CLINICAL STUDY PROTOCOL

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

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Otsuka Pharmaceutical Co., Ltd.

Investigational Medicinal Product

OPC-61815

CLINICAL PROTOCOL

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Protocol No. 263-102-00004

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Protocol Synopsis

Name of Sponsor: Otsuka Pharmaceutical Co., Ltd. Name of Investigational Medicinal Product: OPC-61815	Protocol No.: 263-102-00004
Protocol Title:	A Multicenter, Open-label, Uncontrolled Clinical Trial to Confirm the Tolerability of OPC-61815 in Patients With Congestive Heart Failure Who Have Difficulty With or Are Incapable of Oral Intake
Clinical Phase/Trial Type:	Phase 3/Therapeutic confirmatory (safety)
Treatment Indication:	For the treatment of congestive heart failure (CHF) with volume overload despite having received diuretics other than vasopressin antagonists
Objective(s):	To confirm the tolerability of intravenous administration of OPC-61815 at 8 or 16 mg once daily for a maximum of 5 days to CHF patients with volume overload despite having received diuretics (injection) other than vasopressin antagonists and who have difficulty with or are incapable of oral intake.
Trial Design:	Multicenter, open-label, uncontrolled
Subject Population:	A total of 40 Japanese male and female CHF patients age 20 to 85, inclusive, with volume overload (with lower limb edema, pulmonary congestion, or jugular venous distension) despite having received injection diuretics other than vasopressin antagonists and who have difficulty with or are incapable of oral intake
Inclusion/Exclusion Criteria:	**Inclusion Criteria:** 1) Patients receiving loop diuretic injection at a dose equivalent to furosemide 20 mg/day or higher 2) CHF patients in whom lower limb edema, pulmonary congestion, and/or jugular venous distension due to volume overload is present 3) Male or female patients age 20 to 85, inclusive, at time of informed consent 4) Patients who are judged by the investigator or subinvestigator to have difficulty or be incapable of oral intake, including patients who are judged by the investigator or subinvestigator to require nothing by mouth (NPO) management

5) Patients who are currently hospitalized or who are capable of being hospitalized from the time of informed consent until the end of the treatment period
6) Patients who are capable of giving informed consent

Exclusion Criteria:

1) Patients who are on a ventricular assist device
2) Patients who have any of the following diseases, complications, or conditions:
   - Suspected hypovolemia
   - Hypertrophic cardiomyopathy (excluding dilated phase)
   - Valvular disease with significant valvular stenosis
   - Hepatic encephalopathy with difficulty in adequate fluid intake
3) Patients who have experienced acute myocardial infarction within 30 days prior to the screening examination
4) Patients with a definite diagnosis of active myocarditis or amyloid cardiomyopathy
5) Patients who have any of the following medical histories:
   - History of sustained ventricular tachycardia or ventricular fibrillation within 30 days prior to the screening examination (for patients without an implantable cardioverter defibrillator)
   - History of cerebrovascular disease (excluding asymptomatic cerebral infarction) within 6 months prior to the screening examination
   - History of hypersensitivity or idiosyncratic reaction to benzazepines or benzazepine derivatives such as the ingredients of OPC-61815, tolvaptan, mozavaptan hydrochloride, and benazepril hydrochloride
6) Patients who have any of the following diseases, complications, or conditions:
   - Poorly controlled diabetes mellitus
   - Anuria
   - Dysuria associated with urinary tract obstruction, calculus, or tumor

	7) Patients with supine systolic blood pressure of <90 mmHg 8) Patients with any of the following abnormalities in laboratory test results: • Total bilirubin: >3.0 mg/dL • Serum or plasma creatinine: >3.0 mg/dL • Serum or plasma sodium concentration: <125 mEq/L • Serum or plasma sodium concentration: <147 mEq/L • Serum or plasma potassium concentration: >5.5 mEq/L 9) Patients with current symptoms or a history of hepatic impairment (including patients with aspartate aminotransferase [AST] or alanine aminotransferase [ALT] exceeding 3 times the upper limit of the reference range at the screening examination) 10) Patients who have undergone open-heart surgery (eg, open-heart surgery for valvular disease, coronary bypass surgery, or surgery in thoracic aorta) within 30 days prior to the screening examination 11) Patients who have difficulty with spontaneous respiration or who have been on tracheal intubation under sedative therapy 12) Patients with severe disturbed consciousness (ie, coma or stupor) 13) Women who are breast-feeding or who have a positive pregnancy test result prior to receiving investigational product (IMP) 14) Sexually active men or women of childbearing potential (WOCBP) who do not agree to practice birth control or remain abstinent during the trial and for 30 days after the final IMP administration 15) Patients who are otherwise judged to be ineligible by the investigator or subinvestigator
Trial Site(s):	Approximately 25 sites in Japan

Investigational Medicinal Product(s), Dose, Dosage regimen, Treatment period, Formulation, Mode of Administration:	The IMPs administered in this trial will be a lyophilized formulation containing 8 or 16 mg of OPC-61815. Subjects will receive once-daily 1-hour intravenous administration of OPC-61815 injection, beginning at a starting dose of 8 mg. Dose escalation will be assessed on Day 2 of the treatment period (and again on Day 3 of the treatment period, if applicable). If the dose escalation criteria are met, the dose will be increased to 16 mg; if the criteria are not met, administration will continue at 8 mg. If dose reduction becomes necessary after dose escalation to 16 mg due to occurrence of an adverse event, the dose will be reduced to 8 mg. A second dose escalation to 16 mg following dose reduction will not be allowed. The maximum duration of treatment will be 5 days; however, IMP treatment may be ended at a treatment period of shorter than 5 days at the discretion of the investigator or subinvestigator, if either of the following criteria is met: • All congestive symptoms are resolved and no further improvement in volume overload is necessary. • The subject becomes capable of fluid management by oral intake alone.
Trial Assessments:	**Safety:** Adverse events (AEs), clinical laboratory tests, physical examination, vital signs (blood pressure, pulse rate, and body temperature), and 12-lead electrocardiogram (ECG) **Pharmacodynamics:** Urine volume, fluid intake, serum concentrations of sodium and potassium, serum osmolality, urine concentrations of sodium and potassium, urine osmolality, biomarker measurements (plasma concentrations of arginine vasopressin [AVP] and brain natriuretic peptide [BNP], plasma renin activity, and serum concentrations of N-terminal pro-brain natriuretic peptide [NT proBNP] and troponin I) **Efficacy:** Body weight, congestive symptom findings (lower limb edema, pulmonary congestion, jugular venous distension, hepatomegaly, cardiothoracic ratio, pulmonary rales, and cardiac third sound), dyspnea (respiratory rate, paroxysmal nocturnal dyspnea, orthopnea, and subject-assessed dyspnea), and New York Heart Association (NYHA) classification

	Screening/other: Medical and medication history, physical examination, laboratory tests, vital signs, body weight, urine pregnancy test, and DNA storage
Criteria for Evaluation:	**Safety:** AEs, clinical laboratory tests, physical examination, vital signs, and 12-lead ECG **Pharmacodynamics:** Urine volume, fluid intake, fluid balance, serum concentrations of sodium and potassium, serum osmolality, urine excretions of sodium and potassium, urine osmolality, biomarker measurements (plasma concentrations of AVP and BNP, plasma renin activity, and serum concentrations of NT-proBNP and troponin I) **Efficacy:** Body weight, congestive symptom findings, dyspnea, and NYHA classification
Statistical Methods:	**Rationale for Sample Size:** Sample size: 40 subjects (number of subjects started on OPC-61815) For a sample size of 40 subjects, the probability of AE occurring at an incidence of 5% and 4% is respectively 87% and 80%.
Trial Duration:	Planned duration of the clinical trial: Apr 2019 to Sep 2020 Planned duration of trial participation for each subject: Maximum of 16 days (screening [1 day before start of IMP administration], 6 days for treatment period, and post-treatment follow-up at 7 to 10 days after final IMP administration)

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List of Abbreviations and Definitions of Terms

List of Abbreviations

Abbreviation	Definition
ADPKD	Autosomal dominant polycystic kidney disease
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AVP	Arginine vasopressin
BNP	Brain natriuretic peptide
cAMP	Cyclic adenosine 3',5'-monophosphate
CHF	Congestive heart failure
CI	Confidence interval
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EU	European Union
GCP	Good Clinical Practice
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IMP	Investigational medicinal product
IRB	Institutional review board
IRE	Immediately reportable event
K_i	Inhibition constant
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PD	Pharmacodynamic
PK	Pharmacokinetic
PPK	Population pharmacokinetics
PQC	Product quality complaint
QTc	QT corrected for heart rate
SAE	Serious adverse event
SD	Standard deviation
SIADH	Syndrome of inappropriate secretion of antidiuretic hormone
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States

WOCBP	Women of childbearing potential

List of Pharmacokinetic Parameters

Abbreviation or term	Unit	Definition
AUC_{∞}	ng·h/mL	Area under the concentration-time curve from time zero to infinity
AUC_{24h}	ng·h/mL	Area under the concentration-time curve from time zero to 24 hours
AUC_t	ng·h/mL	Area under the concentration-time curve calculated to the last observable concentration at time t
CL	L/h	Total body clearance of drug from the plasma
C_{max}	ng/mL	Peak (maximum) plasma concentration of the drug
$t_{1/2,z}$	h	Terminal-phase elimination half-life
t_{max}	h	Time to maximum plasma concentration
V_z	L	Apparent volume of distribution during the terminal phase (λz)

1 Introduction

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

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

Tolvaptan has been has been administered to patients in clinical settings as an oral aquaretic and provides a useful treatment option for heart failure patients with volume overload despite having received other conventional diuretics. However, in clinical practice, there are unmet medical needs for intravenously injectable aquaretics with the similar effects to oral tolvaptan for the treatment of heart failure patients who transiently experience mildly decreased levels of consciousness associated with pulmonary edema leading to difficulty in oral drug intake, those in whom the absorption of an oral drug is decreased due to gastrointestinal edema (intestinal edema) associated with an increase in central venous pressure secondary to heart failure, those in whom administration of an oral drug is difficult while receiving oxygen therapy, and elderly patients with decreased swallowing function. Tolvaptan is not readily soluble in water and not suitable for development as an injection. Otsuka Pharmaceutical therefore synthesized the new intravenous aquaretic OPC-61815. OPC-61815 is a compound with improved water solubility of tolvaptan by the phosphorylation of the hydroxy group in the benzazepine ring, and it is readily metabolized to tolvaptan in the body through the hydrolysis of the phosphate ester site by an alkaline or acid phosphatase. OPC-61815 is being developed for “the treatment of volume overload in heart failure when adequate response is not obtained with other diuretics (eg, loop diuretics).”

To date, the following trials of OPC-61815 has been completed: three phase 1 trials in healthy males: a single intravenous dose trial (Trial 263-08-001), a repeated intravenous dose trial (Trial 263-09-001), and a trial investigating the rate of intravenous administration (Trial 263-10-005), as well as one phase 2 clinical pharmacology trial in CHF patients (Trial 263-102-00001). In addition, a phase 3 trial to confirm the non-inferiority of OPC-61815 to tolvaptan tablet is ongoing in patients with CHF (Trial 263-102-00003).

When treated with OPC-61815 just as with tolvaptan, patients with heart failure are required to appropriately maintain control of fluid balance by oral fluid intake to prevent adverse drug reactions associated with the aquaretic effect of the drug, such as hypernatremia, thirst, and dehydration. For adequate fluid management, although it is important for patients to keep an adequate fluid balance by oral fluid intake on their own, some patients have difficulty in keeping an adequate fluid balance by oral fluid intake particularly in patients with decreased swallowing function and those who transiently experience mild decreased levels of consciousness associated with pulmonary edema. The timing of oral fluid intake is affected by the patient's subjective symptoms, such as thirst. In elderly patients and patients with decreased conscious levels who have difficulty

with or are incapable of sensing thirst (or incapable of complaining of thirst), fluid maintenance is expected to be more difficult, raising concerns of a possible higher risk of hypernatremia and other related symptoms compared with those who are capable of oral fluid intake.

The above-mentioned phase 3 confirmatory trial (Trial 263-102-00003) uses tolvaptan tablet as a comparator and excludes patients with difficulty in oral intake. Therefore, a clinical trial to evaluate the tolerability of OPC-61815 in patients with heart failure who have difficulty with or are incapable of oral intake should be conducted separately from the phase 3 confirmatory trial.

This trial will be conducted to confirm the tolerability of intravenous administration of OPC-61815 once daily for a maximum of 5 days to CHF patients who have difficulty with or are incapable of oral intake.

1.1 Nonclinical Data

In a receptor binding study using ^{3}H-AVP as a labeled ligand, OPC-61815 showed affinity for human AVP V_2 receptor with an inhibition constant [K_i] value of 6.13 ± 1.34 nM that was approximately 1/14 that of the main active metabolite tolvaptan (K_i, 0.43 ± 0.06 nM). OPC-61815 showed low affinity for human AVP V_{1a} receptor with a K_i value of 54.2 ± 16.8 nM that was approximately 1/4 that of tolvaptan (K_i, 12.3 ± 0.80 nM). Neither OPC-61815 nor tolvaptan had affinity for human AVP V_{1b} receptor. OPC-61815 and tolvaptan inhibited AVP-induced cyclic adenosine 3',5'-monophosphate (cAMP) production in a human endocervical carcinoma cell line expressing human AVP V_2 receptors, indicating that both drugs have an AVP V_2 receptor antagonistic activity. However, neither OPC-61815 nor tolvaptan alone increased cAMP production, suggesting that they possess no V_2 receptor agonistic activity.

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

increase in plasma renin activity, or activation of the renin-angiotensin system following furosemide administration.

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

In a rat model of hyponatremia, 5-day repeated ascending intravenous administration of OPC-61815 at 0.255 to 5.1 mg/kg dose-dependently increased the lowered plasma sodium concentration and also improved the hyponatremia-associated increases in water content observed in the brain and heart.

Based on the above results, OPC-61815 by intravenous administration shows potent aquaretic effects similar to those of tolvaptan and is expected to demonstrate clinical efficacy in the improvement of various disorders associated with body fluid retention due to abnormal water metabolism (eg, hyponatremia and edematous diseases).

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

1.2 Clinical Data

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

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

In a repeated intravenous dose trial (Trial 263-09-001[4]), OPC-61815 at 1.25, 5, or 20 mg, or placebo was intravenously administered over 1 minute as a single dose followed by once daily dosing for 7 consecutive days after 1-day dose intermission from the initial dose in 36 healthy male subjects. Adverse events, including feeling abnormal, pruritus, and erythema occurred at higher frequency during or immediately after the end of administration of OPC-61815. Most of these events were considered to be related to the

IMP and had not been reported with the oral administration of tolvaptan. All of the AEs were mild or moderate in severity and resolved without treatments.

In order to investigate an injection duration that is capable of reducing the occurrence of the ADRs that had not been reported with oral administration of tolvaptan but reported in the repeated intravenous administration trial (263-09-001), and also to explore the causes of the ADRs, a trial investigating the rate of intravenous administration (Trial 263-10-005[5]) was conducted. A single dose of OPC-61815 at 7.5 or 15 mg, or placebo was intravenously administered over 2 hours, 5 minutes, or 1 minute in 18 healthy male subjects, and AEs categorized as "feeling abnormal, pruritus, and erythema" which occurred at higher frequency in the repeated intravenous dose trial (Trial 263-09-001) were extracted as adverse events of special interest (AESI). The incidences of the AESI with a 2-hour intravenous administration were 1 of 12 subjects in the OPC-61815 group and 3 of 6 subjects in the placebo group; a causal relationship to the investigational medicinal product (IMP) was ruled out for the rash in the OPC-61815 group. The incidences of the AESI with a 5-minute infusion were 9 of 12 subjects in the OPC-61815 group and 2 of 6 subjects in the placebo group, and those with a 1-minute infusion were 10 of 11 subjects in the OPC-61815 group and 4 of 6 subjects in the placebo group. With the exception of 1 occurrence of erythema at the 1-minute intravenous administration, all occurrences in the OPC-61815 group were judged to be related to the IMP. All of the related AEs occurred during or immediately after the end of administration, and most of the events were transient and resolved without treatments. There were no clinically significant changes from baseline in the plasma histamine concentration.

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

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

OPC-61815 at 2, 4, 8, or 16 mg was intravenously administered over 1 hour once daily for 5 consecutive days or tolvaptan 15-mg tablet was orally administered once daily for 5 days in 60 patients with CHF who have volume overload despite having received diuretics other than vasopressin antagonists. A phase 2 trial was conducted with the primary objective to investigate the dose of OPC-61815 injection formulation achieving exposure equivalent to that for tolvaptan 15-mg tablet. The detailed results for the primary endpoint are described in Section 2.2.1.

1) Pharmacokinetics and Pharmacodynamics

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

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

2) Efficacy and Safety

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

The AEs reported by ≥2 subjects in the OPC-61815 group (all dose groups combined) were blood urea increased (4.2% [2 of 48 subjects] in the OPC-61815 group, 8.3% [1

of 12 subjects] in the tolvaptan 15-mg tablet group), and pyrexia, thirst, vessel puncture site reaction, blood creatinine increased, and headache (4.2% [2 of 48 subjects] each in the OPC-61815 group and 0.0% [0 of 12 subjects] in the tolvaptan 15-mg group). No deaths were reported. Two occurrences of serious adverse events (SAEs) (atrial fibrillation, endocarditis) were reported by 1 subject in the OPC-61815 4-mg group. Two subjects in the OPC-61815 4-mg group (atrial fibrillation, renal impairment) and 3 subjects in the tolvaptan 15-mg tablet group (liver disorder, hepatic congestion, renal impairment) discontinued IMP administration due to AEs. No subjects reported any AESI (eg, feeling abnormal, feeling hot, pruritus, rash, urticaria, erythema, hyperhidrosis, nausea, epigastric discomfort, or dyspnea) that occurred at higher frequency following bolus (1- or 5-minute) infusion of OPC-61815 and were considered to be due to IMP in the phase 1 trials (Trials 263-09-001 and 263-10-005).

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

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

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

The changes (mean ± SD) in body weight from baseline at the time of final IMP administration were −1.54 ± 1.61 kg in the tolvaptan 15-mg group and −0.45 ± 0.93 kg in the placebo group. The decrease in body weight in the tolvaptan 15-mg group was significantly greater than that in the placebo group ($p < 0.0001$, t-test), with a difference (the tolvaptan 15-mg tablet group − the placebo group) of −1.09 kg (95% confidence interval [CI], −1.58 to −0.60 kg).

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

in severity. The thirst, constipation, and pollakiuria were considered to be related to the diuretic effect of tolvaptan.

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

1.3 Known and Potential Risks and Benefits

The AEs reported frequently in the completed phase 1 trials of OPC-61815 in healthy male subjects (Trials 263-08-001, 263-09-001, and 263-10-005) are described below.

In a single intravenous dose trial (Trial 263-08-001), the AEs reported by ≥2 subjects in the OPC-61815 group were ventricular extrasystoles, abdominal pain, and blood cholesterol increased.

In a repeated intravenous dose trial (Trial 263-09-001), the AEs reported by ≥3 subjects in the OPC-61815 group were feeling abnormal, pruritus, blood uric acid increased, diarrhoea, pruritus generalised, erythema, and bradycardia.

In a trial investigating the rate of intravenous administration (Trial 263-10-005), the AEs reported by ≥2 subjects receiving OPC-61815 as a 2-hour infusion were activated partial thromboplastin time prolonged at 7.5 mg; those reported by ≥2 subjects receiving OPC-61815 as a 5-minute infusion were erythema, hyperhidrosis, pruritus, and feeling hot at 7.5 mg, and erythema, hyperhidrosis, pruritus, and feeling abnormal at 15 mg; and those reported by ≥2 subjects receiving OPC-61815 as a 1-minute infusion were erythema, pruritus, feeling abnormal, and feeling hot at 7.5 mg, and erythema, hyperhidrosis, pruritus, and feeling abnormal at 15 mg.

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

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

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

In clinical trials involving patients with cardiac edema (Trials 156-03-001, 156-06-002, 156-06-004, 156-06-006, 156-10-005, 156-12-809-01, and 156-TWA-1101), the AEs frequently reported (with an incidence ≥2%, and higher than that in the placebo group) in 437 subjects treated with tolvaptan tablet were 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. For the details regarding the AEs attributable to tolvaptan or OPC-61815 treatment that have been reported in clinical trials, see the IB.

The present trial will enroll patients with CHF who have difficulty with or are incapable of oral intake. In these patients, as compared with those who are able to drink water, the risks of AEs related to the aquaretic effect of OPC-61815 (eg, hypernatremia, dehydration, and thirst) may be increased due to their inability to control fluid balance by oral fluid intake.

2 Trial Rationale and Objectives

2.1 Trial Rationale

OPC-61815 is being developed for an intended approval in the same indication as that of tolvaptan, “the treatment of volume overload in heart failure when adequate response is not obtained with other diuretics (eg, loop diuretics)”

A phase 2 clinical pharmacology trial (Trial 263-102-00001) was conducted in patients with CHF to investigate a dose of OPC-61815 to achieve the exposure equivalent to an oral tolvaptan tablet at 15 mg using exposure of tolvaptan as a measure. The results indicated that OPC-61815 at 16 mg was equivalent to tolvaptan 15-mg tablet, and also indicated that OPC-61815 caused no significant safety concern in the dose range from 2

to 16 mg in patients with CHF. Based on the results of the phase 2 trial, a phase 3 trial (Trial 263-102-00003) was initiated to confirm the non-inferiority of OPC-61815 to tolvaptan 15-mg tablet using an OPC-61815 16-mg injection formulation that had been shown to be equivalent to tolvaptan 15-mg tablet and the trial is currently ongoing. In the phase 3 confirmatory trial (Trial 263-102-00003), tolvaptan is used as a comparator so patients who have difficulty with or are incapable of oral intake are excluded.

In patients with CHF who have difficulty with or are incapable of oral intake, and are thereby unable to control fluid balance by oral rehydration, there is a concern that the adverse drug reactions associated with the aquaretic effect of OPC-61815 including hypernatremia and dehydration may occur at a higher incidence compared with patients who are capable of oral fluid intake. Therefore, a clinical trial to evaluate the tolerability of OPC-61815 in patients with heart failure who have difficulty with or are incapable of oral intake should be conducted separately from the phase 3 confirmatory trial.

In view of the above, the present trial is considered to be appropriate to confirm the tolerability of repeated intravenous administration of OPC-61815 in patients with CHF who have difficulty with or are incapable of oral intake.

2.1.1 Rationale for the Uncontrolled and Open-label Design

Since this trial enrolls patients who have difficulty with or are incapable of oral intake, the use of tolvaptan tablet as a comparator is impossible. In addition, the trial population comprises patients who are judged to have an inadequate response to treatment with conventional diuretics other than vasopressin antagonists (standard treatment); therefore, setting a placebo or standard treatment group as a control group is considerably disadvantageous to the subjects and ethically inappropriate since the delay in care may lead to a poor diagnosis in subjects assigned to standard treatment group. The primary objective of this trial is to confirm the tolerability of OPC-61815 in patients with heart failure who have difficulty with or are incapable of oral intake, which is determined to be an objective that can be attained by an open-label design involving no comparator group.

2.2 Rationale for the Dosage Regimen

OPC-61815 is being developed for an intended approval for the same indication as that of tolvaptan, “the treatment of volume overload in heart failure when adequate response is not obtained with other diuretics (eg, loop diuretics),” and a phase 3 trial to confirm the non-inferiority to tolvaptan 15-mg tablet (Trial 263-102-00003) is ongoing. The only difference between the patient populations enrolled in the above phase 3 confirmatory trial (Trial 263-102-00003) and the present trial is whether or not patients who have

difficulty with or are incapable of oral intake are included. Therefore, the dosage regimen in this trial is set based on that used in the phase 3 confirmatory trial (Trial 263-102-00003).

2.2.1 Selection of Dosage Regimen for the Phase 3 Confirmatory Trial (Trial 263-102-00003)

A phase 2 clinical pharmacology trial (Trial 263-102-00001) was conducted to determine the dose of OPC-61815 injection achieving the tolvaptan (aka, OPC-41061) exposure equivalent to that for tolvaptan 15-mg tablet after intravenous administration of OPC-61815 in patients with CHF.

Table 2.2.1-1 shows the tolvaptan exposure (C_{max} and AUC_{24h}) on Day 1, the primary endpoint of the phase 2 trial (Trial 263-102-00001). Table 2.2.1-2 shows the mean differences, as well as their 95% CIs, in log-transformed tolvaptan exposure (C_{max} and AUC_{24h}) on Day 1 between intravenous administration of OPC-61815 and oral administration of Tolvaptan 15 mg.

Following 1-hour intravenous administration of OPC-61815 at 2, 4, 8, or 16 mg once daily, the exposure of tolvaptan at 16 mg of OPC-61815 was closest and similar to that observed after oral administration of tolvaptan tablet at 15 mg. The incidences of AEs were 53.8% (7 of 13 subjects) in the OPC-61815 2-mg group, 58.3% (7 of 12 subjects) in the OPC-61815 4-mg group, 33.3% (4 of 12 subjects) in the OPC-61815 8-mg group, 72.7% (8 of 11 subjects) in the OPC-61815 16-mg group, and 83.3% (10 of 12 subjects) in the tolvaptan 15-mg tablet group. All events were reported only in 1 or 2 subjects. No deaths occurred in the trial. Two occurrences of SAEs were reported in 1 subject in the OPC-61815 4-mg group. There were no reports of the AESI, which occurred at a higher frequency with bolus (1- or 5-minute) infusion of OPC-61815 and were considered to be related to IMP in the phase 1 trials in healthy adult subjects.

Based on these results, 16 mg once daily administered as a 1-hour infusion are selected as the dosage regimen of OPC-61815 for the ongoing phase 3 trial (Trial 263-102-00003) to confirm the non-inferiority of OPC-61815 to tolvaptan tablet.

Table 2.2.1-1	**Tolvaptan Exposures (Cmax and AUC24h) on Day 1 After Intravenous Administration of OPC-61815 and After Oral Administration of Tolvaptan 15 mg (Mean ± SD)**				
Route of administration	**Intravenous**				**Oral**
Dose	OPC-61815 2 mg	OPC-61815 4 mg	OPC-61815 8 mg	OPC-61815 16 mg	Tolvaptan 15 mg
n	11	12	12	11	12
C_{max} (ng/mL)	41.4 ± 11.4	98.6 ± 43.7	149 ± 61.7	282 ± 96.0	325 ± 194
AUC_{24h} (ng·h/mL)	356 ± 157	983 ± 563	1340 ± 522	2400 ± 1030	2850 ± 1580

Trial 263-102-00001

Table 2.2.1-2	**Mean Differences and 95% Confidence Intervals in Log-transformed Tolvaptan Exposure (Cmax and AUC24h) on Day 1 Between Intravenous Administration of OPC-61815 and Oral Administration of Tolvaptan 15 mg**			
Dose	OPC-61815 2 mg	OPC-61815 4 mg	OPC-61815 8 mg	OPC-61815 16 mg
n	11	12	12	11
C_{max} (ng/mL)	−1.940 (−2.281, −1.598)	−1.114 (−1.447, −0.780)	−0.691 (−1.025, −0.357)	−0.050 (−0.392, 0.291)
AUC_{24h} (ng·h/mL)	−2.003 (−2.408, −1.597)	−1.035 (−1.432, −0.639)	−0.664 (−1.060, −0.267)	−0.125 (−0.530, 0.281)

Trial 263-102-00001

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

2.2.2 Rationale for the Dosage Regimen in This Trial

1) Dose Selection

The target population of this trial is patients with heart failure who have difficulty with or are incapable of oral intake, and are thereby unable to control fluid balance by oral fluid intake. Based on the risk of AEs associated with the aquaretic effect of OPC-61815 is expected to be increased in such subjects, OPC-61815 treatment is to be started with a low dose and the dose is to be increased to 16 mg (the dose used in the phase 3 confirmatory trial [Trial 263-102-00003]) after confirming the insufficient efficacy and allowable safety of the low dose according to prespecified dose escalation criteria.

The starting dose is selected with reference to the Precautions for Dosage and Administration I-(4) of the package insert for Samsca Tablets: “When tolvaptan is administered to a patient in whom a rapid reduction in circulating plasma volume is not preferable, tolvaptan therapy may be started with 7.5 mg (half the usual dose).”

The pharmacodynamic effects of OPC-61815 are considered to vary depending on exposure to tolvaptan, which is the active ingredient of OPC-61815. Accordingly, in view of the pharmacokinetics and pharmacokinetics/pharmacodynamics (PK/PD) characteristics of tolvaptan observed in previous clinical trials of tolvaptan or OPC-61815, the appropriateness of the starting dose selected for this trial was examined as described below.

The dose-proportionality of tolvaptan exposure following intravenous administration of OPC-61815 observed in the phase 2 clinical pharmacology trial (Trial 263-102-00001) was analyzed and the results indicated the dose-proportionality of tolvaptan exposure at 2, 4, 8, and 16 mg.

A population pharmacokinetic (PPK) analysis (Trial 156-08-003) using data from 4 trials of tolvaptan in patients with CHF (Trials 156-03-001, 156-06-002, 156-06-004, and 156-06-006) indicated that a linear model fitted well for the tolvaptan pharmacokinetic profile data, indicating the dose-proportionality of tolvaptan exposure following the oral administration of tolvaptan.

As described above, tolvaptan exposure has been shown to be dose-proportional both after the oral administration of tolvaptan and the intravenous administration of OPC-61815. Therefore, the tolvaptan exposure after the intravenous administration of OPC-61815 at 8 mg (half the dose [16 mg]) was expected to be similar to that observed after the oral administration of tolvaptan at 7.5 mg (half the usual dose [15 mg]).

In a PPK/PD analysis conducted on the plasma tolvaptan concentration and daily urine volume data from 3 trials of tolvaptan in patients with CHF (Trials 156-03-001, 156-06-002, and 156-06-004), the relationship between tolvaptan AUC_{24h} (estimated using posthoc parameter obtained from the PPK analysis) and daily urine volume was assessed. The assessment results showed that an E_{max} model fitted well for the relationship between tolvaptan AUC_{24h} and daily urine volume, indicating that daily urine volume varied depending on tolvaptan AUC_{24h}. The same model was used to estimate daily urine volume and its change from baseline based on the tolvaptan AUC_{24h} observed after the intravenous administration of OPC-61815 at 16 mg and

8 mg in the phase 2 clinical pharmacology trial (Trial 263-102-00001). The estimated urine volume and its change from baseline decreased along with a decrease in tolvaptan AUC_{24h} with a dose decrease from 16 mg to 8 mg.

Based on the above, an OPC-61815 starting dose of 8 mg, which is half the dose (16 mg) used in the phase 3 confirmatory trial (Trial 263-102-00003), is expected to produce a tolvaptan exposure similar to that observed after the oral administration of tolvaptan 7.5 mg. In addition, daily urine volume and its change from baseline at 8 mg are expected to be lower than those at 16 mg. Thus, setting the starting dose of OPC-61815 at 8 mg is considered to be appropriate from the viewpoint of ensuring subject safety in this trial for patients with heart failure who have difficulty with or are incapable of oral intake, and are thereby unable to attain a fluid balance by oral fluid intake.

2) Dosage Regimen Selection
OPC-61815 is to be administered according to the same dosage regimen as that used in the phase 3 confirmatory trial (ie, dosing as a 1-hour infusion once daily). (See Section 2.2.1.)

2.3 Trial Objective

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

3 Trial Design

3.1 Type/Design of Trial

This trial is a multi-center, uncontrolled, open-label trial to confirm the tolerability of intravenous administration of OPC-61815 at 8 or 16 mg once daily for a maximum of 5 days to CHF patients with volume overload despite having received diuretics (injection) other than vasopressin antagonists and who have difficulty with or are incapable of oral intake. An overview of the trial design is presented in Figure 3.1-1.

Subjects who meet all of the inclusion criteria and fall under none of the exclusion criteria at the screening examination will be advanced to the treatment period during which OPC-61815 will be intravenously administered at 8 or 16 mg once daily. OPC-61815 treatment will start at 8 mg, and the investigator or subinvestigator will

increase the dose to 16 mg on Day 2 or 3 after confirming that the subject meets the dose escalation criteria. The procedures for dose escalation decision are shown in Section 3.2.2. The maximum treatment duration is 5 days; however, IMP treatment may be discontinued before Day 5 according to the rules specified in Section 3.2.3. Concomitant use of loop diuretics will continue until the end of the treatment period.

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

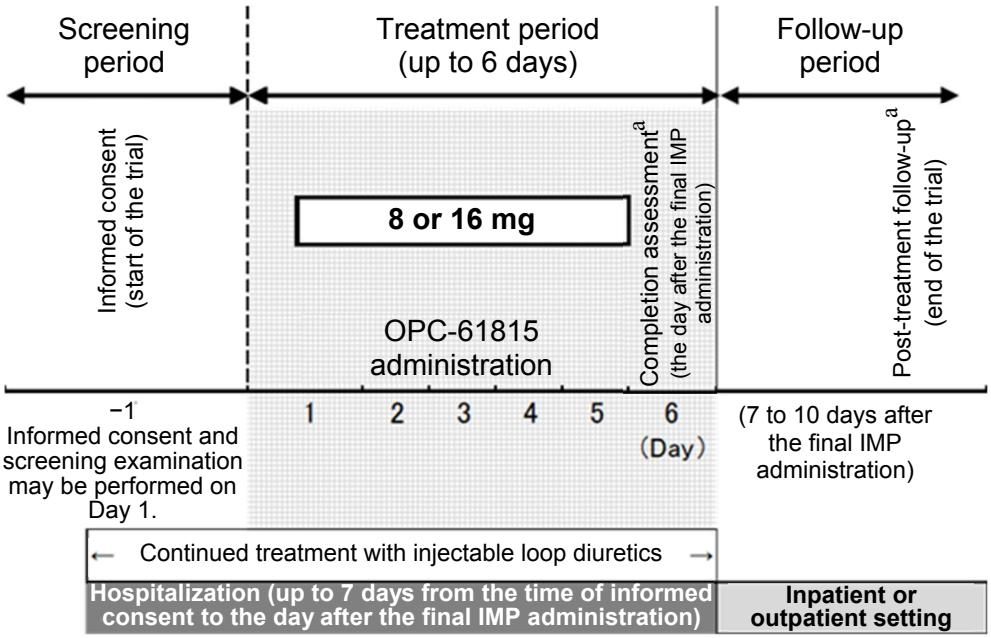

Figure 3.1-1 Trial Design Schematic

[a] If IMP treatment is discontinued before Day 5, the same assessment as the completion assessment scheduled for Day 6 should be conducted on the day after the final IMP administration, followed by the follow-up assessment at any time between 7 and 10 days after the final IMP administration.

3.2 Trial Treatments

3.2.1 Dosage Regimen

The investigator or subinvestigator will administer OPC-61815 once daily as 1-hour infusion (55 to 70 minutes allowable) according to the IMP administration procedures specified separately. OPC-61815 treatment will start with 8 mg, and eligibility for dose escalation will be assessed on Day 2 of the treatment period (and again on Day 3 of the treatment period, if applicable) according to Section 3.2.2. If the dose escalation criteria

are met, the dose will be increased to 16 mg; if the criteria are not met, administration will continue at 8 mg.

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

A flowchart of the dose escalation decision is presented in Figure 3.2.1-1.

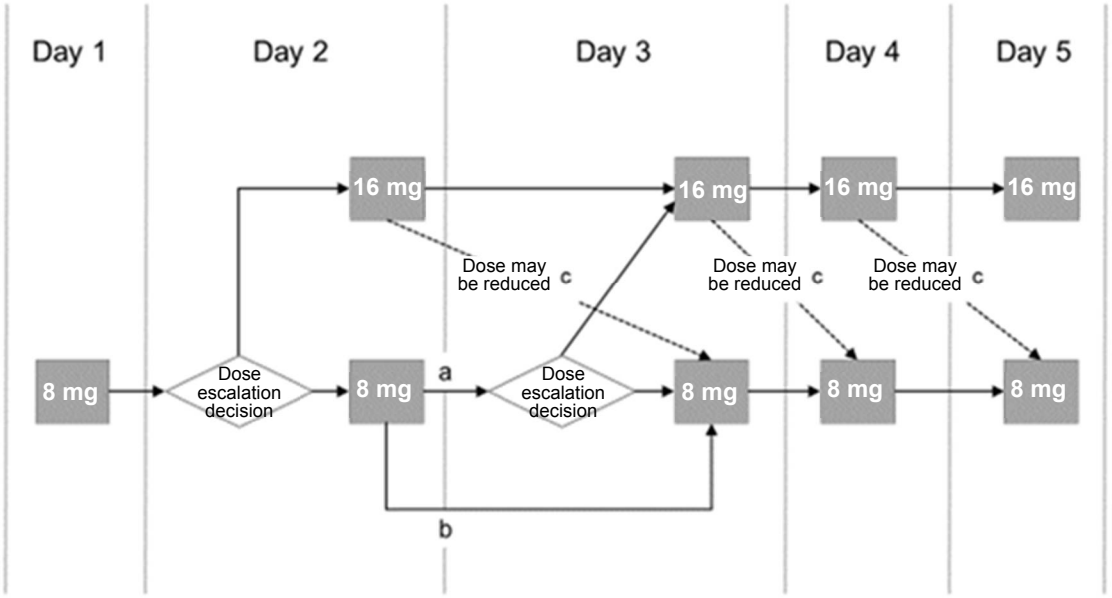

Figure 3.2.1-1 Flowchart of the Dose Escalation Decision

[a]When only No. 2 of the Day 2 dose escalation criteria is not met

[b]When any of No. 1, 3, or 4 of the Day 2 dose escalation criteria are not met

[c]When AEs associated with the aquaretic effect of OPC-61815 including hypernatremia, dehydration, and thirst occur or worsen, and dose reduction is judged to be necessary by the investigator or subinvestigator

The following information will be recorded in the source document and the electronic case report form (eCRF).

- Times and dates at which OPC-61815 intravenous administration is started and ended (and suspension period, if the administration is suspended)
- Dose

- If eligibility for dose escalation is assessed, the result (date of assessment, and whether or not each criterion is met)
- If the dose is reduced, the AE(s) leading to dose reduction

3.2.2 Dose Escalation Decision

1) Predose on Day 2

When all (No. 1 to No. 4) of the Day 2 dose escalation criteria (Table 3.2.2-1) are met, the dose will be increased to 16 mg.

When any of the following criteria are not met, the dose for Day 2 and onward will remain at 8 mg, and dose escalation assessment will not be repeated at predose on Day 3.

- No. 1 of the Day 2 dose escalation criteria
- No. 3 of the Day 2 dose escalation criteria
- No. 4 of the Day 2 dose escalation criteria

Table 3.2.2-1 Day 2 Dose Escalation Criteria

1	An adequate response is absent (when either of the following is met). 1) When the increase in daily urine volume from baseline (the daily urine volume through immediately predose on Day 1) is ≤500 mL: Any congestive symptom (lower limb edema, hepatomegaly, jugular venous distension, cardiothoracic ratio, pulmonary rales, or cardiac third sound) is present. 2) When the increase in daily urine volume from baseline (the daily urine volume through immediately predose on Day 1) is >500 mL or cannot definitely be concluded to be ≤500 mL: Body weight did not decrease as compared with predose on Day 1 with no improvement in congestive symptoms.
2	The serum sodium concentration at predose on Day 2 is ≤147 mEq/L.[a]
3	An increase of >10 mEq/L in serum sodium concentration is not evident within 24 hours after start of IMP administration on Day 1.[a]
4	No safety concerns have arisen since the start of IMP administration on Day 1 at the discretion of the investigator or subinvestigator.

[a]If serum sodium concentration measurement is difficult to perform at the trial site, plasma sodium concentrations will be used for the assessment.

2) Predose on Day 3

When only No. 2 of the Day 2 dose escalation criteria was not met, eligibility for dose escalation will be reassessed on Day 3 according to the Day 3 dose escalation criteria (Table 3.2.2-2).

When all (No. 1 to No. 4) of the Day 3 dose escalation criteria are met, the dose will be increased to 16 mg. When any of the Day 3 dose escalation criteria are not met, the dose for Day 3 onward will remain at 8 mg.

Table 3.2.2-2 Day 3 Dose Escalation Criteria

1	An adequate response is absent. 1) Body weight did not decrease as compared with predose on Day 2 with no improvement in congestive symptoms.
2	The serum sodium concentration at predose on Day 3 is ≤147 mEq/L.[a]
3	An increase of >10 mEq/L in serum sodium concentration is not evident within 24 hours after the start of IMP administration on Day 2.[a]
4	No safety concerns have arisen since the start of IMP administration on Day 2 at the discretion of the investigator or subinvestigator.

[a]If serum sodium concentration measurement is difficult to perform at the trial site, plasma sodium concentrations will be used for the assessment.

[Rationale for the Day 2 dose escalation criteria]

1. The results from the OPC-61815 8-mg group, the OPC-61815 16-mg group, and the tolvaptan 15-mg group of the phase 2 clinical pharmacology trial (Trial 263-102-00001) showed that the mean changes in body weight from baseline to the day after the final IMP administration of 5-day treatment were −2.0 kg and −1.1 kg, respectively, in subjects with a >500 mL change in daily urine volume from baseline to Day 2 (from the start of administration on Day 1 to predose on Day 2) and in those with a ≤500 mL change. This finding suggested that the decrease in body weight (the primary efficacy endpoint in the present trial) might be smaller in subjects in whom the change in daily urine volume from baseline to Day 2 was as small as ≤500 mL.

   However, in some of the subjects with a >500 mL increase in daily urine volume from baseline to Day 2, body weight did not decrease from the previous day with no improvement in congestive symptoms, suggesting an insufficient improvement of volume overload; therefore, this criterion is set to enroll such subjects as well.

2. This criterion is set because the upper limit of reference range of serum sodium concentration is 147 mEq/L.

3. In the treatment of hyponatremia, there is a concern regarding the increased risk of osmotic demyelination syndrome due to a rapid increase in serum sodium concentration, and an alert has been indicating that the increase in serum sodium concentration should be ≤10 mEq/L per 24 hours; therefore, this criterion is set.

4. This criterion is based on safety considerations.

[Rationale for the Day 3 dose escalation criteria]

1. No decrease in body weight combined with no improvement in congestive symptoms as compared with the previous day is considered to indicate an insufficient improvement in volume overload; therefore, this criterion is set.

2 to 4. Same as the Day 2 dose escalation criteria

3.2.3 Treatment Duration

The maximum duration of treatment will be 5 days; however, IMP treatment may be ended at a treatment period of shorter than 5 days at the discretion of the investigator or subinvestigator, if either of the following criteria is met:

- All congestive symptoms are resolved and no further improvement in volume overload is necessary.
- The subject becomes capable of fluid management by oral intake alone.

[Rationale for the treatment duration]

The maximum treatment duration in this trial is 5 days, which is the same as that in the phase 3 confirmatory trial (Trial 263-102-00003).

If all congestive symptoms disappear and further improvement in volume overload is judged unnecessary by the investigator or subinvestigator, IMP treatment will be ended because no additional diuretic treatment is required. In addition, if fluid control by oral intake alone is attained during the treatment period, IMP treatment will be ended because the subject is judged to have recovered from difficulty in or incapability of oral intake.

3.3 Trial Population

3.3.1 Number of Subjects and Description of Population

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

3.3.2 Subject Selection and Numbering

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

3.4 Eligibility Criteria

3.4.1 Informed Consent

Informed consent will be freely obtained from all subjects. The informed consent form (ICF) will be approved by the same institutional review board (IRB) that approves this protocol.

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

Investigators or subinvestigators may discuss trial availability and the possibility for entry with a potential subject without first obtaining consent. However, informed consent must be obtained and documented prior to initiation of any procedures that are performed solely for the purpose of determining eligibility for research, including withdrawal from current medication(s).

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

Once the appropriate essential information has been provided and fully explained in layman's language to the subject by the investigator or subinvestigator, the IRB-approved written ICF will be signed and dated by both the subject and the person obtaining consent (investigator or subinvestigator), as well as by the trial coordinator, if he/she provides supplemental explanation. If the subject is able to consent but unable to sign the ICF for physical or therapeutic reasons, a witness should be present with the subject during the course of informed consent. To prove that the subject has been fully informed and has expressed his/her voluntary consent, the witness must sign and date the ICF, and write the name of the subject, the reason(s) that the subject is not able to personally sign the ICF, and the relationship between the subject and the witness in the margin of the ICF, while the signature section of the ICF should be left blank. The witness should be a person who

is independent of the trial and who cannot be unfairly influenced by persons involved with the trial. The subject will receive a copy of the written information and the signed ICF; the original shall be kept on file by the investigator or subinvestigator.

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

Deoxyribonucleic acid (DNA) storage is optional. Subjects who do not consent to DNA storage may participate in the trial.

Subjects must agree to restrictions to concomitant medications as described in Section 4.1.

Subjects who have consented to participation in the trial, but who does not receive IMP are permitted to be re-screened once. In the event that the screening examination is repeated, a new ICF signed by the subject must be obtained and a new subject identifier will be assigned to the subject (see Section 3.9).

3.4.2 Inclusion Criteria

Subjects must meet all of the inclusion criteria in Table 3.4.2-1.

Table 3.4.2-1 Inclusion Criteria

1	Patients receiving loop diuretic injection at a dose equivalent to furosemide 20 mg/day or higher
2	CHF patients in whom lower limb edema, pulmonary congestion, and/or jugular venous distension due to volume overload is present
3	Male or female patients age 20 to 85, inclusive, at time of informed consent
4	Patients who are judged by the investigator or subinvestigator to have difficulty or be incapable of oral intake, including patients who are judged by the investigator or subinvestigator to require nothing by mouth (NPO) management
5	Patients who are currently hospitalized or who are capable of being hospitalized from the time of informed consent until the end of the treatment period
6	Patients who are capable of giving informed consent

[Rationale for the inclusion criteria]

1 This criterion is set to enroll patients who have volume overload despite having received diuretics other than vasopressin antagonists.

2 Volume overload may be manifested by lower limb edema, pulmonary congestion, jugular venous distension, hepatomegaly, and cardiac third sound. Among these manifestations, lower limb edema, pulmonary congestion, and jugular venous distension are selected for the inclusion criterion, because these symptoms are

hardly affected by other factors and were reported by many subjects in a phase 3 trial of tolvaptan (Trial 156-06-002) and a phase 2 trial (Trial 263-102-00001) of OPC-61815 in patients with CHF.

3 Subjects at lower limit of age 20 years are legal adults in Japan and therefore capable of being responsible for their consent. The upper age limit is set at 85 years because many patients with CHF are elderly and also based on safety considerations.

4 This criterion is set to evaluate the safety of OPC-61815 in patients who have difficulty with or are incapable of oral intake.

5 This criterion is set to appropriately evaluate the safety of the IMP.

6 The criterion is set to ensure the ethically appropriate implementation of the trial.

3.4.3 Exclusion Criteria

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

Table 3.4.3-1 Exclusion Criteria

1	Patients who are on a ventricular assist device
2	Patients who have any of the following diseases, complications, or conditions: • Suspected hypovolemia • Hypertrophic cardiomyopathy (excluding dilated phase) • Valvular disease with significant valvular stenosis • Hepatic encephalopathy with difficulty in adequate fluid intake
3	Patients who have experienced acute myocardial infarction within 30 days prior to the screening examination
4	Patients with a definite diagnosis of active myocarditis or amyloid cardiomyopathy
5	Patients who have any of the following medical histories: • History of sustained ventricular tachycardia or ventricular fibrillation within 30 days prior to the screening examination (for patients without an implantable cardioverter defibrillator) • History of cerebrovascular disease (excluding asymptomatic cerebral infarction) within 6 months prior to the screening examination • History of hypersensitivity or idiosyncratic reaction to benzazepines or benzazepine derivatives such as the ingredients of OPC-61815, tolvaptan, mozavaptan hydrochloride, and benazepril hydrochloride
6	Patients who have any of the following diseases, complications, or conditions: • Poorly controlled diabetes mellitus • Anuria • Dysuria associated with urinary tract obstruction, calculus, or tumor
7	Patients with supine systolic blood pressure of <90 mmHg
8	Patients with any of the following abnormalities in laboratory test results: • Total bilirubin: >3.0 mg/dL • Serum or plasma creatinine: >3.0 mg/dL • Serum or plasma sodium concentration: <125 mEq/L

Table 3.4.3-1 Exclusion Criteria	
	• Serum or plasma sodium concentration: >147 mEq/L • Serum or plasma potassium concentration: >5.5 mEq/L
9	Patients with current symptoms or a history of hepatic impairment (including patients with aspartate aminotransferase [AST] or alanine aminotransferase [ALT] exceeding 3 times the upper limit of the reference range at the screening examination)
10	Patients who have undergone open-heart surgery (eg, open-heart surgery for valvular disease, coronary bypass surgery, or surgery in thoracic aorta) within 30 days prior to the screening examination
11	Patients who have difficulty with spontaneous respiration or who have been on tracheal intubation under sedative therapy
12	Patients with severe disturbed consciousness (ie, coma or stupor)
13	Women who are breast-feeding or who have a positive pregnancy test result prior to receiving IMP
14	Sexually active men or women of childbearing potential (WOCBP) who do not agree to practice birth control or remain abstinent during the trial and for 30 days after the final IMP administration[a]
15	Patients who are otherwise judged to be ineligible by the investigator or subinvestigator

[a]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.

[Rationale for the exclusion criteria]

1	This criterion is set because the use of a ventricular assist device may affect the safety evaluation of the IMP and with a view toward subject safety.
2	Excessive diuretic treatment may adversely affect these symptoms.
3 to 9	These criteria are based on safety considerations.
10	This criterion is set because the safety, efficacy, and pharmacodynamics of the IMP could not be appropriately evaluated in such patients.
11, 12	These criteria are based on safety considerations.
13 to 15	These criteria are based on general safety and ethical considerations.

3.5 Endpoints

3.5.1 Safety Endpoints

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

[Rationale for the safety endpoints]

Adverse events, clinical laboratory tests, physical examination, vital signs (blood pressure, pulse rate, and body temperature), and 12-lead ECG are commonly used as endpoints of general safety.

3.5.2 Pharmacodynamic Endpoints

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

[Rationale for the pharmacodynamic endpoints]

Urine volume, urine osmolality, urine sodium excretion, urine potassium excretion, serum osmolality, serum sodium concentration, and serum potassium concentration are selected as endpoints to evaluate the aquaretic effect of OPC-61815. Fluid intake and fluid balance are selected to evaluate the impact of aquaresis by OPC-61815 on fluid balance. Tolvaptan, which is the active ingredient of OPC-61815, is an AVP V_2-receptor antagonist; therefore, plasma AVP concentration is selected to evaluate the effects on plasma AVP concentration. Plasma renin activity is selected to evaluate the impact of aquaresis by OPC-61815 on the renin-angiotensin system. The plasma concentrations of BNP, serum concentrations of NT-proBNP and troponin I are selected to evaluate the impact of the aquaretic effect of OPC-61815 on cardiac function.

3.5.3 Efficacy Endpoints

- Body weight
- Congestive symptoms

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

- Dyspnea

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

- New York Heart Association (NYHA) classification

[Rationale for the efficacy endpoints]

Body weight is selected as a measure that objectively reflects the general state of volume overload. Congestive symptoms and dyspnea are selected as symptoms or findings that reflect the volume overload state in patients with CHF. NYHA classification is selected as a measure that assesses subjective physical activity in patients with CHF.

3.6 Measures to Minimize/Avoid Bias

This trial is an uncontrolled trial.

3.7 Trial Procedures

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

Serum sodium and potassium concentrations during the treatment period will be measured at both the central laboratory (central measurement) and the trial site (local measurement). If serum sodium and potassium concentration measurement is difficult to perform at the trial site, plasma sodium and potassium concentrations may be measured. Either serum or plasma should be used consistently for measurement of sodium and potassium concentrations in a given subject. However, serum sodium and potassium concentrations will be measured at the central laboratory. Clinical laboratory tests will be conducted at each trial site for the screening examination, and at the central laboratory from Day 1 onward.

Table 3.7-1 Schedule of Assessments

Item \ Day	Screening	Treatment Period						Follow-up
	Day −1 to Predose of Day 1	1	2	3	4	5	Day 6/ At Withdrawal (Day After Final IMP Administration)	Day 12 to 15 /7 to 10 Days After Final IMP Administration
Informed consent	♦							
Informed consent for DNA storage	○							
Subject background	♦							
Inclusion/exclusion criteria	♦	●						
Confirmation of concomitant medication/therapy	←	—	—	—	—	—	—	→
Subject registration	♦							
Hospitalization	←	—	—	—	—	—	—	
IMP administration		X	X	X	X	X		
Administration of diuretic agents		X	X	X	X	X	X	
Dose escalation[a]			●	●				
Confirmation of IMP compliance		♦	♦	♦	♦	♦		
Cumulative urine volume[b]	←	—	—	—	—	—	→	
Urine volume, fluid intake[b]	←	—	—	—	—	—	→	
Urine sodium and potassium concentrations, urine osmolality[c]	←	—	—	—	—	—	→	
Serum sodium[d] and potassium concentrations[d]	♦	●[e]■	●■[f]	●■[f]	●	●	♦	♦
Serum osmolality		●■	●■[f]	●■[f]	●	●	♦	
Body weight	♦	●[e]	●	●	●	●	♦	♦
Dyspnea[g]	♦	♦	♦	♦	♦	♦	♦	

Table 3.7-1 Schedule of Assessments

Item \ Day	Screening	Treatment Period						Follow-up
	Day −1 to Predose of Day 1	1	2	3	4	5	Day 6/ At Withdrawal (Day After Final IMP Administration)	Day 12 to 15 /7 to 10 Days After Final IMP Administration
Congestive symptoms[h]	♦	♦	♦	♦	♦	♦	♦	♦
Chest x-ray (cardiothoracic ratio, pulmonary congestion)[i]	♦	●					♦	
Adverse events	←	—	—	—	—	—	—	→
Laboratory tests	♦[j]	●					♦	♦
Physical examination	♦	♦	♦	♦	♦	♦	♦	♦
Vital signs (blood pressure, pulse rate, body temperature)	♦	●[e]■	●■[f]	●■[f]	●	●	♦	♦
12-Lead ECG[k]		●■		♦			♦	
NYHA classification	♦						♦	
Biomarkers[l]		●					♦	
Urine pregnancy test (WOCBP only)	♦							♦
Blood sampling for DNA storage[m]		○						
		←	—	—	—	→		
Adjustment of infusion solution[n]								

X = Time of drug administration should not be markedly different on each day; ● = Before start of IMP administration; ■ = For measurements on Day 1 and the day of dose escalation assessment, see the corresponding time points after start of IMP administration as specified in Section 3.7.1.2 and Section 3.7.1.5; ♦ = At a feasible time (on Day 1, at a feasible time after start of IMP administration); ○ = Optional (subjects at sites with a DNA storage agreement who have given informed consent for DNA storage prior to start of the trial)

[a]Dose escalation assessment: Required on Day 2, performed on Day 3 if applicable

[b]Measurements of cumulative urine volume, urine volume, and fluid intake (with oral intake and intake via transfusions, nasogastric feeding tubes, and gastronomy tubes): Time intervals for measurement of cumulative urine volume (Table 3.7.5.1.1-1) and urine volume (Table 3.7.5.1.1-2) are set on Day 1

and the day of dose escalation. Cumulative urine volume and urine volume will be measured for each time interval as specified in Section 3.7.1.2 and Section 3.7.1.5. From Days 2 onwards, except the day of dose escalation, cumulative urine will be collected for 24 hours from the time of complete urination at predose and daily urine volume and fluid intake will be measured for that time interval.

[c]Urine sodium and potassium concentrations, and urine osmolality: Urine samples collected at each cumulative urine collection time interval as shown in Table 3.7.5.1.1-1 will be centrally measured by the contract research organization for clinical laboratory tests (central laboratory).

[d]Serum sodium and potassium concentrations: Measured both at the central laboratory and at the trial site for appropriate fluid management. If serum sodium and potassium concentration measurement is difficult to perform at the trial site, plasma sodium and potassium concentrations may be measured. Either serum or plasma samples should be used consistently for measurement of sodium and potassium concentrations in a given subject. However, serum sodium and potassium concentrations will be measured in the central laboratory. (At screening, serum or plasma sodium and potassium concentrations will be measured only at the trial site.)

[e]Serum sodium concentration (local measurement), serum potassium concentration (local measurement), body weight, chest x-ray, and vital signs (blood pressure, pulse rate, and body temperature): If measurements are performed on Day 1 as part of the screening examination, the measurements do not have to be repeated at predose on Day 1.

[f]Performed on the day that the dose is increased to 16 mg.

[g]Dyspnea: Respiratory rate, paroxysmal nocturnal dyspnea, orthopnea, and subject-assessed dyspnea (assessment of presence or absence of symptoms by subjects at screening)

[h]Congestive symptom findings: Lower limb edema, hepatomegaly, jugular venous distension, pulmonary rales, and cardiac third sound

[i]Chest x-ray: Chest x-ray does not have to be repeated if it has been performed within 24 hours before informed consent. The results of chest x-ray performed prior to the acquisition of informed consent can be used to determine eligibility of the subject to participate in the trial.

[j]Laboratory tests: At screening, laboratory tests are performed at the trial site.

[k] If the serum potassium is confirmed to exceed 5.5 mEq/L at the trial site or the central laboratory at any time point in the period with no specified 12-lead ECG, a 12-lead ECG will be performed as an unscheduled examination.

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

[m]DNA storage: In principle, blood sampling for DNA storage will be performed at predose on the day of initial IMP administration (Day 1). Informed consent for DNA storage must be obtained by the blood sampling for DNA storage. If blood sampling is not performed at that time or needs to be repeated, blood sampling will be performed at a feasible time during the trial period.

[n]The infusion solution will be checked and adjusted according to the specifications for each day (see Section 3.7.1.2 to Section 3.7.1.6).

3.7.1 Schedule of Assessments

3.7.1.1 Screening Period (Day −1 to Predose on Day 1)

3.7.1.1.1 Screening Examination

Between Day −1 and predose on Day 1, the investigator or subinvestigator will obtain consent from the subject, and then conduct the following examinations and tests to assess the eligibility of the subject for participation in the trial.

[Examinations and tests]

- Subject background
  (Birth date, sex, height, country, race, ethnicity, underlying disease, type of heart failure, presence and type of arrhythmias, presence of a pacemaker, presence of an implantable cardioverter defibrillator, complications, medical history, and reason(s) why oral intake is considered to be difficult or impossible)
- Serum sodium concentration (local measurement)
- Serum potassium concentration (local measurement)
- Body weight
- Dyspnea (respiratory rate, paroxysmal nocturnal dyspnea, orthopnea, and subject-assessed dyspnea [assessment of the presence of the symptoms by the subject])
- Congestive symptoms (lower limb edema, hepatomegaly, jugular venous distension, pulmonary rales, and cardiac third sound)
- Chest x-ray (cardiothoracic ratio and pulmonary congestion)
  Chest x-ray does not have to be repeated if it has been performed within 24 hours before informed consent. The results of chest x-ray performed prior to the acquisition of informed consent can be used to determine the eligibility of the subject to participate in the trial.
- Clinical laboratory tests (local measurement)
- Physical examination
- Vital signs (blood pressure, pulse rate, and body temperature)
- NYHA classification
- Concomitant medications and therapies
- Urine pregnancy test (WOCBP only)

Date of informed consent, subject identifier, the result of eligibility assessment, and subject characteristics will be recorded in the eCRF. Subjects must be hospitalized from the time of informed consent through the completion (withdrawal) assessment.

3.7.1.1.2 Urine Collection, and Measurement of Urine Volume and Fluid Intake

1) Urine Collection

Subject are required to urinate completely at 24 hours before start of IMP administration on Day 1 and urine collection will be started to measure the daily urine volume through immediately predose on Day 1.

2) Urine Volume and Fluid Intake

At the same interval as the urine collection, urine volume and fluid intake (with oral intake and intake via transfusions, nasogastric feeding tubes, and gastronomy tubes) will be determined.

If the time interval between informed consent to the start of IMP administration is <24 hours, subject are required to urinate completely at a feasible time after informed consent, at which time urine collection will start and continue until immediately before start of IMP administration on Day 1. Urine volume and fluid intake will be determined as follows:

Urine volume and fluid intake for the 24 hours immediately before start of IMP administration on Day 1 during which the subject is receiving injectable loop diuretics will be determined. The measurement period (the dates and times that measurement started and ended), urine volume, and fluid intake will be identified based on the medical record or other records before informed consent (after loop diuretic therapy started).

3.7.1.2 Treatment Period (Day 1)

1) Predose
   - Urine sodium concentration (central measurement)
   - Urine osmolality (central measurement)
   - Urine potassium concentration (central measurement)
   - Serum sodium concentration (local measurement, central measurement)
   - Serum potassium concentration (local measurement, central measurement)
   - Serum osmolality (central measurement)
   - Biomarkers (central measurement)
   - Body weight
   - Chest x-ray (cardiothoracic ratio and pulmonary congestion)
   - Clinical laboratory tests (central measurement)
   - Vital signs (blood pressure, pulse rate, and body temperature)

- 12-Lead ECG
- Blood sampling for DNA storage (central measurement)

If serum sodium concentration (local measurement), serum potassium concentration (local measurement), body weight, chest x-ray, and vital signs (blood pressure, pulse rate, and body temperature) are measured as the screening examination on Day 1, the measurements will not need to be repeated at predose on the same day.

2) Start of urine collection

Subject are required to urinate completely immediately before start of IMP administration to collect urinate at the time intervals shown in Table 3.7.1.2-1. At the end of each interval, subject are required to urinate completely to start urine collection for the next interval.

Table 3.7.1.2-1 Urine Collection Intervals After Start of IMP administration on Day 1

Urine collection interval	Allowable time window for the interval end
0 to 4 hours after start of IMP administration	+1 hour
4 to 8 hours after start of IMP administration	+4 hours
8 hours after start of IMP administration to immediately before IMP administration on the next day	

3) IMP administration

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

4) Administration of diuretic agents

5) Examinations and tests after start of IMP administration

The examinations and tests shown in Table 3.7.1.2-2 will be conducted at each time point.

Table 3.7.1.2-2 Examinations/Tests and Timing After Start of IMP Administration on Day 1

Item	Timing	Allowable time window
Urine volume and fluid intake	0 to 1 hour after start of IMP administration	+15 minutes[a]
	1 to 2 hours after start of IMP administration	+30 minutes[a]
	2 to 4 hours after start of IMP administration	+1 hour[a]
	4 to 6 hours after start of IMP administration	+1 hour[a]
	6 to 8 hours after start of IMP administration	+4 hours[a]
	8 hours after start of IMP administration to immediately before start of IMP administration on the next day	
Urine sampling for the measurement of urine sodium concentration, urine potassium concentration, and urine osmolality	At the end of each urine collection interval shown in Table 3.7.1.2-1	
12-Lead ECG	1 hour after start of IMP administration	+1 hour
Vital signs (blood pressure, pulse rate, and body temperature)	1 hour after start of IMP administration	+1 hour
	4 hours after start of IMP administration	+1 hour
	8 hours after start of IMP administration	+4 hours
Serum osmolality, serum sodium concentration, and serum potassium concentration (Serum sodium and potassium concentrations will be measured also at the trial site.)	4 hours after start of IMP administration	+1 hour
	8 hours after start of IMP administration	+4 hours

[a]Allowable time window for the end of each interval

6) At a feasible time after start of IMP administration
   - Dyspnea (respiratory rate, paroxysmal nocturnal dyspnea, orthopnea, and subject-assessed dyspnea)
   - Congestive symptoms (lower limb edema, hepatomegaly, jugular venous distension, pulmonary rales, and cardiac third sound)
   - Physical examination
   - Adverse Events
   - Concomitant medications and therapies
   - Confirmation of IMP compliance
7) Adjustment of infusion solution

Infusion solution will be checked and adjusted at least 3 times to correct electrolyte abnormalities based on the blood pressure, pulse rate, body weight, serum sodium

concentration, serum potassium concentration, urine volume, fluid intake, and other parameters measured before, and at 4 and 8 hours after start of IMP administration.

3.7.1.3 Treatment Period (Day 2)

1) Predose
   - Urine sodium concentration (central measurement)
   - Urine osmolality (central measurement)
   - Urine potassium concentration (central measurement)
   - Serum sodium concentration (local measurement, central measurement)
   - Serum potassium concentration (local measurement, central measurement)
   - Serum osmolality (central measurement)
   - Body weight
   - Vital signs (blood pressure, pulse rate, and body temperature)
2) Start of urine collection

Subject are required to urinate completely immediately before start of IMP administration and urine collection will start.

3) Dose escalation decision

Eligibility for dose escalation will be assessed as described in Section 3.2.2.

4) IMP administration
5) Administration of diuretic agents
6) 4 and 8 hours after the start of IMP administration (only when the dose is increased on Day 2)

In addition to the examinations and tests scheduled for Day 2, the procedures shown in Section 3.7.1.5 will be conducted.

7) At a feasible time on Day 2
   - Dyspnea (respiratory rate, paroxysmal nocturnal dyspnea, orthopnea, and subject-assessed dyspnea)
   - Congestive symptoms (lower limb edema, hepatomegaly, jugular venous distension, pulmonary rales, and cardiac third sound)
   - Physical examination
   - Adverse Events
   - Concomitant medications and therapies
   - Confirmation of IMP compliance
8) Adjustment of infusion solution

Infusion solution will be checked and adjusted at least once to correct electrolyte abnormalities based on the blood pressure, pulse rate, body weight, serum sodium

concentration, serum potassium concentration, urine volume, fluid intake, and other parameters measured before start of IMP administration.

3.7.1.4 Treatment Period (Day 3)

1) Predose
   - Urine sodium concentration (central measurement)
   - Urine osmolality (central measurement)
   - Urine potassium concentration (central measurement)
   - Serum sodium concentration (local measurement, central measurement)
   - Serum potassium concentration (local measurement, central measurement)
   - Serum osmolality (central measurement)
   - Body weight
   - Vital signs (blood pressure, pulse rate, and body temperature)
2) Start of urine collection

Subject are required to urinate completely immediately before start of IMP administration and urine collection will start.

3) Dose escalation decision (see Figure 3.2.1-1 only when required)

If applicable, eligibility for dose escalation will be reassessed as described in Section 3.2.2.

4) IMP administration
5) Administration of diuretic agents
6) 4 and 8 hours after the start of IMP administration (only when the dose is increased on Day 3)

In addition to the examinations and tests scheduled for Day 3, the procedures shown in Section 3.7.1.5 will be conducted.

7) At a feasible time on Day 3
   - Dyspnea (respiratory rate, paroxysmal nocturnal dyspnea, orthopnea, and subject-assessed dyspnea)
   - Congestive symptoms (lower limb edema, hepatomegaly, jugular venous distension, pulmonary rales, and cardiac third sound)
   - Physical examination
   - 12-Lead ECG
   - Adverse Events
   - Concomitant medications and therapies
   - Confirmation of IMP compliance

8) Adjustment of infusion solution

Infusion solution will be checked and adjusted at least once to correct electrolyte abnormalities based on the blood pressure, pulse rate, body weight, serum sodium concentration, serum potassium concentration, urine volume, fluid intake, and other parameters measured before start of IMP administration.

3.7.1.5 Dose Escalation Day (Day 2 or Day 3)

On the day on which the dose is increased (the first day OPC-61815 is administered at 16 mg), the following examinations and tests will be conducted.

1) Urine Collection

Urine will be collected at the intervals shown in Table 3.7.1.5-1. At the end of each interval, subject are required to urinate completely to start urine collection for the next interval.

Table 3.7.1.5-1 Urine Collection Intervals on the Dose Escalation Day

Urine collection interval	Allowable time window for the interval end
0 to 4 hours after start of IMP administration	+1 hour
4 to 8 hours after start of IMP administration	+4 hours
8 hours after start of IMP administration to immediately before IMP administration on the next day	

2) Examinations and tests after start of IMP administration

In addition to the procedures scheduled for each day, the examinations and tests shown in Table 3.7.1.5-2 will be conducted at each time point.

Table 3.7.1.5-2 Examinations/Tests and Timing on the Dose Escalation Day		
Item	**Timing**	**Allowable time window**
Urine volume and fluid intake	0 to 4 hours after start of IMP administration	+1 hour[a]
	4 to 8 hours after start of IMP administration	+4 hours[a]
	8 hours after start of IMP administration to immediately before start of IMP administration on the next day	
Urine sampling for the measurement of urine sodium concentration, urine potassium concentration, and urine osmolality	At the end of each urine collection interval shown in Table 3.7.1.5-1	
Vital signs (blood pressure, pulse rate, and body temperature)	4 hours after start of IMP administration	+1 hour
	8 hours after start of IMP administration	+4 hours
Serum osmolality, serum sodium concentration, and serum potassium concentration (Serum sodium and potassium concentrations will also be measured at the trial site.)	4 hours after start of IMP administration	+1 hour
	8 hours after start of IMP administration	+4 hours

[a]Allowable time window for the end of each interval

3) Adjustment of infusion solution

The following procedure will be added to the procedures scheduled for each day.

Infusion solution will be checked or adjusted at least twice after start of IMP administration to correct electrolyte abnormalities based on the blood pressure, pulse rate, body weight, serum sodium concentration, serum potassium concentration, urine volume, fluid intake, and other parameters measured at 4 and 8 hours after start of IMP administration.

3.7.1.6 Treatment Period (Days 4 and 5)

1) Predose

- Urine sodium concentration (central measurement)
- Urine osmolality (central measurement)
- Urine potassium concentration (central measurement)
- Serum sodium concentration (local measurement, central measurement)
- Serum potassium concentration (local measurement, central measurement)
- Serum osmolality (central measurement)
- Body weight
- Vital signs (blood pressure, pulse rate, and body temperature)

2) Start of urine collection

Subject are required to urinate completely immediately before start of IMP administration and urine collection will start.

3) IMP administration
4) Administration of diuretic agents
5) At a feasible time on each day
   - Dyspnea (respiratory rate, paroxysmal nocturnal dyspnea, orthopnea, and subject-assessed dyspnea)
   - Congestive symptoms (lower limb edema, hepatomegaly, jugular venous distension, pulmonary rales, and cardiac third sound)
   - Physical examination
   - Adverse Events
   - Concomitant medications and therapies
   - Confirmation of IMP compliance
6) Adjustment of infusion solution

Infusion solution will be checked and adjusted at least once to correct electrolyte abnormalities based on the blood pressure, pulse rate, body weight, serum sodium concentration, serum potassium concentration, urine volume, fluid intake, and other parameters measured before start of IMP administration.

3.7.1.7 Treatment Period (Completion Assessment on Day 6 or Withdrawal Assessment)

The investigator or subinvestigator will conduct the completion assessment at a feasible time on Day 6 as described below. If IMP administration is discontinued before Day 5, the same assessment as the completion assessment on Day 6 will be conducted as the withdrawal assessment on the day after the final IMP administration, whenever possible.

1) At the end of urine collection
   - Urine sodium concentration (central measurement)
   - Urine osmolality (central measurement)
   - Urine potassium concentration (central measurement)
2) At a feasible time
   - Serum sodium concentration (local measurement, central measurement)
   - Serum potassium concentration (local measurement, central measurement)
   - Serum osmolality (central measurement)
   - Biomarkers (central measurement)
   - Body weight

- Dyspnea (respiratory rate, paroxysmal nocturnal dyspnea, orthopnea, and subject-assessed dyspnea)
- Congestive symptoms (lower limb edema, hepatomegaly, jugular venous distension, pulmonary rales, and cardiac third sound)
- Chest x-ray (cardiothoracic ratio and pulmonary congestion)
- Clinical laboratory tests (central measurement)
- Physical examination
- Vital signs (blood pressure, pulse rate, and body temperature)
- 12-Lead ECG
- NYHA classification
- Adverse Events
- Concomitant medications and therapies

3.7.1.8 Follow-up After End of the Treatment Period (7 to 10 Days After the Final IMP Administration)

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

- Serum sodium concentration (central measurement)
- Serum potassium concentration (central measurement)
- Body weight
- Congestive symptoms (lower limb edema, hepatomegaly, jugular venous distension, pulmonary rales, and cardiac third sound)
- Clinical laboratory tests (central measurement)
- Physical examination
- Vital signs (blood pressure, pulse rate, and body temperature)
- Adverse Events
- Urine pregnancy test (WOCBP only)
- Concomitant medications and therapies

3.7.2 Safety Assessments

3.7.2.1 Adverse Events

Refer to Section 5, Reporting of Adverse Events.

3.7.2.2 Clinical Laboratory Assessments

Venous blood and urine samples for clinical laboratory tests (Table 3.7.2.2-1) will be collected at the prespecified time points, and the date and time of blood sampling and urine collection will be recorded in the source document.

At the screening examination, clinical laboratory tests will be conducted at the trial site according to the procedures specified by the site. The status (collected/not collected), the dates and times of blood sampling and urine collection, and the results of measurements will be recorded in the eCRF.

From Day 1 onward, the samples will be shipped to the central laboratory. The central laboratory will measure the prespecified laboratory parameters according to the procedures specified by the laboratory and provide the results of the measurements to the sponsor and the investigator or subinvestigator. The status (collected/not collected), the date and time of blood sampling and urine collection will be recorded in the eCRF. The electronic file submitted to the sponsor by the central laboratory will be regarded as the source document; therefore, entry of the results in the eCRF will be unnecessary.

Serum sodium and potassium concentrations will also be measured at the trial site for appropriate fluid management during the screening and treatment periods. The status (measured/not measured), the date and time of blood sampling, and the result of measurement of the serum sodium concentrations and potassium concentrations during the screening period will be recorded in the source document and the eCRF, and those of the serum potassium concentrations during the treatment period will be recorded in the source document. If serum sodium and potassium concentration measurement is difficult to perform at the trial site, plasma sodium and potassium concentration may be measured. Either serum or plasma should be used consistently for measurement of sodium and potassium concentrations in a given subject. However, serum sodium and potassium concentrations will be measured at the central laboratory. If the serum potassium is confirmed to exceed 5.5 mEq/L at the trial site or the central laboratory at any time point in the period with no specified 12-lead ECG, a 12-lead ECG will be performed in reference to Section 3.7.2.4.

Table 3.7.2.2-1 Clinical Laboratory Assessments

Hematology Red Blood Cell count Hemoglobin Hematocrit White Blood Cell count with differential (neutrophils, eosinophils, basophils, monocytes, and lymphocytes) Platelet count	**Serum Chemistry** Total protein Albumin Total bilirubin AST ALT Alkaline phosphatase γ-Glutamyl transpeptidase Lactate dehydrogenase Creatine kinase (creatine phosphokinase) Glucose Total cholesterol Triglycerides Blood urea nitrogen Creatinine Uric acid Serum or plasma electrolytes (sodium [Na], potassium [K], chloride [Cl], calcium [Ca])
Urinalysis (qualitative) pH Protein Glucose Occult blood Ketone bodies Bilirubin Urobilinogen	
Additional tests Pregnancy test for WOCBP (hCG test)[a]	

hCG = human chorionic gonadotropin

[a]A urine pregnancy test will be conducted at screening and follow-up. If the urine pregnancy test is positive, a serum test will be conducted at the central laboratory as described in Section 5.5.

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

3.7.2.3 Physical Examination and Vital Signs

1) Physical examination

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

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

3.7.2.4 Electrocardiogram Assessments

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

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

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

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

3.7.3 Efficacy Assessments

3.7.3.1 Body Weight

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

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

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

1) Lower limb edema

The tibial border or dorsum pedis, in principle, will be examined for the presence of edema with the subject seated or placed supine, and the severity of edema will be assessed according to the criteria shown in Table 3.7.3.2-1. The body position used during the examination of lower limb edema must not be changed throughout the trial period.

Table 3.7.3.2-1 Criteria for Assessment of Lower Limb Edema

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

2) Jugular venous distension

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

3) Hepatomegaly

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

4) Pulmonary rales

The presence of pulmonary rales will be checked by auscultation.

5) Cardiac third sound

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

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

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

1) Cardiothoracic ratio

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

2) Pulmonary congestion

The investigator or subinvestigator will assess the severity of pulmonary congestion according to the criteria shown in Table 3.7.3.3-1, and record the result of the assessment in the source document and the eCRF.

Table 3.7.3.3-1 Criteria for Assessment of Pulmonary Congestion

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

Adapted from Forrester JS, *et al*.[9]

3.7.3.4 Dyspnea

1) Respiratory rate

The respiratory rate per minute will be measured with the subject seated or placed supine, and the status (measured/not measured) the date, and the result of measurement will be recorded in the source document and the eCRF. The body position while respiratory rate is measured must not be changed throughout the trial period.

2) Paroxysmal nocturnal dyspnea

The presence of paroxysmal nocturnal dyspnea (a sensation of shortness of breath that occurs during sleep and awakens the subject) will be checked by interview.

3) Orthopnea

The presence of orthopnea will be checked by interview.

4) Subject-assessed dyspnea

During the screening period, the subject will personally check for the presence of dyspnea symptoms. From Day 1 onward, the subject will assess the current dyspnea symptoms as compared with his/her own assessment in the screening period using the 7-level Likert scale shown below. If no dyspnea symptoms are present in the screening period, one of the following categories will be chosen on Day 1 onward: "markedly deteriorated," "moderately deteriorated," "mildly deteriorated," or "unchanged."

- Markedly deteriorated
- Moderately deteriorated
- Mildly deteriorated
- Unchanged
- Mildly improved
- Moderately improved
- Markedly improved

The investigator or subinvestigator will ask the following question: "How severe is your current respiratory status as compared with the respiratory discomfort you sensed immediately before the start of the initial IMP administration?"

The status (assessed/not assessed), date of assessment, presence of dyspnea symptoms (paroxysmal nocturnal dyspnea and orthopnea), and result of subject-assessed dyspnea will be recorded in the source document and the eCRF.

3.7.3.5 NYHA Classification

The investigator or subinvestigator will assess the NYHA classification[2] and record the date and result of the assessment in the source document and the eCRF.

Table 3.7.3.5-1 NYHA Classification	
Functional capacity	
Class I	Patients with cardiac disease, but without resulting in a limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Patients with cardiac disease resulting in a mild or moderate limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Patients with cardiac disease resulting in a marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Patients with cardiac disease resulting in an inability to carry on any physical activity. Symptoms of heart failure or anginal syndrome may be present, even at rest. If any physical activity is undertaken, discomfort is increased.

3.7.4 Prior and Concomitant Medications

The investigator or subinvestigator will record all concomitant medications and therapies taken by the subject from the time of informed consent through the post-treatment follow-up assessment in the eCRF. The investigator or subinvestigator will also record all medications and therapies taken by the subject for treatment of an AE or which caused an AE, until the end of the trial (defined as the last schedule visit/contact or final contact attempt with the last subject) on the eCRF.

For concomitant medications, the following information will be recorded in the eCRF: medication, indication, dose, frequency, route, start date, and end date. For concomitant therapies, the following information will be recorded in the eCRF: therapy, indication, start date, and end date.

3.7.5 Pharmacodynamic and Pharmacogenomic Assessments

3.7.5.1 Pharmacodynamic Assessment

3.7.5.1.1 Urine Volume

In this trial, urine collection intervals and urine volume measurement intervals will be defined separately.

1) Urine collection interval

Urine collection intervals are shown in Table 3.7.5.1.1-1. At the end of each urine collection interval, subjects are required to urinate completely.

Table 3.7.5.1.1-1 Urine Collection Intervals

Time point	Start of the interval	End of the interval	Allowable time window for the interval end
Day −1	23 to 25 hours before start of IMP administration on Day 1	Point in time at which urination immediately before start of IMP administration is completed	
Day 1 and the dose escalation day	Point in time at which urination immediately before start of IMP administration is completed	4 hours after start of IMP administration	+1 hour
	4 hours after start of IMP administration	8 hours after start of IMP administration	+4 hours
	8 hours after start of IMP administration	Immediately before IMP administration on the next day[a]	
Day 2 and onward (except for the dose escalation day)	Point in time at which urination immediately before start of IMP administration is completed	Immediately before IMP administration on the next day[a]	

[a]Or 24 hours (allowable time window, ±1 hour) after the complete urination immediately before start of the final IMP administration, if not applicable

2) Urine volume measurement intervals

Urine volume will be measured at the intervals shown in Table 3.7.5.1.1-2, and the status (measured/not measured), the dates and times the measurement started and ended, and the result of measurement will be recorded in the source document and the eCRF.

Table 3.7.5.1.1-2 Urine Volume Measurement Intervals

Time point	Measurement interval	Allowable time window for the interval end
Day −1	Same as the urine collection interval (daily urine volume)	
Day 1	Point in time at which urination immediately before IMP administration is completed to 1 hour after start of IMP administration	+15 minutes
	1 to 2 hours after start of IMP administration	+30 minutes
	2 to 4 hours after start of IMP administration[a]	+1 hour
	4 to 6 hours after start of IMP administration	+1 hour
	6 to 8 hours after start of IMP administration[a]	+4 hours
	8 hours after start of IMP administration to immediately before IMP administration on the next day[a]	
Dose escalation day	Point in time at which urination immediately before IMP administration is completed to 4 hour after start of IMP administration[a]	+1 hour
	4 to 8 hours after start of IMP administration[a]	4 hours
	8 hours after start of IMP administration to immediately before IMP administration on the next day[a]	
Day 2 and onward (except the dose escalation day)	Same as the urine collection interval (daily urine volume)	

[a]Urine volume will be measured after urination at the end of the urine collection period is completed.

If the exact urine volume cannot be measured because part of the urine is discarded or for other reasons, the urine volume for that interval will be handled as missing data. If a diaper or an incontinence pad is used by necessity, urine volume may be estimated by comparing the weight of the diaper or incontinence pad before and after use (converting 1 gram to 1 milliliter).

The daily urine volume on Day 1 or the dose escalation day will be the sum of the urine volumes for all the measurement intervals on that day (the daily urine volume will be calculated by the sponsor; therefore, entry in the eCRF will be unnecessary).

3.7.5.1.2 Fluid Intake

At the same interval as urine volume measurement, fluid intake (with oral intake and intake via transfusions, nasogastric feeding tubes, and gastronomy tubes) will be measured, and the status (measured/not measured), the dates and times the measurement started and ended, and the result of measurement will be recorded in the source document and the eCRF.

The daily fluid intake on Day 1 or the dose escalation day will be the sum of the fluid intakes for all the measurement intervals on that day (the daily fluid intake will be calculated by the sponsor; therefore, entry in the eCRF will be unnecessary).

3.7.5.1.3 Fluid Balance

A fluid balance will be calculated by subtracting the "urine volume" from the "fluid intake." Fluid balances will be calculated by the sponsor; therefore, entry in the eCRF will be unnecessary.

3.7.5.1.4 Serum Sodium Concentration, Serum Potassium Concentration, Serum Osmolality, and Biomarkers (Plasma AVP Concentration, Plasma Renin Activity, Plasma BNP Concentration, Serum NT-proBNP Concentration, and Serum Troponin I Concentration)

At the specified time points, venous blood will be collected for the following examinations and tests, and the date and time of blood sampling will be recorded in the source document and the eCRF.

- Serum sodium concentration
- Serum potassium concentration
- Serum osmolality
- Biomarkers (plasma AVP concentration, plasma renin activity, plasma BNP concentration, serum NT-proBNP concentration, and serum troponin I concentration)

For the procedures for sample collection, processing, and storage, see Appendix 1.

All the samples will be shipped to the central laboratory. The central laboratory will centrally measure the laboratory parameters according to the procedures specified by the laboratory and report the results of the measurements to the sponsor and the investigator or subinvestigator. An electronic file containing the measurement results will be provided to the sponsor from the central laboratory; therefore, entry in the eCRF will be unnecessary.

In addition to the serum sodium and potassium measurement at central laboratory, serum sodium and potassium concentrations will also be measured at the trial site for appropriate fluid management during the screening and treatment periods and the results of the local measurements will be recorded in the source document. The result of the serum sodium concentration measurement will also be recorded in the eCRF. If serum sodium and potassium concentration measurement is difficult to perform at the trial site, plasma sodium and potassium concentrations may be measured. Either serum or plasma

samples should be used consistently for measurement of sodium and potassium concentrations in a given subject. However, serum sodium and potassium concentrations will be measured in the central laboratory.

Serum sodium and potassium concentrations for pharmacodynamic assessment will be replaced by the data obtained as part of the clinical laboratory tests performed at the same blood sampling point as specified in Section 3.7.2.2.

3.7.5.1.5 Urine Sodium Excretion, Urine Potassium Excretion, and Urine Osmolality

1) Measurements at the central laboratory

From the urine collected for each interval shown in Table 3.7.5.1.1-1, a sample will be taken. For the procedures for sample collection, processing, and storage, see Appendix 1.

All the samples will be shipped to the central laboratory. The central laboratory will centrally measure the laboratory parameters according to the procedures specified by the laboratory and report the results of the measurements to the sponsor and the investigator or subinvestigator. The original document for the measurement results is an electronic file provided to the sponsor from the central laboratory; therefore, entry of the measurement results in the eCRF will be unnecessary.

If urine collection for measuring daily urine volume cannot be made because part of the urine is discarded or for other reasons, no sample will be shipped to the central laboratory. The urine sodium concentration, urine potassium concentration, and urine osmolality on that day will be handled as missing data.

2) Urine sodium excretion and urine potassium excretion

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

Urine sodium and potassium excretions will be calculated by the sponsor; therefore, entry in the eCRF will be unnecessary.

3.7.5.2 Pharmacogenomic Assessment

3.7.5.2.1 DNA Storage

1) Rationale for DNA Storage

In this trial, DNA samples will be stored on a voluntary basis. DNA storage will be conducted on subjects who provide written consent, only at trial sites that provide prior agreement regarding DNA storage.

In Q&A 1 in the "Clinical Trials using Pharmacogenomics" (PFSB/ELD Notification No. 0930007 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare [MHLW] dated 30 Sep 2008)[10], the MHLW states that DNA samples for possible genomic/genetic analysis to evaluate the IMP (PK, efficacy, safety, etc.) may be collected from subjects during the clinical trial in either of the following cases: 1) the target and timing of the potential genomic/genetic analysis has been specifically identified at the time of the trial, or 2) although the target or timing of the potential genomic/genetic analysis has not been specifically identified at the time of the trial, but it is planned to conduct analysis for the evaluation of the IMP in future. The MHLW also states in Q&A 2 in the same notification, that samples for possible genomic/genetic analysis with a purpose independent of the evaluation of the IMP may be collected from subjects during the trial. Furthermore, Section 1.4 General Principles of The International Council for Harmonization (ICH) E18 Guidelines, "Genomic Sampling and Management of Genomic Data" states that, "With advances in science and increased awareness of the impact of genomics, there is a need and an opportunity to maximize the value of collected samples and the data generated therefrom. Therefore, genomic sample acquisition is strongly recommended in all phases and studies of clinical development."[11]

In this trial, the collection of DNA samples is planned to coincide with other trial examinations and tests to minimize the burden on the subjects. Thus, the voluntary collection and storage of DNA samples in this trial is appropriate.

2) Purposes

Samples for DNA analysis will be collected from the subjects to enable a future exploratory investigation regarding DNA variants relating to individual differences in responsiveness (eg, efficacy, safety, PK) to the IMP, and/or the disease-associated DNA variants.

3) Target subject group

DNA storage will be conducted at trial sites at which the IRB provides prior approval for blood sampling for DNA storage. A blood sample for DNA storage will be collected only from subjects who provide voluntary consent to DNA storage.

4) Timing of blood sampling

A blood sample for DNA storage will be collected at predose on Day 1. If a blood sample cannot be collected at predose on Day 1 or re-collection is required for any reason, blood sampling may be repeated at a feasible time during the trial period. The date and time of blood sampling will be recorded in the source document and the eCRF.

5) Sample for DNA storage

For the detailed procedures for sample collection, handling, and shipment, see Appendix 1. The DNA samples will be stored until 1) possible genomic/genetic analysis is determined to be unnecessary, 2) 15 years has passed since informed consent has been obtained from the first subject, or 3) the subject withdraws consent to DNA storage, whichever comes first.

3.7.5.2.2 Potential Genomic/Genetic Analysis

Genomic/genetic analysis will be conducted if analysis is determined to be useful for the purposes described in Section 3.7.5.2.1 2).

When it is determined to conduct genomic/genetic analysis, a pharmacogenomics protocol will be prepared and approved by the research review committee at the sponsor, and the analysis will be then conducted according to applicable regulations. The results of the genomic/genetic analysis will not be included in the final study report, but documented separately as a research report.

The target of potential genomic/genetic analysis has not yet been identified. Genome-wide association analysis using DNA chips, DNA microarrays, or next-generation DNA sequencers may be conducted, however, the results of the analysis will not be used for purposes other than those described in Section 3.7.5.2.1 2).

DNA samples for possible genomic/genetic analysis will be double coded by the DNA repository and shipped to the genomic/genetic analysis laboratory (not yet designated), at which the genomic/genetic analysis will be conducted using the double-coded samples.

1) Informed consent for participation in DNA storage and its withdrawal

Written information regarding DNA storage and possible genomic/genetic analysis using DNA samples will be prepared separately from written information for the trial,

and informed consent for participation in DNA storage will be obtained from the subject. The date of the informed consent obtained from the subject will be recorded in the source document and the eCRF. Consent from subjects who are able to consent, but unable to sign the ICF for physical or therapeutic reasons will be obtained in a manner similar to that described in Section 3.4.1.

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

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

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

3.7.6 End of Trial

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

3.8 Stopping Rules, Withdrawal Criteria, and Procedures

3.8.1 Entire Trial

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

3.8.2 Individual Site

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

3.8.3 Individual Subject Discontinuation

3.8.3.1 Treatment Discontinuation

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

A subject who initiates treatment and then discontinues the treatment will be encouraged to undergo all of the examinations and tests specified for the withdrawal assessment. The withdrawal assessment will be conducted according to Section 3.7.1.7.

3.8.3.2 Documenting Reasons for Treatment Discontinuation

A subject may discontinue participation in the trial at any time, and the investigator or subinvestigator may discontinue a subject's participation in the trial if medically necessary. Subjects who fall under any of the following must be withdrawn from the trial. If a subject discontinues treatment, a single reason for the discontinuation (the main reason) will be recorded in the eCRF.

1) Reasons related to AE:
    - Subject decides to discontinue because of annoyance or discomfort due to a non-serious AE which is not otherwise determined to be an undue hazard
    - AST or ALT value is ≥3 times the upper limit of normal (ULN).
    - Serum or plasma sodium concentration measured at the trial site or the central laboratory increases by ≥12 mEq/L from immediately predose within 24 hours after start of the IMP administration.
    - The serum or plasma sodium concentration measured at the trial site or the central laboratory is ≥155 mEq/L during the treatment period.
    - The onset of drug-induced hypersensitivity is suspected.

- Any severe AESI (feeling abnormal, feeling hot, erythema, hyperhidrosis, pruritus, rash, urticaria, nausea, epigastric discomfort, or dyspnea) occurs.
- Continuing IMP places the subject at undue risk as determined by the investigator or subinvestigator (eg, a safety concern that is possibly, probably, or likely related to IMP).
  - Serious adverse event
  - Other potentially IMP-related safety concerns or AEs

2) Withdrawal of informed consent by the subject (when it is confirmed to be unrelated to AEs)
3) Protocol deviations (other than poor compliance with the IMP administration rules)
   - Deviations related to the inclusion or exclusion criteria
   - Deviations related to prohibited concomitant medications
4) Judgment by the investigator or subinvestigator (for the reasons other than an AE)
5) Death
6) Lost to follow-up
7) Pregnancy (see Section 5.5)
8) Technical problems (eg, malfunctions of medical devices)
9) Premature termination of the entire or part of the trial by the sponsor

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

3.8.3.3 Withdrawal of Consent

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

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

- Participation in all follow-up procedures specified in the protocol (whether at trial site, by telephone, or by an in-home visit).

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

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

3.8.3.4 Procedures to Encourage Continued Trial Participation

In all cases of impending IMP discontinuation or consent withdrawal, investigators or subinvestigators will be given instructions to meet and discuss with the subject their options of continuing in the trial, preferably on therapy. The investigator 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, but who does not receive the IMP.

Subjects who have consented to participation in the trial but did not receive the IMP are permitted to be re-screened once. In the event that the screening examination is repeated, a new ICF signed by the subjects must be obtained and a new subject identifier will be assigned to the subject.

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

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

3.10 Definition of Completed Subjects

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

3.11 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted on or before the completion assessment on Day 6 of the treatment period (or the day after the final IMP administration), who do not have a known reason for discontinuation (eg, withdrew consent or AE), and for whom a survival status at the end of the trial cannot be determined will be classified as “lost to follow-up.” Survival status can be determined from a variety of sources, either by obtaining

acceptable documentation for death (ie, death certificate, medical records, public records, statement by a family member or primary care physician) or acceptable documentation for life (ie, direct contact with the subject, medical records, successful telephone contact with the subject, statement by a family member or primary care physician, or public records).

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

3.12 Subject Compliance

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

- Subjects must follow the prespecified trial schedule.
- Subjects must not use the prohibited concomitant medications (see Section 4.1).

3.13 Protocol Deviations

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

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

4 Restrictions

4.1 Prohibited Medications

From the time of informed consent to the completion assessment on Day 6 (the day after the final IMP administration) or the withdrawal assessment, use of the following items listed in Table 4.1-1 and Table 4.1-2 will be prohibited.

Table 4.1-1 List of Prohibited Concomitant Medications and Foods

No.	Prohibited medications and foods
1	Vasopressin antagonists
2	Medications and foods which may inhibit or induce the activity of CYP 3A4 (see Table 4.1-2)
3	Medications including investigational drugs other than OPC-61815 that are unapproved in Japan

CYP = cytochrome P450

[Rationale for the prohibited concomitant medications and foods]

1,2 These medications and foods may confound the safety evaluation of the IMP.

3 The safety of these medications has not been established in Japanese patients.

Table 4.1-2 Medications and Foods Which May Inhibit or Induce CYP3A4 Activity	
Therapeutic category	**Drugs**
(1) CYP3A4 inhibitors (except external use agents)	
Antimicrobial drugs	Clarithromycin, erythromycin, fluconazole, itraconazole, miconazole, norfloxacin, chloramphenicol, voriconazole, and ciprofloxacin
Anti-HIV drugs	Atazanavir, indinavir, nelfinavir, ritonavir, saquinavir, lopinavir, telaprevir, fosamprenavir, cobicistat, darunavir, and elvitegravir
Drugs for viral liver diseases	Ombitasvir, paritaprevir, and ritonavir
Calcium channel blockers	Diltiazem and verapamil
Antidepressants	Fluvoxamine
Antiulcer drugs	Cimetidine
Anticancer drugs	Imatinib and crizotinib
Immunosuppressants	Cyclosporine
Antiemetics	Aprepitants
Other medications	Tofisopam, istradefylline, and clotrimazole
Foods	Grapefruit, star fruit, Seville orange, and their processed products
(2) CYP3A4 inducers (except external use agents)	
Barbiturates	Phenobarbital, amobarbital, pentobarbital, barbital, secobarbital, and primidone
Adrenal corticosteroids	Cortisone, hydrocortisone, prednisolone, methylprednisolone, triamcinolone, dexamethasone, betamethasone, paramethasone, and fludrocortisone
Antihypertensive drugs	Bosentan
Anti-HIV drugs	Efavirenz, etravirine, and nevirapine
Antiepileptics	Carbamazepine, phenytoin, and oxcarbazepine
Antitubercular drugs	Rifampicin and rifabutin
Anticancer drugs	Enzalutamide and mitotane
Other medications	Modafinil
Foods	Products containing St. John's Wort

HIV = human immunodeficiency virus

5 Reporting of Adverse Events

5.1 Definitions

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

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

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

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

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

Immediately Reportable Event (IRE):

- Any SAE.
  - All SAEs occurring during the trial period
  - An SAE that occurs during the follow-up period and is considered to be reasonably related to the IMP; or, an AE that exists before the start of the follow-up period, and falls under the definition of an SAE during the follow-up period and is considered to be reasonably related to the IMP.
- Any AE related to occupational exposure.
- Potential serious hepatotoxicity (see Section 5.4).
- Pregnancies are also defined as IREs. Although normal pregnancy is not an AE, it will mandate IMP discontinuation and must be reported on an IRE form to the sponsor. Pregnancy will only be documented on the AE eCRF if there is an abnormality or complication. The above applies to pregnancies of both subjects and their partners.

Clinical Laboratory Test Value Changes: It is the investigator or subinvestigator's responsibility to review the results of all laboratory tests as they become available. This review will be documented by the investigator or subinvestigator's dated signature on the laboratory report. For each abnormal laboratory test result, the investigator needs to ascertain if this is an abnormal (ie, clinically significant) change from baseline for that individual subject. This determination, however, does not necessarily need to be made the first time an abnormal value is observed. The investigator or subinvestigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. If this laboratory value is considered medically relevant by the investigator or subinvestigator (subject is symptomatic, requiring corrective treatment or further evaluation), or if the laboratory value leads to discontinuation, and/or fulfills a seriousness criterion, this is considered an AE.

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

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

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

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

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

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

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

5.2 Eliciting and Reporting Adverse Events

The investigator or subinvestigator will periodically assess subjects for the occurrence of AEs. To avoid bias in eliciting AEs, subjects should be asked the non-leading question: "How have you felt since your last visit?" All AEs (serious and nonserious) reported by the subject must be recorded on the source documents and eCRFs provided by the sponsor. The AE, onset date, resolution date, seriousness, severity, causal relationship to the IMP (IMP Causality), action taken with IMP treatment, and outcome will be recorded in the source document and the eCRF. If any AESI (feeling abnormal, feeling hot, erythema, hyperhidrosis, pruritus, rash, urticaria, nausea, epigastric discomfort, or

dyspnea) occurs, also the time of onset and the time of resolution will be recorded. Adverse event and SAE collection will begin after the subject consents to participation in the trial.

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

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

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

- Adverse event
- Onset date (also the time, for AEs occurring during stay at the trial site, whenever possible) and resolution date
- Severity
- Seriousness (If serious, specify the category of seriousness.)
- IMP causality
- Measures taken with IMP administration
- Outcome

5.3 Immediately Reportable Events

The investigator must report within 24 hours after either the investigator, subinvestigator, or site personnel become aware of any SAE, potential serious hepatotoxicity, or confirmed pregnancy, by e-mail to the sponsor using the contact information on the cover page of this protocol. An IRE form must be completed and sent by e-mail to the sponsor. (Please note that the IRE form is NOT the AE eCRF.)

Subjects experiencing SAEs or IREs should be followed until the event has resolved or stabilized, or until the subject is lost to follow-up or has died. Resolution means that the subject has returned to the baseline state of health and stabilized means that the investigator or subinvestigator does not expect any further improvement or worsening of

the subject's condition. It is expected that the investigator or subinvestigator will provide or arrange appropriate supportive care for the subject and will provide prompt updates on the subject's status to the sponsor.

5.4 Potential Serious Hepatotoxicity

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

5.5 Pregnancy

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

For WOCBP and for men who are sexually active, there must be a documented agreement that the subject and/or their partner will take effective measures (ie, double barrier method) to prevent pregnancy during the course of the trial and for 30 days after the last dose of IMP. Unless the subject is sterile (ie, women who have had a bilateral oophorectomy and/or hysterectomy or who have been postmenopausal for at least 12 consecutive months; or men who have had a bilateral orchidectomy) or remains abstinent, 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pills, or condom with spermicide.

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

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

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

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

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

If a subject is suspected to be pregnant before she receives IMP, the IMP administration must be withheld until the results of serum pregnancy tests are available. If the pregnancy is confirmed, the subject must not receive the IMP and must not be enrolled in the trial. If pregnancy is suspected while the subject is taking IMP, the IMP must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of the pregnancy test is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety) and the subject will be withdrawn from the trial. (In an exceptional case where the subject is in a potentially life threatening situation, continuation of participation in the trial may be considered, but it should be determined after consultations with the Department of Pharmacovigilance, Otsuka Pharmaceutical [for the contact information, see the cover page of this protocol]).

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

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

5.6 Procedure for Breaking the Blind

Not applicable, as this trial is an open-label trial.

5.7 Follow-up of Adverse Events

5.7.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified at any time during the trial must be recorded on the AE eCRF with the current status (ongoing or resolved/recovered) noted. All nonserious events (that are not IREs) that are ongoing at the last scheduled contact will be recorded as ongoing on the eCRF. For any AE having been identified throughout the trial, during analysis, additional relevant medical history information may be requested by the sponsor to further ascertain causality (including, but not limited to, information such as risk related behavior, family history, and occupation). Follow-up information after the end of the trial date (the date of the last scheduled contact) will be recorded in the subject's medical record.

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

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

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

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

Any new SAEs or IREs reported to the investigator or subinvestigator, which occur after the end of trial (last scheduled contact) and are determined by the investigator or subinvestigator to be reasonably associated with the use of the IMP, should be reported to the sponsor. This may include SAEs or IREs that are captured on follow-up telephone contact or at any other timepoint after the defined trial period. The investigator or subinvestigator should follow SAEs or IREs identified after the defined trial period, and

continue to report any significant follow-up information on an IRE form to the sponsor until the events are resolved or stabilized, or the subject is lost to follow-up or has died.

6 Pharmacodynamic and Pharmacogenomic Analyses

For pharmacodynamic analyses, see Section 7.4.2, and for pharmacogenomic analyses, see Section 3.7.5.2.

7 Statistical Analyses

7.1 Target Sample Size

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

7.2 Datasets for Analysis

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

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

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

7.3 Handling of Missing Data

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

7.4 Safety, Pharmacodynamic, and Efficacy Endpoint Analyses

7.4.1 Safety Analysis

The following analyses will be conducted on the safety dataset. The same analyses will be conducted by the timing of dose escalation (ie, subjects achieving a dose escalation to 16 mg on Day 2, those achieving a dose escalation to 16 mg on Day 3, and those achieving no dose escalation to 16 mg).

7.4.1.1 Adverse Events

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

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

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

7.4.1.2 Clinical Laboratory Data

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

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

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

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

7.4.1.3 Vital Signs Data

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

7.4.1.4 Electrocardiogram Data

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

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

A shift table showing QTc interval interpretation (normal or abnormal) will be prepared at each postdose time point and at the time of final IMP administration compared to baseline.

7.4.2 Pharmacodynamic Analyses

A pharmacodynamic analysis will be conducted on the pharmacodynamic dataset. In the analysis of serum sodium and potassium concentrations, the results of central measurement will be used. The same analyses will also be conducted by the timing of dose escalation (ie, subjects achieving a dose escalation to 16 mg on Day 2, those achieving a dose escalation to 16 mg on Day 3, and those not achieving a dose escalation to 16 mg).

For the following parameters, measured values and changes from baseline will be summarized at each time point.

- Urine volume
- Fluid Intake
- Fluid Balance
- Serum sodium concentration
- Serum potassium concentration
- Serum osmolality
- Biomarkers (plasma AVP concentration, plasma renin activity, plasma BNP concentration, serum NT-proBNP concentration, and serum troponin I concentration)
- Urine sodium excretion
- Urine potassium excretion

- Urine osmolality

In subgroups composed of subjects achieving a dose escalation to 16 mg on Day 2 and Day 3 changes in serum sodium concentration, serum potassium concentration, and serum osmolality at each time point during the period from predose on the dose escalation day to predose on the following day will be summarized using descriptive statistics.

7.4.3 Efficacy Analyses

The following analyses will be conducted on the efficacy dataset. The same analyses will be conducted by the timing of dose escalation (ie, subjects achieving a dose escalation to 16 mg on Day 2, those achieving a dose escalation to 16 mg on Day 3, and those not achieving a dose escalation to 16 mg).

7.4.3.1 Body Weight

Measured values, and changes and percent changes from baseline at each time point and at the time of final IMP administration will be summarized using descriptive statistics.

7.4.3.2 Congestive Symptoms

7.4.3.2.1 Lower Limb Edema and Pulmonary Congestion

The improvement rate and the resolution rate at the time of final IMP administration will be determined. The improvement rate is defined as the proportion of subjects in whom a symptom is present at baseline and then markedly improves or improves after IMP administration (for the improvement category, see Table 7.4.3.2-1). The resolution rate is defined as the proportion of subjects in whom a symptom is present at baseline and then resolves after IMP administration.

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

Table 7.4.3.2-1 Improvement Category of Lower Limb Edema and Pulmonary Congestion

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

7.4.3.2.2 Jugular Venous Distension, Hepatomegaly, and Cardiothoracic Ratio

Measured values and changes from baseline at each time point and at the time of final IMP administration will be summarized using descriptive statistics. For the presence of jugular venous distension and hepatomegaly, shift tables in changes from baseline at the final IMP administration and at each timepoint following IMP administration will be prepared by each treatment group.

7.4.3.2.3 Pulmonary Rales and Cardiac Third Sound

The resolution rates of pulmonary rales and cardiac third sound at the time of final IMP administration will be determined. The resolution rate is defined as the proportion of subjects in whom a symptom is present compared with baseline and disappears after IMP administration.

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

7.4.3.3 Dyspnea

7.4.3.3.1 Respiratory Rate

Measured values and changes from baseline at each time point and at the time of final IMP administration will be summarized using descriptive statistics.

7.4.3.3.2 Orthopnea and Paroxysmal Nocturnal Dyspnea

The resolution rates of orthopnea and paroxysmal nocturnal dyspnea at the time of final IMP administration will be determined. The resolution rate is defined as the proportion of subjects in whom a symptom is present compared with baseline and then disappears after IMP administration.

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

7.4.3.3.3 Subject-Assessed Dyspnea

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

7.4.3.4 NYHA Classification

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

7.5 Analysis of Demographic and Baseline Characteristics

In the safety dataset and the efficacy data set, the frequency distributions and descriptive statistics of the subject characteristics will be calculated.

8 Management of Investigational Medicinal Product

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

8.1 Packaging and Labeling

The IMP will be provided to the IMP storage manager by the sponsor or designated agent. The IMP will be supplied in OPC-61815 8-mg and 16-mg vials. Six vials are contained in a kit box. Each vial and each kit box will be labeled to clearly state “For clinical trial use only,” and disclose the protocol number, name of the IMP, batch number, expiration date, storage methods, and sponsor’s name and address.

8.2 Storage

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

The IMP will be stored at room temperature.

The trial site staff will check the temperature in the IMP storage area at least once each working day and record the observed temperature.

8.3 Accountability

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

8.4 Returns and Destruction

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

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

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

8.5 Reporting of Product Quality Complaints

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

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

8.5.1 Eliciting and Reporting Product Quality Complaints

The investigator, subinvestigator, or designee must record all PQCs identified through any means from the receipt of the IMP from the sponsor or sponsor's designee, through and including reconciliation and up to destruction, including subject dosing. The investigator, subinvestigator, or designee must notify the sponsor or sponsor's designee (contact information: PQC_263-102-00004@otsuka.jp) of the information listed in Section 8.5.2 by e-mail immediately after becoming aware of the PQC.

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

8.5.2 Information Required for Reporting Purposes

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

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

8.5.3 Return Process

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

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

8.5.4 Assessment/Evaluation

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

9 Records Management

9.1 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include but are not limited to progress notes, electronic data, screening logs, and recorded data from automated instruments. All source documents will be maintained by the trial site and made available for direct inspection by authorized persons. The investigator or the trial site will permit trial-related monitoring, audits, IRB review, and regulatory inspection(s) by providing direct access to source data/documents by authorized persons as defined in the ICF. In all cases, subject confidentiality must be maintained in accordance with local regulatory requirements.

9.2 Data Collection

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

- Documentation of the informed consent process, including any revised consents;
- Documentation of the investigator or subinvestigator's decision to enroll the subject into the trial, the review of all inclusion/exclusion criteria prior to IMP administration, and confirmation of the subject's actual participation in the trial;

- The date of the visit and the corresponding Visit or Day in the trial schedule;
- General subject status remarks, including any significant medical findings. The severity, frequency, duration, action taken, and outcome of any AEs and the investigator's assessment of relationship to IMP must also be recorded;
- Any changes in concomitant medications or dosages;
- A general reference to the procedures completed;
- The signature (or initials) and date of investigator or subinvestigator (or designee) who made an entry in the progress notes.

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

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

9.3 File Management at the Trial Site

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

9.4 Records Retention at the Trial Site

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

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

- A period of at least 3 years after the trial is terminated or completed

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

10 Quality Control and Quality Assurance

10.1 Monitoring

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

10.2 Auditing

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

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

11 Ethics and Responsibility

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

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

12 Confidentiality

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

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

13 Amendment Policy

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

apparent immediate hazard to subjects should be implemented immediately followed by IRB notification within local applicable timelines. The sponsor will submit protocol amendments to the applicable regulatory agencies within local applicable timelines.

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

14 Publication Authorship Requirements

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

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

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

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

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Appendix 1 Handling and Shipment of Bioanalytical Samples

1) Sample collection and processing procedures

Samples will be collected, processed, and stored according to procedures specified separately by the sponsor.

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

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

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

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

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

- Urine sodium concentration, urine potassium concentration, and urine osmolality
  The collected urine will be aliquoted into sample stock tubes and stored refrigerated.

2) Blood sample for DNA storage

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

Appendix 2 Protocol Amendments/Administrative Changes

Amendment Number: 1

Issue Date: 18 Mar 2019

PURPOSES: Adding descriptions pertaining to clinical laboratory tests performed at each trial site using plasma samples, and correcting entry omissions and writing errors.

BACKGROUD: The use of plasma samples was considered appropriate in clinical laboratory tests at each trial site. Some entry omissions and writing errors were discovered in the protocol.

MODIFICATIONS TO PROTOCOL:

- Protocol Synopsis, Section 3.4.3
  "Serum creatinine," "serum sodium concentration," and "serum potassium" were changed to "serum or plasma creatinine," "serum or plasma sodium concentration," and "serum or plasma potassium concentration," respectively.
- Table 3.2.2-1 and Table 3.2.2-2
  The following description was added: "[a]If serum sodium concentration measurement is difficult to perform at the trial site, plasma sodium concentrations will be used for the assessment."
- Section 3.7
  The following description was added: "If serum sodium concentration measurement is difficult to perform at the trial site, plasma sodium concentration may be measured. Either serum or plasma should be used consistently for measurement of sodium concentration in a given subject. However, serum sodium concentration will be measured at the central laboratory."
- Table 3.7-1
  Writing errors in the note were collected. The following description was added to Note d): "If serum sodium concentration measurement is difficult to perform at the trial site, plasma sodium concentration may be measured. Either serum or plasma samples should be used consistently for measurement of sodium concentration in a given subject. However, serum sodium concentration will be measured in the central laboratory."
- Table 3.7.1.2-2 and Table 3.7.1.5-2

"Urine sampling for the measurement of urine sodium concentration and urine osmolality" was changed to "urine sampling for measurement of urine sodium concentration, urine potassium concentration, and urine osmolality."

- Section 3.7.2.2
  The following description was added: "If serum sodium concentration measurement is difficult to perform at the trial site, plasma sodium concentration may be measured. Either serum or plasma samples should be used consistently for measurement of sodium concentration in a given subject. However, serum sodium concentration will be measured in the central laboratory."
- Table 3.7.2.2-1
  "Serum electrolytes (sodium [Na], potassium [K], chloride [Cl], calcium [Ca])" was changed into "serum or plasma electrolytes (sodium [Na], potassium [K], chloride [Cl], calcium [Ca])."
- Table 3.7.5.1.1-1
  "24 hours before the start of IMP administration on Day 1" was changed into "23 to 25 hours before the start of IMP administration on Day 1."
- Section 3.7.5.1.4
  The following description was added: "If serum sodium concentration measurement is difficult to perform at the trial site, plasma sodium concentration may be measured. Either serum or plasma samples should be used consistently for measurement of sodium concentration in a given subject. However, serum sodium concentration will be measured in the central laboratory."
- Section 3.8.3.2
  "Serum sodium concentration" was changed into "serum or plasma sodium concentration."

ADDITIONAL RISK TO THE SUBJECTS:

No additional risks will be imposed upon the subjects.

Amendment Number: 2

Issue Date: 26 Jun 2019

PURPOSES: Changing the protocol to enroll subjects who are not able to personally sign the ICF, but from whom verbal consent can be obtained in the presence of a witness; clarifying the definition of treatment duration; and, correcting writing errors.

BACKGROUND: It was found that some subjects are unable to personally sign the ICF due to physical or therapeutic reasons, even though they are able to verbally consent to participation in the trial; therefore, a procedure to enroll such subjects was added. The definition of treatment duration, which had been insufficiently documented was clarified. In addition, some errors were corrected.

MODIFICATIONS TO PROTOCOL:

- Throughout the protocol (Sections 3.3.2, 3.7.1, 3.7.4, 3.7.5.2.1, 3.9, 5.2, and 5.5)
  The wording was changed so that subjects who express verbal consent can participate in the trial without obtaining written consent from these subjects (with this change, subjects may participate in the trial with verbal consent provided in the presence of a witness without providing written consent).

- Section 3.4.1
  The wording was changed so that subjects who are able to consent but unable to sign the ICF for physical or therapeutic reasons can participate in the trial through the acquisition of verbal consent from these subjects in the presence of a witness. In the course of informed consent, the witness will sign and date the witness section of the ICF, and write the name of the subject, the reason(s) that the subject is not able to sign by him/herself, and the relationship between the subject and the witness in the margin of the ICF.

- Protocol Synopsis, Section 3.2.3
  It was clarified that the participation of subjects in the trial would end when they become able to control fluid balance by oral fluid intake alone (the end of treatment period was clarified).

- Others: Errors were corrected.

ADDITIONAL RISK TO THE SUBJECTS:
No additional risks will be imposed upon the subjects.

Amendment Number: 3

Issue Date: 17 Apr 2020

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

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

MODIFICATIONS TO PROTOCOL:

- Table 3.7-1
  - Item: The underlined parts were added.

    Changed into "Serum sodium[d] and potassium concentrations[d]," in consideration of ensuring the safety of subjects.
  - Changed into "12-Lead ECG[k]" in consideration of ensuring the safety of subjects.
  - Note d: The underlined parts were added.

    Changed into "Serum sodium and potassium concentrations"

    Changed into the following statement in consideration of ensuring the safety of subjects: "If serum sodium and potassium concentration measurement is difficult to perform at the trial site, plasma sodium and potassium concentrations may be measured. Either serum or plasma samples should be used consistently for measurement of sodium and potassium concentrations in a given subject. However, serum sodium and potassium concentrations will be measured in the central laboratory."
  - Note e: The underlined parts were added.

    Changed into the following statement in consideration of ensuring the safety of subjects: "Serum sodium concentration (local measurement), serum potassium concentration (local measurement), body weight, chest x-ray, and vital signs (blood pressure, pulse rate, and body temperature)"
  - Note k: An addition of the statement.

    The following statement was added in consideration of ensuring the safety of subjects: "If the serum potassium is confirmed to exceed 5.5 mEq/L at the trial site or the central laboratory at any time point in the period with no specified 12-lead ECG, a 12-lead ECG will be performed as an unscheduled examination."
- Sections 3.7, 3.7.1, 3.7.2.2 and 3.7.5.1.4

  The statements indicating that "serum potassium concentration measurement is performed during the treatment period at the trial site" were added in consideration of ensuring the safety of subjects.

- Section 3.7.2.2 and 3.7.2.4
  The statements indicating that “if the serum potassium is confirmed to exceed 5.5 mEq/L at the trial site or the central laboratory at any time point in the period with no specified 12-lead ECG,, a 12-lead ECG will be performed as an unscheduled examination” were added in consideration of ensuring the safety of subjects.
- Others: Errors were corrected.

ADDITIONAL RISK TO THE SUBJECTS:
No additional risks will be imposed upon the subjects.

Agreement

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

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

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

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

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

Principal Investigator Print Name	Trial Site
Signature	Signature Date

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