that after single administration. Tolvaptan exposure is measured after administration on Day 1 to avoid dropouts.
Secondary Endpoints	
Efficacy Endpoints Body weight	This is a generic index of systemic fluid retention and used for evaluation of diuretic effects. It is considered appropriate for efficacy evaluation of OPC-61815 in CHF patients compared with tolvaptan tablets (control).
Congestive symptoms	These symptoms indicate the presence of fluid retention due to CHF. They are used for efficacy evaluation of OPC-61815 compared with tolvaptan tablets (control).
NYHA Classification	This index evaluates the severity of heart failure based on subjective symptoms. It is considered necessary for evaluating the efficacy of OPC-61815 compared with tolvaptan tablets (control).
Pharmacokinetic Endpoints	To evaluate the pharmacokinetics of the unchanged drug, tolvaptan (active metabolite), and other main metabolites following the administration of OPC-61815 in patients with heart failure.
Pharmacodynamic Endpoints	Daily urine volume is a measure of the pharmacodynamic effect (aquaretic effect) of tolvaptan and is used for pharmacodynamic evaluation of OPC-61815 compared with tolvaptan 15-mg tablet (control). Daily fluid intake, daily fluid balance (fluid intake - urine volume), urine osmolality, and serum osmolality are selected for evaluation of the diuretic effect of OPC-61815. Urine electrolyte (sodium and potassium) excretion and serum electrolyte concentrations (sodium and potassium) are selected to investigate the effects of tolvaptan on electrolytes (sodium and potassium). Plasma AVP concentration is used to investigate the antagonistic action of OPC-61815 against AVP. Other pharmacodynamic endpoints are for monitoring of subjects and evaluating the safety of OPC-61815 compared with tolvaptan tablets (control).
Safety Endpoints	Common safety endpoints are selected for safety evaluation of OPC-61815 compared with tolvaptan tablets (control).

3.6 Measures to Minimize/Avoid Bias

3.6.1 Randomization

Subjects who meet the criteria for enrollment in the treatment period are randomized by the Interactive Web Response System (IWRS) to OPC-61815 injection 2 mg group, OPC-61815 injection 4 mg group, OPC-61815 injection 8 mg group, OPC-61815 injection 16 mg group, and tolvaptan 15-mg tablet group at a ratio of 1:1:1:1:1. Allocation of subjects to treatments will be documented in a separate allocation record. The date of randomization and the assigned number will be documented in the CRF.

3.6.2 Blinding

The vials of lyophilized OPC-61815 injection and placebo injection appear alike, but the prepared solutions will look different. (Foaming may remain immediately after preparation but will disappear shortly thereafter.) To maintain blinding of all trial site staff participating in assessment during the trial, the trial site will appoint one person (non-blinded staff) as a person responsible for IMP preparation to prepare all the IMP. The person responsible for IMP preparation (non-blinded staff) must be qualified for dispensing prepared drugs and appointed at trial site. The person responsible for IMP preparation (non-blinded staff) will also prepare tolvaptan and placebo tablets. The procedure for preparing the IMP and the procedure for maintaining blinding at the trial site by appointing the person responsible for IMP preparation (non-blinded staff) will be specified separately in writing. The person responsible for IMP preparation (non-blinded staff) will be obliged to keep confidential all information acquired through IMP preparation. Any queries related to the IMP are to be addressed to the contact person specified in the procedure rather than the trial monitor.

To maintain access to the IMP throughout the trial, the trial site may appoint a deputy person responsible for IMP preparation (non-blinded staff).

3.7 Trial Procedures

Table 3.7-1 summarizes the scheduled observations/tests and assessments.

Table 3.7-1 Schedule of Observations/Tests and Assessments

Item \ Time Point	Screening		Run-in Period			Treatment Period						Follow-up
	Day−7 to −4	Day−4	Day−3	Day−2	Day−1	Day1	Day2	Day3	Day4	Day5/ End of treatment	End-of-trial/At discontinuation (day after final administration)	Day12 to 15/ 7 to 10 days after final administration
Informed consent	■											
Consent for DNA storage (optional)			○									
Subject demographics	■											
Inclusion/Exclusion criteria	■				●							
Confirmation of use of concomitant medications/ therapies	←											→
Subject registration, randomization[a]	■					●■	●				●	
Hospitalization		←									→	
IMP administration						■	■	■	■	■		
Treatment compliance						←				→		
Use of diuretics (dose fixed)			■	■	■	■	■	■	■	■	■	
Plasma drug concentration (See Table 3.7-2)						●■	●	●	●	●	●	
Pharmacodynamics												
Serum sodium and potassium concentrations[b]	■					●■	●	●	●	●	●	■
Serum osmolality, biomarkers[c]						●					●	
Daily urine volume, daily fluid intake, urine sodium/potassium concentrations, urine osmolality			←	><	><	><	><	><	><	><	→	
Efficacy												
Body weight	■		●	●	●	●	●	●	●	●	●	■
Congestive symptoms[g]	■		■	■	■	■	■	■	■	■	■	■
Chest X-ray[h]	■			■[j]							■	
NYHA Classification				■[j]							■	
Safety												
AEs	←											→
Clinical laboratory test	■					●					●	■
Physical examination	■		■	■	■	■	■	■	■	■	■	■
Vital signs[d]	■		●	●	●	●	●	●	●	●	●	■
12-Lead ECG[e]				■[j]		■		■			■	
Pregnancy test[f]	■											■
Pharmacogenomics												
DNA Storage[i]						○						

●, Mandatory (before breakfast and IMP administration [before breakfast on the day on which IMP administration is not scheduled]); ■, Mandatory (at the specified time point)

○, Optional (only applicable to the trial sites that have agreed to collect samples for DNA storage in advance. Samples for DNA storage will only be collected from subjects who have given written consent to DNA storage.)

[a]Subject enrollment/randomization:

Subjects are registered and randomized at screening and on Day 1, respectively, in the IWRS. Only the subjects who meet all the inclusion criteria (including the criteria specified in "Table 3.4.3-1 Criteria for Enrollment in the Treatment Period (Inclusion Criteria of Run-in Period)") and do not fall under any of the exclusion criteria are assigned to IMP administration. Randomization normally takes place on Day 1 (or Day -1 if justified. Each subject's fulfillment of inclusion criterion 8 will be verified on Day 1). Completion of the initial administration (Day 1), completion of blood sampling

for plasma drug concentration measurement up to 24 hours after start of IMP administration on Day 1 (Day 2), and trial completion/discontinuation (end-of-trial/withdrawal) will be recorded in the IWRS.

[b]Timing of blood sampling on Day 1 for measurement of serum sodium/potassium concentration:
Before IMP administration (before breakfast), between 4 and 6 hours after start of IMP administration, and between 8 and 12 hours after start of IMP administration. Measurement of serum sodium concentration during the treatment period takes place at the trial site in addition to at the central laboratory.

[c]Biomarkers:
Plasma AVP concentration, plasma BNP concentration, plasma renin activity, serum NT-proBNP concentration, serum troponin concentration will be measured.

[d]Vital signs: Blood pressure, pulse rate, and body temperature will be measured.

[e]12-lead ECG: Between 1 and 2 hours after start of IMP administration on Day 1 and Day 3.
Subsequently when possible.

[f]Pregnancy test: Applicable to only female subjects of childbearing potential.

[g]Congestive symptoms: Lower limb edema, other edema, jugular venous distension, pulmonary rales, third cardiac sound, hepatomegaly will be assessed.

[h]Chest X-ray: Cardiothoracic ratio and pulmonary congestion will be assessed.
If the subject underwent chest X-ray at examination before participation in the trial, cardiothoracic ratio and pulmonary congestion may be assessed using the radiograph (must be taken within 14 days before consent) instead of obtaining a new one at the screening examination.

[i]DNA storage: Blood will be collected before IMP administration on Day 1.
If blood cannot be collected at the above time point, collection may take place at any subsequent time point during the trial.

[j]12-lead ECG, chest X-ray, and assessment for NYHA classification will each be conducted once during the run-in period.

Table 3.7-2 Blood Sampling Schedule for Plasma Drug Concentration Measurement

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

3.7.1 Schedule of Assessments

3.7.1.1 Screening

After obtaining informed consent, the investigator or subinvestigator will assign a subject identifier to each subject according to Section 3.3.2 Subject Selection and Numbering. The date of consent and subject identifier will be recorded in source documents and CRF. The subject will then be registered in the IWRS. The IWRS will be used to monitor subject registration, etc. The use of the system will be described in a separate procedure.

After acquisition of informed consent, subjects will undergo the following screening (examinations/tests) between 7 days and 4 days before administration (Day −7 to Day −4) for eligibility assessment. The result of eligibility assessment will be recorded in source documents and CRF.

[Tests/Examinations]

Subject demographics [birth date, sex, height, nationality, race, ethnicity, underlying disease, heart failure subtype, presence/absence and type of arrhythmia, presence/absence of pacemaker, presence/absence of ICD, complications, and medical history], serum sodium concentration, serum potassium concentration, clinical laboratory tests, physical examination, vital signs (blood pressure, pulse rate, and body temperature), body weight, congestive symptoms, chest X-ray[Note] (cardiothoracic ratio and pulmonary congestion), confirmation of use of concomitant medications and therapies, urine pregnancy test (only in female subjects of childbearing potential)

Note) If the subject underwent chest X-ray at examination before participation in the trial, cardiothoracic ratio and pulmonary congestion may be assessed using the radiograph (must be taken within 14 days before consent) instead of obtaining a new one at the screening examination.

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

The investigator or subinvestigator will perform the tests and examinations specified below to decide whether the subject is eligible for enrollment in the treatment period. The dose and regimen of the diuretics the subject is using at the start of the run-in period (on Day −3) will not be modified until the end-of-trial examination (or withdrawal examination), irrespective of prior use of diuretics and its administration methods before the run-in period.

The subject will be hospitalized from the day before the run-in period to the end-of-trial (or discontinuation) examination.

(1) Each Day during Run-in Period (3 Days)

(a) Before breakfast

- Vital signs
- Body weight

(b) After breakfast

The subject will be asked to void his/her bladder immediately before breakfast to start pooling of urine and measurement of fluid intake for the following measurements:

- 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 using urine sodium concentration, urine potassium concentration, and daily urine volume)
- Urine osmolality

(c) Administration of diuretics

(d) At an appropriate time point of the scheduled day

- Physical examination
- Congestive symptoms
- Confirmation of use of concomitant drugs and therapies
- AEs

(2) On 1 Day during the Run-in Period (3 Days)

Each will be performed/assessed once, when appropriate.

- 12-lead ECG
- Chest X-ray
- NYHA Classification

3.7.1.3 Randomization and Initiation of Treatment Period

(1) Assessment of Eligible for Enrollment in the Treatment Period

Whether or not the subject fulfills the criteria presented in Table 3.4.3-1 Criteria for Enrollment in the Treatment Period (Inclusion Criteria of Run-in Period) is decided based

on the use of diuretics, body weight, and congestive symptoms during the run-in period. The decision is entered into the IWRS.

(2) Assignment of Subjects to Treatments

The subject who fulfills the criteria for enrollment in the treatment period will be randomized to one of the 5 groups listed below for IMP administration in a double-blind manner. The investigator or subinvestigator will verify the drug number assigned on the IWRS.

- OPC-61815 injection 2 mg group
- OPC-61815 injection 4 mg group
- OPC-61815 injection 8 mg group
- OPC-61815 injection 16 mg group
- Tolvaptan 15-mg tablet group

3.7.1.4 Treatment Period (Day 1)

(1) Before IMP Administration (Before Breakfast)

- Plasma drug concentration (within 2 hours before IMP administration)
- Serum sodium concentration, serum potassium concentration, serum osmolality, and biomarkers
- Clinical laboratory tests and vital signs
- Body weight
- Blood sampling for DNA storage (The subject may or may not agree to DNA storage. The subject's consent to DNA storage will be obtained before blood sampling.)

(2) After Tests/Blood Sampling and After Breakfast

The subject will be asked to void his/her bladder immediately after breakfast to start pooling of urine and measurement of fluid intake for the following measurements:

- 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 administer the IMP to the subject after verifying that the subject meets the inclusion criteria and does not fall under any of the exclusion criteria. The investigator or subinvestigator subsequently will record IMP administration in the IWRS.

(4) Administration of Diuretics

(5) Tests and Assessments

The investigator or subinvestigator will perform the tests described below.

Table 3.7.1.4-1 Tests on Day 1, Their Scheduled Time Points, and Blood Sampling Time Points After IMP Administration

Item	Time Point	Time Window
Plasma drug concentration	1 hour after start of IMP administration	Within 5 minutes after end of IMP administration
	1.5 hours after start of IMP administration	Specified time point ± 5 minutes
	2 hours after start of IMP administration	Specified time point ± 5 minutes
	4 hours after start of IMP administration	Specified time point ± 20 minutes
	6 hours after start of IMP administration	Specified time point ± 30 minutes
	12 hours after start of IMP administration	Specified time point ± 1 hour
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	
Physical examination	When appropriate on Day 1	
Congestive symptoms	When appropriate on Day 1	
Confirmation of use of concomitant drugs and therapies	When appropriate on Day 1	
Treatment compliance	When appropriate on Day 1	
AEs	When appropriate on Day 1	

3.7.1.5 Treatment Period (Day 2)

(1) Before IMP Administration (Before Breakfast)

- Plasma drug concentration (24 hours after start of IMP administration on Day 1)
- Serum sodium concentration and serum potassium concentration
- Vital signs
- Body weight

(2) After Tests/Blood Sampling and After Breakfast

The subject will be asked to void his/her bladder immediately after breakfast to start pooling of urine and measurement of fluid intake for the following measurements:

- 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) Administration of Diuretics

(5) When Appropriate on Day 2

- Physical examination
- Congestive symptoms
- Confirmation of use of concomitant drugs and therapies
- Treatment compliance
- AEs

3.7.1.6 Treatment Period (Day 3)

(1) Before IMP Administration (Before Breakfast)

- Plasma drug concentration (24 hours after start of IMP administration on Day 2)
- Serum sodium concentration and serum potassium concentration
- Vital signs
- Body weight

(2) After Tests/Blood Sampling and After Breakfast

The subject will be asked to void his/her bladder immediately after breakfast to start pooling of urine and measurement of fluid intake for the following measurements:

- 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) Administration of Diuretics

(5) One to 2 Hours after IMP Administration

- 12-lead ECG

(6) When Appropriate on Day 3

- Physical examination
- Congestive symptoms
- Concomitant drugs and therapies
- Treatment compliance

- AEs

3.7.1.7 Treatment Period (Day 4 and Day 5)

(1) Before IMP Administration (Before Breakfast)

- Plasma drug concentration (24 hours after start of IMP administration on Day 3 and Day 4)
- Serum sodium concentration and serum potassium concentration
- Vital signs
- Body weight

(2) After Tests/Blood Sampling and After Breakfast

The subject will be asked to void his/her bladder immediately after breakfast to start pooling of urine and measurement of fluid intake for the following measurements:

- 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) Administration of Diuretics

(5) Each Day, When Appropriate

- Physical examination
- Congestive symptoms
- Concomitant drugs and therapies
- Treatment compliance
- AEs

3.7.1.8 Treatment Period (End-of-trial or at Discontinuation)

When the subject completes trial treatment on Day 5, he/she will undergo the tests and assessments specified below as the end-of-trial examination on Day 6. If the subject discontinues trial treatment prematurely before the duration of administration reaches 5 days (see Section 3.8.3.1 Treatment Discontinuation), he/she will be requested to undergo the same tests and assessments the day after the final IMP administration, if possible. Completion of the end-of-trial or withdrawal examination will be recorded in the IWRS.

(1) Before Breakfast

- Plasma drug concentration (24 hours after start of IMP administration on Day 5)

- Serum sodium concentration, serum potassium concentration, serum osmolality, and biomarkers
- Clinical laboratory tests and vital signs
- Body weight

(2) Administration of Diuretics

(3) When Appropriate on the Day after Final Administration

- Physical examination
- 12-lead ECG
- Congestive symptoms
- Chest X-ray
- NYHA Classification
- Confirmation of use of concomitant drugs and therapies
- AEs

3.7.1.9 Post-treatment Follow-up Period (7 to 10 days after final administration)

The investigator or subinvestigator will perform the following tests or examinations between 7 and 10 days after final IMP administration. The tests/examinations may be performed on an outpatient basis if the subject has been discharged.

- Serum sodium concentration and serum potassium concentration
- Clinical laboratory tests, physical examination, and vital signs
- Body weight and congestive symptoms
- Urine pregnancy test (only in female subjects of childbearing potential)
- Confirmation of use of concomitant drugs and therapies
- AEs

3.7.1.10 Follow-up

If an AE has not resolved by the end-of-trial examination or the time of discontinuation, the event will be followed as described in Section 5.7 Follow-up of Adverse Events After Treatment Period.

3.7.2 Prior and Concomitant Medication

The investigator or subinvestigator will document in the CRF all the drugs and therapies given to the subject between the day of signing informed consent and end-of-trial/withdrawal examination. The investigator or subinvestigator will also document in

the CRF the drugs and therapies given for the treatment of AEs by the last scheduled contact or the drugs/therapies that caused AEs.

3.7.3 Efficacy Assessments

3.7.3.1 Body Weight

The investigator or subinvestigator will have the subject void his/her bladder at least once after awakening and subsequently weigh the subject on an appropriately calibrated scale before breakfast after taking precautions to minimize the effect of defecation and clothing. The date and time of measurement and the weight (read to 1 decimal place in kilograms) will be recorded in the source documents and CRF. If the scale used measures to 2 or more decimal places, the reading is rounded to 1 decimal place and recorded.

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

The investigator or subinvestigator will examine the subject for congestive symptoms (lower limb edema, other edema, jugular venous distension, hepatomegaly, pulmonary rales, and third cardiac sound) and decides whether the subject has the symptoms and assesses the severity of each symptom in the manner described below. The investigator or subinvestigator will document the date of assessment together with the results of assessment in the source documents and CRF.

(1) Lower Limb Edema

The severity of edema in the subject's tibial border or dorsum of the foot will be assessed in the sitting position using the scale below.

Table 3.7.3.2-1 Scale for Lower Limb Edema

	Severity	Description
0	Absent	No indentation
1	Mild	Slight indentation
2	Moderate	Deep indentation
3	Severe	Visible edema

(2) Other Edema

The same scale to be used in assessment of lower limb edema will be used. The same area will be used for assessment both before and after IMP administration. The area of assessment will be recorded in the source documents and CRF.

(3) Jugular Venous Distension

Whether or not the subject has jugular venous distension will be documented, together with the vertical height (in centimeters, to 1 decimal place) from the sternal angle to the highest point of pulsation of the internal jugular vein if distension is observed.

(4) Pulmonary Rales

Whether pulmonary rales are heard on auscultation will be documented.

(5) Third Cardiac Sound

Whether third cardiac sound is heard on auscultation will be documented.

(6) Hepatomegaly

Whether or not the liver is palpable will be documented, together with the palpated width (distance from the costal arch on the right nipple line, to 1 decimal place in centimeters) if palpable.

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

The investigator or subinvestigator will perform chest X-ray and document the date in the source documents and CRF. The cardiothoracic ratio and pulmonary congestion will be assessed as described below.

(1) Cardiothoracic Ratio

The investigator or subinvestigator will calculate the cardiothoracic ratio to 2 decimal places or lower if possible, rounds the value to 1 decimal place, and document the value to 1 decimal place in source documents and CRF.

(2) Pulmonary Congestion

The investigator or subinvestigator will assess the severity of pulmonary congestion using the scale below and document the assessment in the source documents and CRF.

Table 3.7.3.3-1 Scale of Pulmonary Congestion

	Severity	Description
0	Absent	No congestion
1	Mild	Pulmonary vein congestion
2	Moderate	Interstitial lung edema
3	Severe	Pulmonary alveolar edema

Source: Forrester JS, et.al.,[9] with modification

3.7.3.4 NYHA Classification

The investigator or subinvestigator will classify the extent of heart failure in the subject using the NYHA classification system.[10] The investigator or subinvestigator will document the date of assessment together with the results of assessment in the source documents and CRF.

Table 3.7.3.4-1 NYHA Classification

Functional capacity	
Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, dyspnea, and/or angina.
Class II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, and/or angina.
Class III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitations, dyspnea, and/or angina.
Class IV	Unable to carry out any physical activity without discomfort. Symptoms of fatigue, palpitations, or dyspnea are present at rest. If any physical activity is undertaken, discomfort increases.

3.7.4 Safety Assessments

3.7.4.1 Adverse Events

Refer to Section 5, Reporting of Adverse Events.

3.7.4.2 Clinical Laboratory Assessments

The patient will undergo venous blood withdrawal and urine collection for the clinical laboratory tests specified in Table 3.7.4.2-1 at specified time points. The date and time of blood sampling and the date of urine collection will be recorded in source documents. The samples will be sent to the contract laboratory for central testing.

To ensure subject safety and to facilitate close monitoring of serum sodium concentration by the investigator or subinvestigator, serum sodium concentration will be determined at the trial site during the treatment period separately from the measurement at the contract laboratory. Whether blood for measurement of serum sodium concentration is collected and, if collected, the date and time of blood sampling and the result of measurement will be recorded in the source documents and CRF.

The contract laboratory will perform the measurements for the parameters listed in the table below according to their established procedure and report the results to the sponsor and the investigator or subinvestigator. Whether blood and urine have been collected as well as the date and time of blood sampling and the date of urine collection (if collected) will be recorded in the CRF. The electronic file documenting the test results will be

delivered from the contract laboratory to the sponsor and kept as source data. Transcription of the results into the CRF is unnecessary.

Table 3.7.4.2-1 Clinical Laboratory Assessments

Hematology: Red Blood Cell count Hemoglobin Hematocrit White Blood Cell count with differential (neutrophil, eosinophil, basophil, monocyte, lymphocyte) Platelet count	Serum Chemistry: Protein, total Albumin Bilirubin, total AST (GOT) ALT (GPT) Alkaline phosphatase (ALP) γ-Glutamyl transferase (γ-GTP) Lactic dehydrogenase (LDH) Creatine kinase (CK [CPK]) Blood glucose Cholesterol, total Triglyceride Urea nitrogen Creatinine Uric acid Serum electrolytes (sodium, potassium, chloride, calcium) PAP, TRACP-5b[b]
Urinalysis (qualitative): pH Protein Glucose Blood Ketone body Bilirubin Urobilinogen	
Additional Tests: Pregnancy test (hCG test)[a] in WOCBP	

[a]Urine pregnancy test will be performed at screening and follow-up. If a female subject has a positive urine pregnancy test, she will undergo a serum pregnancy test according to Section 5.5 Pregnancy.
[b]Prostatic acid phosphatase (PAP) and tartrate-resistant acid phosphatase (TRACP-5b): Only on Day 1

A pregnancy test will be conducted in women of childbearing potential (WOCBP) at the screening examination; the test result must be available prior to IMP administration. A pregnancy diagnosis support reagent provided by the sponsor will be used to perform the urine human chorionic gonadotropin (hCG) test. The test will be repeated if the result is inconclusive. The investigator or subinvestigator will review the test result and record whether or not the test is performed together with the test date and result (positive or negative) if performed in source documents and CRF.

3.7.4.3 Physical Examination and Vital Signs (Blood Pressure, Pulse Rate, and Body Temperature)

(1) Physical Examination

The subject will undergo a physical examination at specified time points. In the physical examination, the head, ears, eyes, nose and pharynx, chest, abdomen, urogenital organs, limbs, nerve, and skin and mucous membrane will be examined. The investigator or subinvestigator will bear the primary responsibility for assessment based on the physical

examination. Wherever possible, the physical examination of a subject will be performed by the same doctor.

The date of each physical examination and the findings will be recorded in source documents and CRF.

If, based on the physical examination, there is a new (ie, not present at baseline) clinically significant finding after IMP administration, the finding will be recorded as an AE and followed until its outcome has been sufficiently evaluated.

(2) Blood Pressure and Pulse Rate

Blood pressure (both diastolic and systolic) and pulse rate will be measured in the supine position using a well-maintained instrument after the subject has rested for at least 3 minutes. Whether or not the measurement has been performed, together with the date and time of measurement and the blood pressure and pulse rate measurements will be recorded in source documents and CRF.

(3) Body Temperature

Axillary temperature will be measured to 1 decimal place in Celsius using a well-maintained thermometer. Whether or not the measurement has been performed, together with the date and time of measurement and the measured temperature will be recorded in source documents and CRF. When the thermometer used measures to 2 or more decimal places, the reading is rounded to 1 decimal place and documented.

3.7.4.4 12-lead Electrocardiogram

The 12-lead electrocardiograph sent from the central ECG analysis laboratory will be used to obtain resting 12-lead ECG according to the method specified by the central ECG analysis laboratory. The investigator or subinvestigator assesses whether the ECG finding is normal or abnormal. He/she then will record whether or not the ECG is performed in source documents and CRF, together with the date of ECG and normal/abnormal assessment (including a description of any abnormal finding) if performed.

The ECG is sent to the central ECG analysis laboratory for calculation of heart rate, PR interval, RR interval, QRS interval, QT interval, and QTc intervals (QTcB and QTcF). The central ECG analysis laboratory will deliver the 12-lead ECG analysis report to the investigator or subinvestigator.

The investigator or subinvestigator will then review their ECG assessment with reference to the analysis report and signs and files the report.

The 12-lead ECG analysis report (in electronic format) sent from the central ECG analysis laboratory to the sponsor constitutes source data. Transcription of the heart rate, PR interval, RR interval, QRS interval, QT interval, and QTc intervals (QTcB and QTcF) to the CRF is unnecessary.

3.7.5 Pharmacokinetic/pharmacodynamic/pharmacogenomic Assessments

3.7.5.1 Pharmacokinetic Assessments

3.7.5.1.1 Pharmacokinetic Blood Samples

(1) Blood Sampling Schedule

- Day 1 of treatment period: Before IMP administration and 1, 1.5, 2, 4, 6, 12, and 24 hours after start of IMP administration
- Day 3 of treatment period: 24 hours after start of IMP administration on Day 2 (and before administration on Day 3)
- Day 4 of treatment period: 24 hours after start of IMP administration on Day 3 (and before administration on Day 4)
- Day 5 of treatment period: 24 hours after start of IMP administration on Day 4 (and before administration on Day 5)
- Day 6 of treatment period: 24 hours after start of IMP administration on Day 5

See Table 3.7-2 for the time windows for individual sampling points.

(2) Blood Sampling and Test Method

The contract laboratory will collect blood samples and send them to the bioanalytical laboratory. Detailed sample handling and shipping instructions are provided in Appendix 1.

The bioanalytical laboratory will determine plasma concentrations of OPC-61815 free form, tolvaptan, DM-4103, and DM-4107. The bioanalytical laboratory will report the test results to the sponsor while maintaining blinding. After unblinding, they will submit bioanalytical data in electronic format to the sponsor.

Whether or not blood is collected, type of blood collected (venous or arterial), and date and time of blood sampling will be recorded in the CRF. Transcription of the test results (reported directly from the bioanalytical laboratory to the sponsor) to the CRF is unnecessary.

When new information related to the IMP becomes available, analysis of a metabolite not specified in the protocol may additionally be performed.

(3) Rationale for Blood Sampling Schedule

This trial will investigate the dose of OPC-61815 that achieves tolvaptan exposure similar to tolvaptan 15-mg tablet in patients with heart failure. At the same time, plasma drug concentration data will be collected for evaluation of the pharmacokinetics following multiple OPC-61815 administration in patients with heart failure. For Day 1 of the treatment period, a blood will be collected predose, at the simulated t_{max} of OPC-61815 (1 hour after the start of administration), 3 time points around the t_{max} of tolvaptan (1, 1.5, and 2 hours after the start of administration), 3 time points in the estimated elimination phase of OPC-61815 (2, 4, and 6 hours after the start of administration), 3 time points in the estimated elimination phase of tolvaptan (6, 12, and 24 hours after the start of administration). These have been selected to calculate relevant pharmacokinetic parameters of OPC-61815 and tolvaptan based on the simulation of 1-hour intravenous administration using a population pharmacokinetic model based on data from 3 trials (the single intravenous dose trial of OPC-61815 in healthy adults [263-08-001], repeated intravenous dose trial of OPC-61815 in healthy adults [263-09-001], and trial investigating the rate of intravenous OPC-61815 administration in healthy adults [263-10-005]) and considering feasibility referring clinical pharmacology trial in Japanese patients with heart failure (156-06-004). One sampling time point (24 hours after the start of administration) for each of Day 2, Day 3, Day 4, and Day 5 of the treatment period is selected to confirm steady-state has been reached. A total of 12 blood sampling time points will be selected.

3.7.5.2 Pharmacodynamic Assessments

3.7.5.2.1 Clinical Laboratory Tests for Pharmacodynamic Analysis (Serum Sodium Concentration, Serum Potassium Concentration, Serum Osmolality, Biomarkers, Daily Urine Sodium Excretion, Daily Urine Potassium Excretion, and Urine Osmolality)

Samples for the parameters specified in Table 3.7.5.2.1-1 will be collected according to the schedule shown in Section 3.7.1 Schedule of Assessments. The date and time of sampling of venous blood will be recorded in source documents and CRF. Serum sodium and potassium concentrations will be obtained using the data generated in clinical laboratory tests conducted at the same sampling time points discussed in Section 3.7.4.2 Clinical Laboratory Assessments. The sampling, processing, and storage procedure are provided in Appendix 1.

Table 3.7.5.2.1-1 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 Activity
Urine: Urine sodium concentration Urine potassium concentration Urine osmolality	

All samples will be sent to the contract laboratory. The contract laboratory will perform testing on all the samples according to their established procedure and report the results to the sponsor and investigator or subinvestigator. The test results reported from the contract laboratory to the sponsor in electronic format will constitute the source data. Transcription of results to the CRF is unnecessary.

To ensure subject safety and to facilitate close monitoring of serum sodium concentration by the investigator or subinvestigator, serum sodium concentration will be determined at the trial site during the treatment period separately from the measurement at the contract laboratory. Whether blood for measurement of serum sodium concentration is collected and, if collected, the date and time of blood sampling and the result of measurement will be recorded in source documents and CRF.

Daily urine sodium excretion and daily urine potassium excretion are calculated by multiplying urine sodium concentration and urine potassium concentration, respectively, by daily urine volume. Urine excretion will be calculated by the sponsor and not need to be recorded in the CRF.

3.7.5.2.2 Daily Urine Volume

During the run-in period, urine volume will be measured each day from immediately after voiding after breakfast to voiding after breakfast the following day (measurement of the last day of the run-in period ends before IMP administration on Day 1 of the treatment period).

During the treatment period (after start of IMP administration on Day 1), urine volume will be measured each day from after voiding immediately before administration to after voiding immediately before administration the next day (continued until the day after final IMP administration).

Whether or not urine volume is measured will be recorded in source documents and CRF, together with the start and end date and time of each measurement and daily urine volume (if measured).

3.7.5.2.3 Daily Fluid Intake

The subject's fluid intake (including beverages [eg, fruit juice, milk, tea], water, and infusion solution) will be measured daily for the same period as urine. Whether or not fluid intake is measured will be recorded in source documents and CRF, together with the start and end date and time of each measurement and daily fluid intake (if measured). Water taken together with IMP will be included as fluid intake during the period that starts after administration.

3.7.5.2.4 Daily Fluid Balance

Daily fluid balance is calculated by subtracting daily urine volume from daily fluid intake. It will be calculated by the sponsor and not need to be recorded in the CRF.

3.7.5.3 Pharmacogenomic Assessments

3.7.5.3.1 DNA Storage

(1) Purpose for Storage

DNA samples will be stored so that the relationships between interindividual differences in the efficacy, safety, or pharmacokinetics of OPC-61815 and variations of DNA characteristics can be investigated in the future.

(2) Target Subjects for Storage

Sampling for DNA storage will take place only at the trial sites that have agreed to perform sampling for DNA storage prior to the trial. DNA samples will be collected only from subjects who have given consent to DNA storage in writing. Withdrawing consent to participate in the trial does not constitute withdrawal of consent for DNA storage. DNA samples will be retained only if the IRB of the trial site grants approval. Consent for DNA storage will be obtained before blood sampling for DNA storage.

(3) Procedure for Storage

1) Blood sampling schedule
   Blood sampling will be performed on Day 1 (predose). If blood cannot be collected on Day 1 (predose), blood sampling may again take place at any subsequent time point during the trial. Whether or not a blood sample for DNA storage is collected will be recorded in source documents and CRF, together with the date of collection (if collected).

2) Blood sampling procedure
   Two milliliters of blood (venous or arterial, either is acceptable) will be collected by venous puncture or via an indwelling catheter into a plastic collection tube (containing ethylenediaminetetraacetic acid [EDTA]). After inverting to mix the content, the tube will be frozen.
3) Sample shipment
   The trial site will include the protocol number, subject number, and date of blood sampling on the label of the blood sample for DNA storage. The contract laboratory will keep the sample frozen and send it to the DNA storage facility.
4) DNA isolation and storage
   At the DNA storage facility, the personal information manager will assign a new personal code to each sample to make it double-coded, followed by isolation and freezing of DNA.
5) DNA storage period
   DNA will be stored until (1) genomic/genetic analysis becomes unnecessary, (2) clinical development is discontinued, (3) 15 years after consent, or (4) the subject withdraws consent for DNA storage, whichever comes earlier.
6) DNA destruction
   When the sponsor requests destruction of a stored DNA sample, the DNA storage facility will destroy it by incineration according to their established procedure.

(4) Genomic/genetic Analysis

Genomic/genetic analysis will be performed only when investigating the relationships between interindividual differences in the efficacy, safety, or pharmacokinetics of OPC-61815 and variations of DNA characteristics is expected to produce meaningful results. When it has been decided to perform the genomic/genetic analysis, a pharmacogenomics protocol will be prepared. The analysis will be performed in compliance with GCP.

Genomic/genetic analysis will analyze genes that may be correlated with interindividual differences in the efficacy, safety, or pharmacokinetics of OPC-61815, but no such genes have been identified at this point.

A genome wide association study using DNA chip/microarray/next-generation sequencer may also be performed in conjunction with genomic/genetic analysis. Even in such cases, the results will never be used for reasons other than identifying the genes correlated with interindividual differences in the efficacy, safety, or pharmacokinetics of OPC-61815. The genomic/genetic analysis laboratory will report the results of genomic/genetic analysis of double-coded samples to the sponsor.

If a subject requests to be withdrawn from the trial, the results of genomic/genetic analysis obtained from the subject's DNA sample by the time the request is made will not be destroyed.

(5) Disclosure of the Results of Genomic/genetic Analysis to the Subject

Genomic/genetic analysis using DNA samples collected in this trial will target genes correlated with interindividual differences in the efficacy, safety, or pharmacokinetics of OPC-61815. Any correlation discovered in the analysis will only be exploratory or at an early stage of research without sufficient scientific reliability in terms of accuracy, certainty, and other relevant elements. The sponsor will not disclose the results of genomic/genetic analysis to subjects because providing scientifically ambiguous information would be of no benefit to subjects.

(6) Consent for DNA Storage and Withdrawal

Written information about DNA storage and genomic/genetic analysis will be prepared separately from that about the trial. The subject's signature will be obtained on the ICF for DNA storage. If a subject withdraws consent for DNA storage during the storage period, the sponsor will request the DNA storage facility to destroy his/her DNA. Withdrawing consent to participate in the trial does not constitute withdrawal of consent for DNA storage. When the sponsor requests destruction of a subject's DNA, the DNA storage facility will destroy the subject's DNA sample while keeping the sample anonymity. If a subject requests to be withdrawn from the trial, the results of genomic/genetic analysis obtained from the subject's DNA sample by the time the request is made will not be destroyed.

3.7.6 End of Trial

The end of trial date is defined as the last date of contact or the date of final contact attempt from the post-treatment follow-up case report form (CRF) 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 Arms

If the sponsor terminates or suspends the trial for any reason, prompt notification will be given to the heads of trial sites 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

In the event of any of 1) through 10) below, IMP administration in the subject will be stopped followed by the withdrawal examination specified in Section 3.7.1 Schedule of Assessments. The investigator or subinvestigator will record the event in detail in source documents and CRF together with the date and reason for discontinuation.

1) Subject's request for withdrawal
2) Discovery that the subject does not meet the inclusion criteria (including those for enrollment in the treatment period) or falls under any of the exclusion criteria after the start of the treatment period
3) Occurrence of an AE(s) that makes continued IMP administration difficult
4) A clinical laboratory value (AST or ALT) is obtained that equals or exceeds 3 times the upper limit of normal (ULN)
5) It is found that the serum sodium concentration determined at the trial site or central laboratory has increased to 12 mEq/L or higher from the predose value within 24 hours after the start of IMP administration
6) It is found that the serum sodium concentration determined at the trial site or central laboratory has increased to 155 mEq/L or higher during the treatment period
7) Use of prohibited concomitant drugs
8) Noncompliance with rule 1) in the restrictions for concomitant drugs
9) Confirmed or suspected pregnancy after the start of the treatment period
10) Deviation from the protocol becomes inevitable or the investigator or subinvestigator decides that the subject needs to be withdrawn from the trial for any other reason

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.

3.8.3.2 Documenting Reasons for Treatment Discontinuation

A subject may discontinue IMP for a number of reasons including those listed below:

- 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
  - 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 (SAE)
    - A clinical laboratory value (AST or ALT) is obtained that equals or exceeds 3 times the ULN
    - An increase in the serum sodium concentration to 12 mEg/L or higher from the predose value within 24 hours after the start of administration
    - An increase in the serum sodium concentration to 155 mEq/L or higher during the treatment period
    - Other potentially IMP-related safety concerns or AEs
- Death
- Reasons unrelated to medical condition (provide detail and review AE history with subject)
- Withdrawal of informed consent (complete written withdrawal of consent form)
- Lost to follow-up
- Pregnancy (see Section 5.5)
- Termination of all or part of the trial by the sponsor

If the subject discontinues IMP due to an AE, the investigator or subinvestigator, or other trial personnel, will make every effort to follow the event until it has resolved or stabilized. Follow up 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 in-clinic, 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, 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 [interrupt or] 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, investigator or subinvestigator will be given instructions to meet and discuss with the subject their options of continuing in the trial, preferably on therapy. The investigator or subinvestigator 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 started on treatment, whether through randomization or open assignment.

Subjects who signed the ICF but were not subsequently allocated to a trial treatment are eligible for rescreening. In the event that the screening examination is again performed, a new written consent must be obtained and a new subject identifier assigned before rescreening.

The following information will be recorded in the CRF of a screen failure subject.

- Date of informed consent
- Date of investigation
- Sex
- Date of birth
- Race
- Ethnicity
- Nationality
- Whether the inclusion criteria were satisfied (each criterion number the subject failed to meet will be specified)
- Whether the subject fell under any of the exclusion criteria (together with each criterion number the subject fell under)
- Date screen failure was confirmed
- Reason for screen failure assessment

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 received all doses of the IMP. Subjects who complete the end-of-trial examination scheduled on the last day of the treatment period 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" as the reason for discontinuation. 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, records of direct contact with the subject, medical records, records of successful telephone contact with the subject, statement by a family member or primary care physician, or public records).

The investigator or subinvestigator, or designee will make 3 documented attempts to contact the subject by telephone and in the event the investigator or designee is unable to reach the subject by telephone, the investigator or subinvestigator, or designee will attempt to contact the subject via certified mail or an alternative similar method, where appropriate, before assigning a "lost to follow-up" status.

The investigator or subinvestigator will document the following information about the subject lost to follow-up in source documents and CRF:

- Last date of contact or contact attempt
- Investigation method
- Whether or not the subject is reached
- Presence/absence of an AE(s), together with each AE term, date of occurrence and date of resolution, severity, and relationship to the IMP if present
- Action taken regarding the IMP administration, action taken for AE(s), outcome of AE(s)

3.12 Subject Compliance

The subject will remain under the supervision of the investigator or subinvestigator during the trial period. The investigator or subinvestigator will instruct the subject to comply with the following restrictions:

- The IMP and coadministered diuretics should be taken according to the instructed dose and regimen.
- The trial schedule should be followed during the trial.
- Prohibited concomitant drugs (see Section 4.1 Prohibited Medications) must not be used.

- The dose(s)/regimen(s) of restricted concomitant drugs (see Section 4.2 Restricted Concomitant Drugs, etc.) should not be modified.
- Any information acquired through participation in the trial must not be disclosed to any third person.

3.13 Protocol Deviations

The investigator or subinvestigator will not deviate from or change the protocol without a prior written agreement between the investigator and sponsor and also a prior written IRB approval issued after review by the IRB.

However, when a deviation from or change to the protocol is medically necessary to eliminate immediate hazards to the subjects, the investigator or subinvestigator may deviate from or change the protocol without a prior written agreement with the sponsor or a prior written IRB approval. When the investigator deviates from or changes the protocol without a prior written agreement with the sponsor or a prior written IRB approval, he/she promptly submits a document describing the deviation or change and the reason for the deviation or change to the sponsor and the head of trial site and obtains the IRB's approval. The investigator will also obtain the sponsor's agreement via the head of trial site after obtaining approval from the head of trial site.

(1) Reporting to the Sponsor

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 or 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.

(2) Documenting Deviations

The investigator or subinvestigator will document all protocol deviations in source documents.

For the protocol deviations specified in the protocol, all the required information will be documented in the CRF according to the sponsor's procedure for CRF preparation.

4 Restrictions

4.1 Prohibited Medications

Use of the drugs named in Table 4.1-1 will be prohibited from the run-in period to the end-of-trial/withdrawal examination.

Table 4.1-1	**Prohibited Concomitant Drugs**
1	Vasopressin antagonist
2	The following heart failure medications (injections) a) Human atrial natriuretic peptide b) Phosphodiesterase III inhibitor c) Catecholamine d) Colforsin
3	Diuretic injections
4	Drugs and food that may inhibit or induce Cytochrome P450 (CYP)3A4 (see Table 4.1-2)
5	Drugs unapproved in Japan, including IMP other than OPC-61815

	[Rationale for prohibited concomitant drugs]
1, 2	Use of these drugs can make efficacy evaluation difficult.
3	Patients who are receiving common treatment for cardiac edema (loop diuretics equivalent to furosemide at dose of 40 mg/day or higher, a combination of a loop diuretic(s) and thiazide diuretic(s), or a combination of a loop diuretic(s) and aldosterone antagonist(s); all of these drugs must be orally administered) are the target population of this trial.
4	Use of such drugs and food can make pharmacokinetic, safety, and efficacy evaluation difficult.
5	The safety of such drugs in the Japanese population has not been established.

Table 4.1-2 Drugs and Food That Induce or Inhibit CYP3A4	
Category	**Drugs/Food**
(1) CYP3A4 inhibitor (excluding topical preparation)	
Antimicrobial agents	Clarithromycin, erythromycin, fluconazole, itraconazole, miconazole, norfloxacin, chloramphenicol, voriconazole, ciprofloxacin
Anti-HIV drugs	Atazanavir, indinavir, nelfinavir, ritonavir, saquinavir, lopinavir, telaprevir, fosamprenavir, cobicistat, darunavir, elvitegravir
Drugs for viral liver diseases	Ombitasvir/paritaprevir/ritonavir
Calcium antagonists	Diltiazem, verapamil
Antidepressants	Fluvoxamine
Agents for peptic ulcer	Cimetidine
Anticancer drugs	Imatinib, crizotinib
Immunosuppressants	Ciclosporin
Antiemetics	Aprepitant
Others	Tofisopam, istradefylline, clotrimazole
Foods	Grapefruit, star fruit, Seville orange, and their products (eg, juice)
(2) CYP3A4 inducer (excluding topical preparation)	
Barbiturates	Phenobarbital, amobarbital, pentobarbital, barbital, secobarbital, primidone
Adrenocortical hormones	Cortisone, hydrocortisone, prednisolone, methylprednisolone, triamcinolone, dexamethasone, betamethasone, paramethasone, fludrocortisone
Antihypertensive drugs	Bosentan
Anti-HIV drugs	Efavirenz, etravirine, nevirapine
Antiepileptic drugs	Carbamazepine, phenytoin, oxcarbazepine
Antitubercular agents	Rifampicin, rifabutin
Anticancer drugs	Enzalutamide, mitotane
Others	Modafinil
Foods	Foods containing St. John's wort

4.2 Restricted Concomitant Drugs, etc.

Subjects may use drugs (other than OPC-61815 and tolvaptan) and therapies under the following conditions from the run-in period to the end-of-trial (or withdrawal) examination:

1) Diuretics other than vasopressin antagonists may be used if the dose and regimen are kept unchanged from the start of the run-in period to the end-of-trial (or withdrawal) examination.
2) The drugs that may affect fluid retention or underlying disease (specified in Table 4.2-1) may be used if the dose and regimen are kept unchanged.

Table 4.2-1	Restricted Concomitant Drugs and Therapies
1	Infusion solutions (no restriction applies if used as the solvent of a drug(s))
2	Potassium supplements
3	Xanthine
4	Nonsteroidal anti-inflammatory drugs (excluding one used as needed or used topically)
5	Antihypertensive agents
6	Heart failure drugs other than the prohibited concomitant drugs

3) Salt content in meals must not be changed in subjects on diet therapy (salt restriction).

[Rationale for Restricted Concomitant Drugs/Therapies]
1) to 3) These are set to control the diuretic effect and the effects on electrolyte concentration of drugs (other than the IMP) and diet therapy (salt restriction).

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. AEs 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 Drug Induced Liver Injury (DILI) case (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 CRF if there is an abnormality or complication.

Clinical Laboratory Test Value Changes: It is the investigator's or subinvestigator's responsibility to review the results of all laboratory tests as they become available. This review will be documented by the investigator's or subinvestigator's dated signature on the laboratory report. For each abnormal laboratory test result, the investigator or subinvestigator 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 and reported as indicated on the CRF. 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 CRFs provided by the sponsor. AE and serious AE collection is to begin after a 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.

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

The following information will be documented in the CRF according to the sponsor's procedure for CRF preparation.

- Event term
- Date (and time, if known, during hospitalization) of occurrence and date of resolution
- Severity
- Seriousness (together with detailed description of the event if serious)
- Causal relationship to the IMP
- Action taken regarding IMP administration
- Outcome

5.3 Immediately Reportable Events

The investigator or subinvestigator must immediately report after either the investigator or subinvestigator or site personnel become aware of any SAE, DILI, 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 to the sponsor.

Subjects experiencing SAEs should be followed clinically until the events are resolved, the condition is considered clinically stable, or the subject is lost to follow-up. 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 Drug-Induced Liver Injury

For a subject who experiences an elevation in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) that is ≥3 times the upper limit of normal (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 CRF.

5.5 Pregnancy

Women of child-bearing potential (WOCBP) 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 to prevent pregnancy during the course of the trial and for 30 days after the last administration 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, either 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, the investigator or subinvestigator 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 pregnancy test for hCG will be performed at screening on all WOCBP. If a urine test is performed and is positive, the investigator or subinvestigator will follow up with a confirmatory serum test.

During the trial, all WOCBP should be instructed to contact the investigator or subinvestigator 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 administration 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 is encouraged to contact the sponsor to discuss their rationale for unblinding. However, to prevent delays to the investigator or subinvestigator or medical personnel responding to a potentially emergent situation, unblinding of IMP will not be dependent upon the investigator or subinvestigator receiving approval from the sponsor (ie, the investigator or subinvestigator will be able to obtain the code break information independent of the sponsor). The investigator or subinvestigator may access the code breaking information via the IWRS. 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 After Treatment Period

In this trial, collection of AEs will continue until the post-treatment follow-up scheduled to occur between 7 and 10 days after the final IMP administration (Day 12 to 15). After the trial completion, AEs that meet any of the cases described in Section 5.7.1 Follow-up of Nonserious Adverse Events, Section 5.7.2 Follow-up of Serious Adverse Events, and Section 5.7.3 Follow-up and Reporting of Serious Adverse Events Occurring after Last Scheduled Contact will also be followed up as specified in the relevant section.

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 CRF with the current status noted. If a subject has an AE or has not recovered from an AE at the last scheduled contact, follow-up contacts will be scheduled at least every 4 weeks until resolution of the AE is confirmed, the condition is considered clinically stable, or the subject is lost to follow-up. All nonserious events that are ongoing at the last scheduled contact will be recorded as ongoing on the CRF. For any AE having been identified throughout the trial, during analysis, additional relevant medical history information may be requested to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history and occupation). The follow-up information after the last scheduled contact will be recorded in the subject's medical record.

5.7.2 Follow-up of Serious Adverse Events

This trial requires that subjects be actively monitored for SAEs up to the last scheduled contact.

Serious AEs that are **identified or ongoing at the last scheduled contact** must be recorded on the AE CRF page and reported to the sponsor according to the reporting procedures outlined in Section 5.3. This may include **unresolved previously reported SAEs, or new SAEs**. All serious adverse events that are ongoing at the last scheduled contact will be recorded as ongoing on the CRF. The investigator or subinvestigator will follow SAEs until the events are resolved, the condition is considered clinically stable, or the subject is lost to follow-up. The investigator or subinvestigator will continue to report any significant follow-up information to the sponsor using the IRE form up to the point the event has been resolved, the condition is considered clinically stable, or the subject is lost to follow-up.

5.7.3 Follow-up and Reporting of Serious Adverse Events Occurring after Last Scheduled Contact

Any new SAEs reported by the subject to the investigator or subinvestigator that occur **after the 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 that are captured on follow-up telephone contact or at any other time point after the defined trial period (ie, up to last scheduled contact). The investigator or subinvestigator should follow SAEs identified after the last scheduled contact until the events are resolved, stabilized, or the subject is lost to follow-up. The investigator or subinvestigator should continue to report any significant follow-up information to the sponsor until the event is resolved, the condition is considered clinically stable, or the subject is lost to follow-up with the IRE form.

6 Pharmacokinetic/pharmacodynamic/pharmacogenomic Analysis

6.1 Pharmacokinetics

This section only describes the primary and secondary pharmacokinetic endpoints.

6.1.1 Pharmacokinetic Analysis Set

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

administration. However, subjects whose data are rejected entirely after assessment according to the step in Section 6.1.2(3)1) will be excluded from the analysis set.

6.1.2 Pharmacokinetic Analysis

(1) Endpoints

(a) Primary Endpoint:

1) C_{max} and AUC_{24h} of plasma tolvaptan on Day 1 of treatment period

(b) Secondary Endpoints

1) Plasma concentrations of OPC-61815, tolvaptan, DM-4103, and DM-4107
2) Plasma pharmacokinetic parameters of OPC-61815, tolvaptan, DM-4103, and DM-4107

- Day 1 of treatment period: C_{max},[#1] AUC_{24h},[#1] AUC_t, AUC_∞, t_{max}, λ_z, AUC_%Extrap, t_{last}, $t_{1/2,z}$, CL,[#2] CL/BW,[#2] V,[#2] CL/F,[#3] CL/F/BW[#3]
- Day 1, Day 2, Day 3, Day 4, and Day 5 of treatment period: C_{24h}
- Day 5 of treatment period: $R_{5,ac}$ (C_{24h})

#1: Excluding tolvaptan

#2: Calculated only for OPC-61815 after administration of OPC-61815 injection

#3: Calculated only for tolvaptan after administration of tolvaptan 15-mg tablet

3) Ratio of the AUC of metabolite to that of OPC-61815[#4]

Day 1 of treatment period: AUC_∞, AUC_{24h}, and AUC_t

#4: Calculated only for the OPC-61815 injection groups

(2) Dataset for Analysis

Pharmacokinetic analysis set

(3) Analysis Method

1) Acceptance or nonacceptance of data will be determined in accordance with Section 3.4 Exclusion From Pharmacokinetic Analysis of the Manual Standard Practice for Noncompartmental Pharmacokinetic Analysis (Version 1.0).[11]
2) For each parameter specified under Section 6.1.2(1)(a) "Primary endpoints 1)," descriptive statistics will be calculated for each group. For Section 6.1.2(1)(b) "Secondary endpoints 1)," descriptive statistics will be calculated by date of administration, compound, and group at each blood sampling time point. For each parameter of Section 6.1.2(1)(b) "Secondary endpoints 2)," descriptive statistics will also be calculated by date of administration, compound, and group. Descriptive statistics calculated will include number of subjects, arithmetic mean, standard deviation, coefficient of variation, minimum, median, and maximum for

plasma drug concentration and number of subjects, arithmetic mean, standard deviation, coefficient of variation, geometric mean, minimum, median, and maximum for other than plasma drug concentration. Descriptive statistics will be calculated only for the groups in which over 50% of subjects have the data.

3) For each parameter of Section 6.1.2(1)(a) "Primary endpoint 1)," the difference (each OPC-61815 injection group − tolvaptan 15-mg group) in mean value and its 95% confidence interval will be calculated using logarithmic transformation (natural logs).

6.2 Pharmacodynamics

Analyses will be performed in the pharmacodynamic analysis set (see Section 7.2 Datasets for Analysis).

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

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

6.3 Pharmacokinetics/Pharmacodynamics

No pharmacokinetic/pharmacodynamic analyses are planned.

6.4 Pharmacogenomics

See Section 3.7.5.3.1(4) for analyses related to pharmacogenomic.

7 Statistical Analysis

7.1 Sample Size

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

7.2 Datasets for Analysis

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

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

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

7.3 Handling of Missing Data

The last observation before the day after final IMP administration will be carried forward if the measurement of the day after final IMP administration is missing.

7.4 Analysis of Efficacy Endpoints

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

7.4.1 Body Weight

Analysis of covariance using baseline weight (before IMP administration on Day 1) as covariate will be performed on the change (absolute change and percent change) from baseline in body weight after final administration (the day after final IMP administration) to calculate the least-square mean of the difference between each OPC-61815 injection group and tolvaptan 15-mg tablet group and its 95% confidence interval. At each time point, descriptive statistics of measurement and change (absolute change and percent change) from baseline will be calculated for each group.

7.4.2 Congestive Symptoms

7.4.2.1 Lower Limb Edema, Other Edema, and Pulmonary Congestion (Chest X-ray Finding)

The proportion of responders (subjects with a "markedly improved" or "improved" response is evaluated with reference to Table 7.4.2.1-1) and the proportion of subjects who achieve resolution [subjects who have congestive symptoms at baseline (immediately before first IMP administration) and in whom the symptoms resolve after IMP administration] of lower limb edema, other edema, and pulmonary congestion after final administration are calculated for each OPC-61815 injection group, together with the difference in the proportions between each OPC-61815 injection group and tolvaptan 15-mg group with the 95% confidence interval of each difference.

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

Table 7.4.2.1-1 Response of Lower Limb Edema, Other Edema, and Pulmonary Congestion

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

7.4.2.2 Jugular Venous Distension, Hepatomegaly, and Cardiothoracic Ratio

Change from baseline (immediately before first IMP administration) in jugular venous distension, hepatomegaly, and cardiothoracic ratio after final administration will be analyzed using analysis of covariance with baseline value as covariate to calculate the least square mean of the difference between each OPC-61815 injection group and tolvaptan 15-mg tablet group and its 95% confidence interval. Descriptive statistics of the measurements and their changes from baseline at each time point will be calculated for each group.

7.4.2.3 Pulmonary Rales and Third Cardiac Sound

The proportion of subjects who achieve resolution of pulmonary rales and third cardiac sound [subjects who have the sign at baseline (immediately before first IMP

administration) and who do not have the sign after IMP administration] will be calculated in each OPC-61815 injection group together with the difference in the proportion between each OPC-61815 injection group and tolvaptan 15-mg group and its 95% confidence interval.

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

7.4.3 NYHA Classification

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

7.5 Analysis of Demographic and Baseline Characteristics

A frequency distribution table will be created by group for subject demographic and other baseline characteristics for the pharmacokinetic and safety analysis sets. Descriptive statistics of demographic and other baseline characteristics will also be calculated for each group in the pharmacokinetic and safety analysis sets.

7.6 Safety Analysis

The following analyses will be performed for each group and IMP in the safety analysis set.

7.6.1 Adverse Events

All AEs will be coded by system organ class and Medical Dictionary for Regulatory Activities (MedDRA) 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

The above summaries will also be prepared for TEAEs potentially causally related to the IMP.

7.6.2 Clinical Laboratory Data

Descriptive statistics of clinical laboratory values (excluding qualitative urinalysis) as well as of the changes from baseline (before IMP administration on Day 1) in values at each time point and after final administration will be calculated. The results of qualitative urinalysis at each postdose time point and after final administration compared with baseline results will be summarized in a shift table. Each clinical laboratory value excluding qualitative urinalysis will be categorized into “within reference range,” “below the lower limit of reference range,” or “above the upper limit of reference range” using standard values to generate a shift table summarizing laboratory data at each postdose time point and after final administration compared with baseline.

7.6.3 Vital Signs Data

Descriptive statistics will be calculated for vital signs together with the changes from baseline (immediately before first IMP administration) at each time point and after final administration.

7.6.4 Electrocardiogram Data

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

The number and percentage of subjects who have a QTc interval (QTcB, QTcF) of “> 450,” “> 480,” and “> 500” between baseline and after final administration will be calculated. In addition, the number and percentage of subjects who show a change of “> 30” and “> 60” in QTc interval from baseline at each postdose time point or after final administration are calculated. "Normal” and “abnormal” assessments at each postdose time point and after final administration compared with baseline will be summarized in a shift table.

8 Management of Investigational Medicinal Product

For full details on IMP management, please refer to the OPC-61815 IB and the Clinical Operation Manual.

8.1 Packaging and Labeling

Trial medication will be provided to the IMP manager by the sponsor or designated agent. IMPs will be provided as subject kits. Each kit consists of 8 vials of OPC-61815 injection (2 mg, 4 mg, 8 mg, 16 mg, or placebo) and a small box containing a blister sheet of 10

tolvaptan tablets (15-mg tablet or placebo). A label stating that the content is for clinical trial use, protocol number, IMP names, quantity, lot number, expiration date, storage conditions, and sponsor's name and address will be affixed to each vial and small box. Each subject kit also displays the statement that the content is for clinical trial use, protocol number, drug number, IMP names, quantity, lot number, expiration date, storage conditions, 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 IMP manager, the person responsible for IMP preparation at the trial site (non-blinded staff), to prevent any other person from preparing the drugs. The IMP manager must not provide IMP to any subject not participating in this protocol.

The IMP will be stored at room temperature. The clinical 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 manager must maintain an inventory record of IMP received, dispensed, administered, and returned.

8.4 Returns and Destruction

Upon completion or termination of the trial, all unused and/or partially used IMP 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 with trial site number on the outermost shipping container. Returned supplies should be in the original packages. The assigned trial monitor will facilitate the return of unused and/or 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 or 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 or subinvestigator, or designee must notify the sponsor (or sponsor's designee) by e-mail (PQC_263-102-00001@otsuka.jp) immediately after becoming aware of the PQC according to the procedure outlined in Section 8.5.2 (Information Required for Reporting Product Quality Complaints).

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

Precautions should be taken to maintain blinding at the trial site when reporting PQC.

8.5.2 Information Required for Reporting Product Quality Complaints

- Description of compliant
- Reporter identification (eg, subject, investigator or subinvestigator, trial site, whether blinded [IMP preparer] or not)
- Reporter contact information (eg, address, phone number, e-mail address)
- ID of material (product/compound name, drug number)
- Clinical protocol reference (number and/or trial name)
- Dosage form/strength (if known)
- Pictures (if available)
- Complaint sample availability for return

8.5.3 Return Process for Product Quality Complaints

Indicate during the report of the PQC if the complaint sample is available for return. If complaint sample is available for return, sponsor will provide instructions for sample return, when applicable.

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 plasma concentration data will be retained by the bioanalytical laboratory. The sponsor will keep the electronic file submitted by the bioanalytical laboratory as a copy.

All source documents pertaining to this trial other than the above (drug concentration data) will be maintained by the trial site and made available for direct inspection by authorized persons. Investigator(s)/institution(s) will permit trial-related monitoring, audits, 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 clinic, 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's 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 or subinvestigator'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 each 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 the trial progress notes and other source documents will be initialed and dated on the day the change is made by a 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. If electronic data systems are being utilized, a full audit trail of changes must be maintained.

Information from the trial progress notes and other source documents will be entered by investigative site personnel directly onto electronic CRFs in the sponsor's electronic data capture (EDC) system. 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 site will retain all trial-related documents and records for the period of time indicated below or until the decision to discontinue DNA storage is made, whichever is the longest. However, if the sponsor requires a longer period of archiving, the head of the trial site will consult with the sponsor on the period and procedures of record retention.

- The date 2 years after manufacturing and marketing approval date. However, if the head of the trial site receives notification from the sponsor that development has been terminated or that results of the trial will not be submitted with the approval application, the date 3 years after receipt of such notification.

- The date 3 years after termination or completion of the trial.

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 sponsor to collect such records. The trial site will be responsible to maintain adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial including any data clarification forms received from the sponsor. Such documentation is subject to inspection by the sponsor and 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 or subinvestigators and clinical 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 CRFs with source documents. The investigator agrees to participate with audits.

Regulatory authorities may inspect the investigator 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 (CIOMS) guidelines, and applicable local laws and regulations.

Each trial site will seek approval/favorable opinion 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 CRFs, the investigator, subinvestigator and their staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject number and subject identification code 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 identifier in CRFs. 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 "non-substantial" amendments, the investigator or subinvestigator 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 ICF will require similar modification. In such cases, after approval/favorable opinion of the new ICF by the IRB, repeat written 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

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Appendix 1 Handling and Shipment of Bioanalytical Samples

(1) Handling

Each sample tube for storage is labeled properly. The label should display the protocol number, subject number, test parameter(s), sampling time, etc. Each tube should be labeled to check the protocol number, subject identifier, test parameter(s), sampling time, etc. The actual sampling time should be accurately recorded in the CRF rather than the scheduled time of sampling.

(2) Blood Samples for Pharmacokinetics

About 2 mL of blood should be collected in an EDTA-coated tube. Normally, venous blood should be collected by venous puncture or via an indwelling catheter. Arterial blood collected via an indwelling catheter is acceptable if this is judged desirable by the investigator or subinvestigator. The tube is gently inverted a few times to mix the content and placed in an ice water bath. The tube is immediately (within 45 minutes after sampling) centrifuged at about 4°C and approximately 1500 × G for about 10 minutes to obtain plasma. Plasma is divided evenly into 2 labeled sample stock tubes (primary sample and backup sample) and frozen at −15°C or below. Plasma samples will be collected from the trial site by the contract laboratory. The contract laboratory will ship plasma samples to the bioanalytical laboratory according to the schedule agreed to with the sponsor. Samples are packed in a polystyrene foam box with sufficient dry ice for shipment.

(3) Clinical Laboratory Samples for Pharmacodynamic Evaluation

The trial site will collect, treat, and store samples according to the sponsor's procedure.

- Serum sodium concentration, serum potassium concentration, and serum osmolality
  Blood should be collected in a tube for serum separation, and the tube is inverted a few times to mix the content. After being left to stand at room temperature for at least 30 minutes, the tube is centrifuged to collect serum. The serum is transferred to a sample stock tube and refrigerated.
- Plasma AVP concentration
  Blood should be collected in an EDTA-coated tube, and the tube is inverted a few times to mix the content. The tube is centrifuged under cooling, and plasma is transferred into a sample stock tube and frozen.
- Plasma BNP concentration and plasma renin activity
  Blood should be collected in an EDTA-coated tube after the subject has rested in the supine position. The tube is then inverted a few times to mix the content. The

tube is centrifuged under cooling, and plasma is transferred into a sample stock tube and frozen.

- Serum NT-proBNP concentration
  Blood should be collected in a tube for serum separation. The tube is inverted a few times to mix the content. After being left to stand at room temperature for at least 30 minutes, the tube is centrifuged to collect serum. The serum is transferred into a sample stock tube and frozen.
- Serum troponin-I concentration
  Blood should be collected in a tube for serum separation. The tube is inverted a few times to mix the content. After being left to stand at room temperature for at least 30 minutes, the tube is centrifuged to collect serum. The serum is transferred into a sample stock tube and frozen.
- Urine sodium concentration, urine potassium concentration, and urine osmolality
  An adequate volume of urine is collected from pooled urine in a sample stock tube and refrigerated. Urine volume should be measured before sample collection.

(4) Blood Sample for DNA Storage

Blood collection kit (eg, EDTA-coated tube), instruction for blood treatment and storage, and materials for transportation of blood sample are prepared per subject. Two milliliters of blood should be collected in an EDTA-coated tube for DNA storage. The tube is inverted a few times to mix the content before frozen (at −15°C or below). Trial site will follow the instructions specified for the sampling kit for blood collection, treatment, storage, and transportation. The contract laboratory will collect blood samples from each trial site and ship them to the DNA storage facility. Samples are packed in a polystyrene foam box with sufficient dry ice for shipment.

Appendix 2 Protocol Amendment(s)/Administrative Change(s)

Amendment Number: 1

Issue Date: 19 Jun 2017

PURPOSE: Addition of exclusion criteria, correction of trial procedure, and correction of errata and omission

BACKGROUND: The protocol is amended based on the PMDA's inquiries regarding the exclusion criteria. Trial procedure (timing of randomization, type of blood sampling) is also modified for feasibility reasons. Errata are also corrected.

MODIFICATIONS TO PROTOCOL:

- Main criteria for exclusion in Synopsis and Table 3.4.4-1 Exclusion Criteria "Subjects with a history of hypersensitivity to any of ingredients of OPC-61815 or tolvaptan" was added (as a safety precaution).
- Footnote "a" under Table 3.7-1 Schedule of Observations/Tests and Assessments "Randomization normally takes place on Day 1 (or Day -1 if justified. Each subject's fulfillment of the inclusion criterion 8 will be verified on Day 1)" was added (for feasibility reasons).
- 3.7.5.1.1 Pharmacokinetic Blood Samples (2) Blood Sampling and Test Method "type of blood collected (venous or arterial)" was added to the information required to be recorded in the CRF (for feasibility reasons).
- 3.7.4.3 Physical Examination and Vital Signs: "Sitting position" (during blood pressure measurement) was replaced with "supine position" (erratum).
- 3.7.4.4 12-lead Electrocardiogram: "He/she then will document ... date and time of ECG" was replaced with "He/she then will record ... date of ECG" (erratum).
- 3.7.5.2.1 Clinical Laboratory Tests for Pharmacodynamic Analysis: A new requirement that only venous blood is acceptable was added (for clarification).
- 3.7.5.3.1 (3) Procedure for Storage: "Venous puncture" was replaced with "venous puncture or via indwelling catheter" and "venous blood" with "blood (venous or arterial, either is acceptable)" (for feasibility reasons).
- 3.9 Screen Failures: "Sex" was added to the information required to be recorded in the CRF (omission).
- Appendix 1 (2) Blood Samples for Pharmacokinetics: Text was added to clarify that venous blood should normally be collected and that arterial blood is acceptable only if it is judged desirable by the investigator or subinvestigator (for feasibility reasons).
- Appendix 1 (4) Blood sample for DNA storage: "without further treatment" was deleted. (erratum)

- Correction of email address (erratum)
  Immediately Reportable Event: IRE_263-102-00001@otsuka.jp
  Email address for reporting PQC: PQC_263-102-00001@otsuka.jp

Agreement

I, the undersigned 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 them 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 case report forms 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.

_____	_____
Investigator Print Name	Trial Site Name
_____	DD Mon YYYY
Signature	Date

This agreement has been signed electronically. The electronic signature page is attached to this agreement.