CLINICAL STUDY PROTOCOL

A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Dose-ranging Trial of OPC-131461 for Cardiac Edema (Congestive Heart Failure)

NCT Number: NCT05615363
Protocol No. 351-102-00004
Version Date: 27 Dec 2023

Otsuka Pharmaceutical Co., Ltd.

Investigational Medicinal Product

OPC-131461
Translation of Japanese Original
CLINICAL PROTOCOL AMENDMENT

A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Dose-ranging Trial of OPC-131461 for Cardiac Edema (Congestive Heart Failure)

A Dose-ranging Trial of OPC-131461 for Cardiac Edema (Congestive Heart Failure)

Protocol No. 351-102-00004

CONFIDENTIAL — PROPRIETARY INFORMATION

Clinical Development Phase:	2
Sponsor:	Otsuka Pharmaceutical Co., Ltd.
Immediately Reportable Event	[redacted]
Amendment 4 Approval:	27 Dec 2023
Amendment 3 Approval:	15 Jun 2023
Amendment 2 Approval:	07 Mar 2023
Amendment 1 Approval:	31 Aug 2022
Approval:	14 Jun 2022

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List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APTT	activated partial thromboplastintime
AST	aspartate aminotransferase
AUC_{∞}	area under the concentration-time curve from time zero to infinity
AUC_t	area under the concentration-time curve calculated to the last observable concentration at time t
AUC_{24h}	area under the concentration-time curve from time zero to 24 hours
AUC_{24h}/D	AUC_{24h} normalized by dose
AVP	arginine vasopressin
BA	bioavailability
BCRP	breast cancer resistance protein
BMI	body mass index
BNP	brain natriuretic peptide
BSEP	bile salt export pump
[redacted]	[redacted]
cAMP	cyclic adenosine 3',5'-monophosphate
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK (CPK)	creatine kinase (creatine phosphokinase)
CL/F	apparent clearance of drug from plasma after extravascular administration
CL/F/BW	CL/F normalized in body weight
C_{max}	maximum (peak) plasma concentration of the drug
C_{max}/D	C_{max} normalized by dose
CRO	contract research organization
C_{trough}	trough drug concentration
CYP	cytochrome P450
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EDTA	ethylenediaminetetraacetic acid
eGFRcre	estimated glomerular filtration rate using the creatinine
eGFRcys	estimated glomerular filtration rate using the cystatin C
FBR	future biospecimen research
FOCBP	females of childbearing potential
GCP	Good Clinical Practice
GFR	glomerular filtration rate
γ-GTP	γ-glutamyl transpeptidase
hCG	human chorionic gonadotropin

Abbreviation	Definition
HIV	human immunodeficiency virus
HMG-CoA	β-hydroxy β-methylglutaryl-CoA
IB	investigator's brochure
IC_{50}	concentration of drug producing 50% inhibition
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
IUD	intrauterine device
IWRS	interactive web response system
Ki	inhibition constant
LDH	lactate (lactic acid) dehydrogenase
LOCF	last observation carried forward
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
λ_z	apparent terminal-phase disposition rate constant (first-order)
[redacted]	[redacted]
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PD	pharmacodynamic
[redacted]	[redacted]
PK	pharmacokinetic
PQC	product quality complaint
PT-INR	prothrombin time international normalized ratio
QTc	corrected QT interval
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
$R(AUC_{24h})$	accumulation ratio of multiple dose to first dose at regular administration for AUC_{24h}
$R(C_{max})$	accumulation ratio of multiple dose to first dose at regular administration for C_{max}
$R(C_{trough})$	accumulation ratio of multiple dose to first dose at regular administration for C_{trough}
SAE	serious adverse event
SGLT2	sodium-glucose cotransporter 2
$t_{1/2,z}$	terminal-phase elimination half life

Abbreviation	Definition
TEAE	treatment-emergent adverse event
t_{max}	time to maximum plasma concentration
t_{last}	time of last measurable (positive) concentration
UGT	uridine diphosphate glucuronosyltransferase

1 Protocol Summary

1.1 Synopsis

Name of Sponsor:

Otsuka Pharmaceutical Co., Ltd.

Name of Investigational Medicinal Product:

OPC-131461

Protocol No.:

351-102-00004

Protocol Title:

A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Dose-ranging Trial of OPC-131461 in Cardiac Edema (Congestive Heart Failure [CHF])

Protocol Lay Person Short Title:

A Dose-ranging Trial of OPC-131461 in Cardiac Edema (CHF)

Clinical Phase/Trial Type:

Phase 2/dose-ranging

Treatment/Indication:

Patients with CHF with volume overload despite having received diuretics other than vasopressin antagonists

Objectives and Endpoints:

Objectives	Endpoints
Primary Objectives: To investigate the dose response in respect of weight decrease following repeated oral administration of OPC-131461 at 1, 2, 5, and 10 mg or placebo in patients with CHF with volume overload despite having received diuretics other than vasopressin antagonists	Primary Efficacy Endpoint: Change in body weight from baseline to last assessment time point (the day after investigational medicinal product [IMP] administration) by Day 8 Secondary Efficacy Endpoints: Change in body weight from baseline to last assessment time point (the day after IMP administration) by Day 15 Percent change in body weight from baseline to last assessment time point (the day after IMP administration) by Day 8 Percent change in body weight from baseline to last assessment time point (the day after IMP administration) by Day 15 Improvement of or change in congestive findings (lower limb edema, pulmonary congestion, jugular venous distension, hepatomegaly, cardiothoracic ratio, pulmonary rales, and cardiac third sound) from baseline to last assessment time point (the day of IMP administration) by Day 7 Improvement of or change in congestive findings (lower limb edema, pulmonary congestion, jugular venous distension, hepatomegaly, cardiothoracic ratio, pulmonary rales, and cardiac third sound) from baseline to last assessment time point (the day after IMP administration) by Day 15 Congestive findings (lower limb edema, pulmonary congestion, jugular venous distension, hepatomegaly, cardiothoracic ratio, pulmonary rales, and cardiac third sound), time to resolution of congestive findings, and the New York Heart Association (NYHA) Functional Classification
Secondary Objectives: To confirm the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of OPC-131461 versus placebo in patients with CHF with volume overload despite having received diuretics other than vasopressin antagonists	Safety: Adverse events (AEs), clinical laboratory test values, physical examination findings, vital signs, and 12-lead electrocardiogram (ECG) Pharmacodynamic endpoint: Serum osmolality, serum electrolyte (sodium, potassium) concentrations, serum troponin I concentration, serum N-terminal pro-brain natriuretic peptide (NT-proBNP) concentration, serum creatinine concentration, serum cystatin C concentration, estimated glomerular filtration rate (estimated glomerular filtration rate using the creatinine [eGFRcre], estimated glomerular filtration rate using the cystatin C [eGFRcys]),

Objectives	Endpoints
	plasma arginine vasopressin (AVP) concentration, plasma brain natriuretic peptide (BNP) concentration, plasma renin activity, and plasma aldosterone concentration Daily urine volume/fluid intake/fluid balance Urine volume/fluid intake/fluid balance in a time point set Urine volume/fluid intake/fluid balance per hour Urine osmolality, urine sodium excretion, urine potassium excretion, urine aquaporin 2 concentration, and free water clearance Pharmacokinetic endpoint: Plasma concentrations and PK parameters of OPC-131461 and its metabolites
Exploratory Objective: To conduct an exploratory investigation of OPC-131461 compared to placebo.	Exploratory endpoint: [redacted]

Trial Design:

Multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging trial

Trial Population:

Total of 155 Japanese male and female subjects (31 subjects each in 5 groups; the target number of subjects who begin trial treatment), between ages of 18 and 89 years, inclusive, at the time of informed consent, with CHF with volume overload (lower limb edema, pulmonary congestion, or jugular venous distension) despite having received diuretics other than vasopressin antagonists

Key Inclusion/Exclusion Criteria:

Inclusion Criteria

Screening Period

Subjects who meet all of the following inclusion criteria (screening period) will be selected.

1)	Subjects with CHF with any of lower limb edema, pulmonary congestion, or jugular venous distension due to volume overload. Subjects with pulmonary congestion confirmed by a chest X-ray taken within 14 days before informed consent may be included.
2)	Subjects undergoing any of the following diuretic therapies (including subjects scheduled to begin such therapy during the run-in period) • Loop diuretics at a dosage equivalent to 40 mg/day or more of furosemide tablet/fine granule • Concomitant administration of a loop diuretic and a thiazide diuretic (including similar drugs) at any doses • Concomitant administration of a loop diuretic and a mineralocorticoid receptor antagonist or potassium-sparing diuretic at any doses Note: The type and dosages of concomitant diuretics are specified as follows: a) Loop diuretics at a dosage equivalent to 40 mg/day or more of furosemide tablet/fine granule Bumetanide tablet, 1 mg; azosemide tablet, 60 mg; and torasemide tablet, 8 mg b) Thiazide diuretics (including similar drugs) Hydrochlorothiazide tablet, trichlormethiazide tablet, benzylhydrochlorothiazide tablet, and mefruside tablet c) Mineralocorticoid receptor antagonists or potassium-sparing diuretics Spironolactone tablet/fine granule and triamterene capsules
3)	Males or females between the ages of 18 and 89 years inclusive (at the time of informed consent)
4)	Subjects who were currently hospitalized or who are able to be hospitalized from the day before the run-in period (Day −4) until the end of the post-treatment examination (Day 16)
5)	Subjects who are able to take oral medications
6)	Subjects capable of providing written informed consent prior to the initiation of any trial-related procedures and capable, in the opinion of the investigator or subinvestigator, of complying with all the requirements of the trial.

Run-in Period

Subjects who meet all of the following inclusion criteria (run-in period) will proceed to the treatment period.

7)	Subjects with lower limb edema, jugular venous distension (on Day −1 in the run-in period), or pulmonary congestion (by chest X-ray in the run-in period)
8)	Subjects who received diuretics without any change in the dose or regimen during the run-in period
9)	Subjects whose body weight changed by no more than 1.0 kg in 2 days before trial treatment begins (ie, between Day −2 and Day −1 in the run-in period)

Exclusion Criteria

Subjects who meet any of the following exclusion criteria in the screening period will be excluded.

1)	Subjects with acute heart failure
2)	Subjects with an assisted circulation device
3)	Subjects with any of the following diseases, complications, or symptoms: • Suspected decrease in the circulating blood volume • Hypertrophic cardiomyopathy (other than the dilated phase) • Cardiac valve disease with significant valve stenosis • Hepatic encephalopathy with difficulty in adequate hydration
4)	Subjects with acute myocardial infarction occurred within 30 days before screening examination
5)	Subjects with confirmed active myocarditis or amyloid cardiomyopathy
6)	Subjects with any of the following diseases, complications, or symptoms: • Uncontrolled diabetes mellitus • Anuria • Urinary excretion disorders due to urinary stenosis, urinary calculus, tumor
7)	Subjects with any of the following medical histories: • Occurrence of sustained ventricular tachycardia or ventricular fibrillation within 30 days prior to screening examination in subjects not using an implantable cardioverter defibrillator • Occurrence of a cerebrovascular disorder within 6 months prior to screening examination (excluding asymptomatic cerebral infarction) • History of hypersensitivity or idiosyncratic reaction to benzazepines (tolvaptan sodium phosphate, tolvaptan, mozavaptan hydrochloride, and benazepril hydrochloride)
8)	Subjects who have undergone surgical gastrectomy or small intestine resection
9)	Morbidly obese subjects with the body mass index (BMI = body weight [kg] / height [m]^2) of more than 35 kg/m^2
10)	Subjects with supine systolic blood pressure of less than 90 mmHg
11)	Subjects with any of the following clinical laboratory abnormalities: • Total bilirubin > 3.0 mg/dL • Serum creatinine > 3.0 mg/dL • Serum sodium < 125 mEq/L, serum sodium > 147 mEq/L • Serum potassium > 5.5 mEq/L
12)	Subjects with prior or concurrent hepatic impairment (including subjects with aspartate aminotransferase [AST] or alanine aminotransferase [ALT] greater than 3 times the upper limit of reference range at screening examination)
13)	(Removed due to deletion in Protocol Amendment 3)
14)	Subjects who cannot sense thirst or who have difficulty in ingesting water
15)	Females who are breastfeeding or have a positive pregnancy test before trial treatment begins
16)	Sexually active males of reproductive potential or sexually active females of childbearing potential who do not agree to practice 2 different methods of birth control or remain fully abstinent during the trial and for 90 days (males) or for 180 days (females) after the final administration of IMP. If employing birth control, 2 of the following methods must be used: vasectomy, tubal ligation, intrauterine device (IUD), birth control pill, and condom (all of these methods are approved or certified in Japan)

17)	Subjects who used any of the following drugs/foods/beverages/supplements at and after the specified time point

Drug, Food, Beverage, Supplement	Timing
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

18)	Subjects who, in the opinion of the investigator or subinvestigator, are inappropriate for inclusion in the trial for any other reason

Trial Site(s):

Approximately 60 sites in Japan

Investigational Medicinal Product(s), Dose, Dosage Regimen, Treatment Duration, Formulation, Mode of Administration:

[Investigational Medicinal Products]

- OPC-131461 tablet 1 mg
- OPC-131461 tablet 5 mg
- Placebo tablet

[Dose, Dosage Regimen, and Treatment Duration]

- Dosage regimen: once-daily oral administration
- Dose: 1, 2, 5, or 10 mg/day or 0 mg of OPC-131461

- Treatment duration: 14 days (However, the treatment will be terminated before completing 14 days of treatment, if the investigator or subinvestigator judges that no further improvement of volume overload is necessary in a case that any of congestive findings [lower limb edema, pulmonary congestion, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound] were resolved or in other cases.)

The investigator or subinvestigator will orally administer to subjects 2 tablets of either the OPC-131461 tablet at 1 or 5 mg or the placebo tablet with water once daily for 14 days immediately after urination for urine volume measurement following breakfast. From Day 2 onward, IMP administration should take place at the clock time within ± 20 minutes of the dosing time on Day 1. Subjects who did not have any breakfast on a day of administration will also receive the IMP.

Trial Assessments:

Assessments for Efficacy:

Body weight, assessment of congestive findings (lower limb edema, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound), chest X-ray (cardiothoracic ratio and pulmonary congestion), and assessment of NYHA Functional Classification

Assessments for Safety:

AEs, clinical laboratory tests (hematology, biochemistry, coagulation test, and urinalysis), physical examination, vital signs (blood pressure, pulse rate, and temperature), and 12-lead ECG

Assessments for Pharmacodynamics:

- Blood sampling for assessment of serum osmolality, serum electrolyte (sodium, potassium) concentrations, serum cystatin C concentration, serum creatinine concentration, AVP concentration, plasma renin activity, plasma aldosterone concentration, plasma BNP concentration, serum troponin I concentration, and serum NT-proBNP concentration
- Measurement of daily or sectional urine volume/fluid intake
- Urine collection for assessment of urine osmolality, urine sodium excretion, urine potassium excretion, and urine aquaporin 2 concentration

Assessments for Pharmacokinetics:

Blood sampling for assessment of plasma concentrations and PK parameters of OPC-131461 and its metabolites

Exploratory Assessment:

[redacted]

Screening/Other:

Subject demographics including complications and medical history, urine pregnancy test (only for female subjects of childbearing potential), serum pregnancy test (only for female subjects with a positive urine pregnancy test), deoxyribonucleic acid (DNA) storage (optional), and storage of biomarker samples (optional)

Data Monitoring Committee:

None

Statistical Methods:

The primary endpoint is the change in body weight from baseline (before IMP administration on Day 1) to last assessment time point (the day after IMP administration) by Day 8.

The primary analysis will use an analysis of covariance model with treatment group as a fixed effect and baseline body weight as a covariate. Each OPC-131461 dose group will be compared with the placebo group at a two-sided significance level of 5%, and the difference in the least squares mean between the treatment groups and the two-sided 95% confidence interval will be determined.

The necessary sample size is set as 31 subjects per group.

Assuming that a dose of OPC-131461 5 mg or higher is equivalent to that of tolvaptan 15 mg in patients with CHF, the sample size required to demonstrate the superiority of OPC-131461 over placebo in terms of the primary endpoint, ie, the change in body weight from baseline to the last assessment time point (the day after IMP administration)

by Day 8, was determined (multiplicity relating to the use of more than one OPC-131461 dose group was not considered).

The results of the phase 3 confirmatory trial of tolvaptan (Protocol 156-06-002; placebo-controlled 7-day treatment) demonstrated that the change from baseline in body weight on the day after the final IMP administration (LOCF) was −0.45 ± 0.93 kg (mean ± standard deviation [hereinafter, the same applies]) for the placebo group and −1.54 ± 1.61 kg for the tolvaptan 15-mg group. Based on these results, assuming a treatment difference of −1.09, standard deviation (combined) of 1.30, statistical power of 90%, and two-sided significance level of 5%, the sample size required is set as 31 subjects per group for a total of 155 subjects.

Trial Duration:

Each subject in this trial is expected to participate in the following periods of the trial:

- Screening period: a maximum of 4 days
- Run-in period: 3 days
- Treatment period: 15 days (14 days of trial treatment + 1 day of end-of-treatment [EOT] examination)
- Post-treatment observation period: 1 day
- Follow-up period: a maximum of 12 days

Overall, the trial duration is from signing of the first informed consent form to the final subject assessment is expected to be approximately 21 months.

All subjects should undergo EOT/withdrawal examination, post-treatment observation, and follow-up after the final IMP administration even if the actual treatment duration is less than 14 days as specified in the protocol.

1.2 Schema

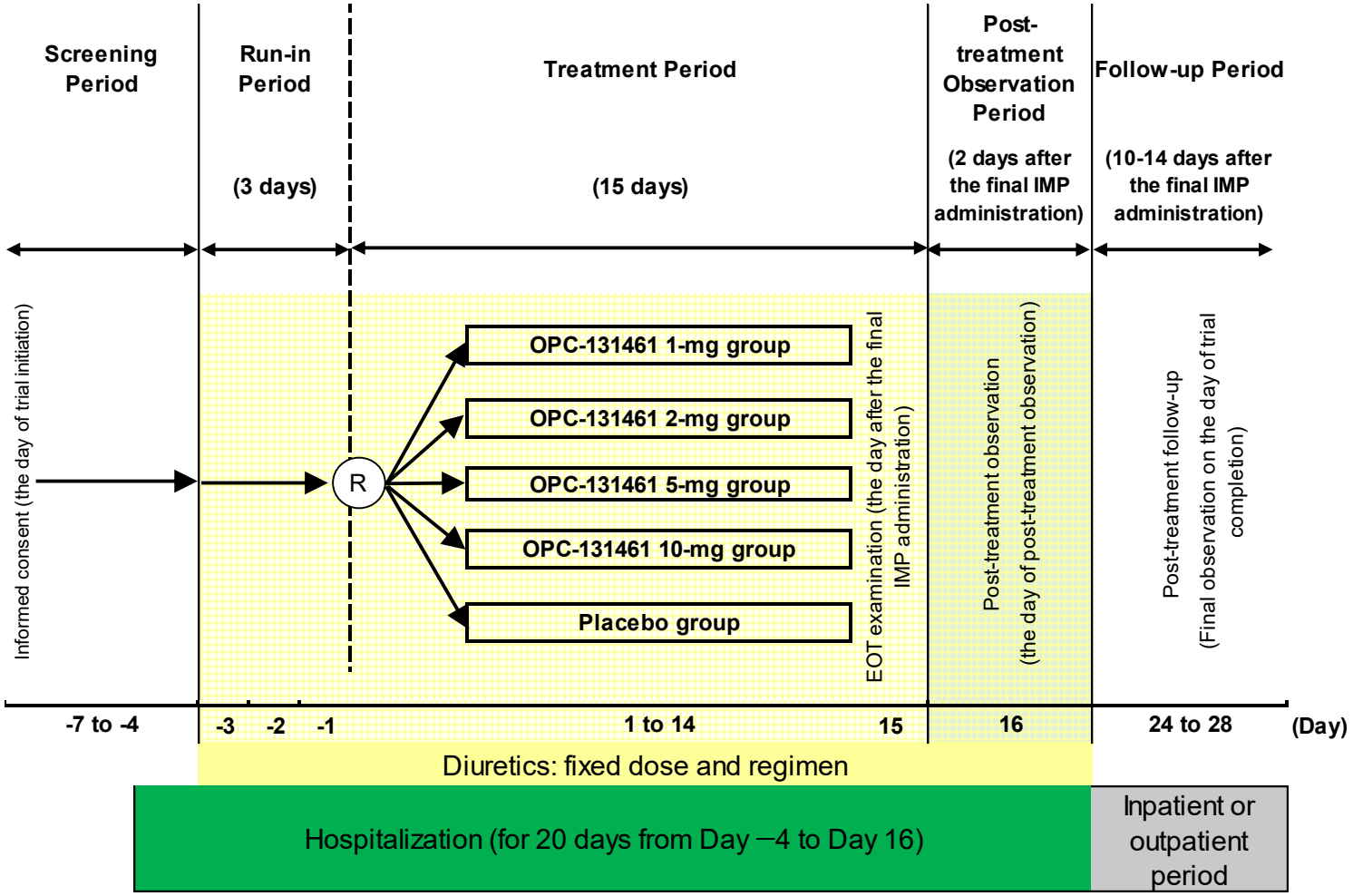


Figure 1.2-1 Trial Design Schematic

1.3 Schedule of Assessments

Table 1.3-1 Schedule of Assessments

Period (Day)	Screening Period		Run-in Period			Treatment Period														Post-treatment Observation Period	Follow-up Period
																			EOT Examination (Withdrawal Examination)	Post-treatment Observation	Follow-up Examination
Item	−7 to −4	−4	−3	−2	−1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15 Day after the final IMP administration	16 2 days after the final IMP administration	24 to 28 10 to 14 days after the final IMP administration
Hospitalization		←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→	
Informed consent	◆																					
Informed consent for optional programs	○ (optional participation)																					
Demographics	◆																					
Inclusion/exclusion criteria	◆				◆																	
Subject enrollment and randomization[a]	◆					●														◆		
IMP administration						⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙			
Check on concomitant diuretics			←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—		→	
Plasma drug concentration						■	■					■	■				■		■	■[b,c]	■[b,d]	◆[d]
Urine volume, fluid intake Urine sodium and potassium concentrations, urine osmolality, urine aquaporin 2 concentration[e]			←	↔	↔ ■	↔ ■	↔	↔	↔	↔	↔	↔ ■	↔	↔	↔	↔	↔	↔	↔ ■	↔ ■[f]	→	
Serum electrolyte (sodium, potassium) concentrations[g], serum osmolality	◆					■	■	■	■	■	■	■	■		■		■		■	●	●	●
Pharmacodynamic laboratory tests (serum, plasma)[h]						●							●							●		
[redacted]						●							●							●		●
Clinical laboratory tests	◆					●							●							●	●	●
Body weight	◆		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Congestive findings[i]	◆		◆	◆	◆	▼	▼	▼	▼	▼	▼	▼	▼	▼	▼	▼	▼	▼	▼	◆	◆	◆
Chest X-ray[j] (cardiothoracic ratio, pulmonary congestion)	◆		◆ Once in the run-in period									▼								◆		
NYHA Functional Classification			◆ Once in the run-in period									▼								◆		
Physical examination	◆		◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Vital Signs (blood pressure, pulse rate, body temperature)	◆		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●

Period (Day)	Screening Period		Run-in Period			Treatment Period													EOT Examination (Withdrawal Examination)	Post-treatment Observation Period: Post-treatment Observation	Follow-up Period: Follow-up Examination
Item	−7 to −4	−4	−3	−2	−1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15 Day after the final IMP administration	16 2 days after the final IMP administration	24 to 28 10 to 14 days after the final IMP administration
12-Lead ECG (central)[k]	◆		◆ Once in the run-in period			■		◆				▼								◆	◆	◆
[redacted]			◆ Once in the run-in period																	◆ Once by 2 days after the final IMP administration		
Urine pregnancy test (only for female subjects of childbearing potential)	◆																					◆
DNA storage[m]						○																
Storage of biomarker samples (plasma and urine)[n]						□						□										
Check on concomitant medications/therapies	←																		→			
Adverse events	←																		→			

EOT = end-of-treatment.

●, Before breakfast and before IMP administration (before breakfast on non-dosing days); ◎, After breakfast; ■, At the specified time point (see Table 1.3-2); ◆, At a feasible time; ▼, At a feasible time after IMP administration; ○, Optional program; □, Optional program (at the specified time point; see Table 1.3-2)

Optional programs will be conducted only in subjects from whom optional informed consent was obtained at trial sites that agreed to store DNA and/or biomarker samples.

Items that are not permitted to measure at hospitals during the trial period (See Section 6.3): Serum osmolality, plasma AVP concentration, urine osmolality, urine sodium concentration, urine potassium concentration, and urine aquaporin 2 concentration

[a]Subject enrollment and randomization:

The interactive web response system (IWRS) will be used to enroll subjects at the time of informed consent and to randomize them on Day 1. Subjects who meet all of the inclusion criteria and do not fall under any of the exclusion criteria will be randomized to the IMP. Randomization will take place on Day 1 in principle (in the event of absolute necessity only, the subject may be randomized on Day −1, and in that case, the investigator or subinvestigator must reconfirm on Day 1 that the subject meets the inclusion criteria related to concomitant diuretics). Information on IMP administration and trial completion or discontinuation (at completion/discontinuation) will be entered via IWRS.

[b]For subjects who complete the trial early, blood sampling for plasma drug concentration measurement scheduled at the EOT examination and post-treatment examination will be conducted within the specified allowable time windows (see Table 1.3-2) with the time of the final IMP administration as a starting point.

[c]For subjects who discontinue the trial, blood sampling for plasma drug concentration measurement will be conducted at one feasible time point on the day of withdrawal examination.

[d]For subjects who discontinue the trial, blood sampling for plasma drug concentration measurement is not necessary.

[e]Urine aquaporin 2 concentration will be measured on Day −1 and Day 14 (or the final IMP administration day).

[f]For subjects who complete the trial early and those who discontinue the trial, measurement of urine volume and fluid intake at the specified time points is not necessary; only daily urine volume and fluid intake will be measured.

[g]Serum sodium and potassium concentrations will be measured at the central laboratory during the screening period, post-treatment observation period, and follow-up period, and will be measured not only at the central laboratory but also at the trial site during the treatment period.

[h]Serum cystatin C concentration, serum creatinine concentration, plasma AVP concentration, plasma renin activity, plasma aldosterone concentration, plasma BNP concentration, serum troponin I concentration, and serum NT-proBNP concentration

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

[j]Chest X-ray: Cardiothoracic ratio and pulmonary congestion
Only pulmonary congestion will be assessed at screening. For subjects who underwent chest X-ray at clinical examination before participating in the trial, chest X-ray may be omitted at screening examination and instead the X-ray images obtained at the pre-trial examination (within 14 days before informed consent) will be used in assessment.

[k]12-lead ECG will be performed at a predose time and 2 to 4 hours postdose on Day 1, at a feasible postdose time on Day 7, and at a feasible time on other days. If a local measurement of serum potassium concentration is found to exceed 5.5 mEq/L on any day in the treatment period when 12-lead ECG is not scheduled in the protocol, then an additional 12-lead ECG will be performed as an unscheduled examination.

[redacted]

[m]DNA storage: Informed consent will be obtained before blood sampling for DNA storage. The blood sample will be collected before IMP administration on the day of initial administration (Day 1) in principle. If the blood sample is not collected at the specified time point or needs to be recollected, the blood sample will be collected at a feasible time during the trial.

[n]Storage of biomarker samples: Informed consent will be obtained before blood and urine collections. Part of the urine sample will be used in a quantitative test of protein (before IMP administration on Day 1, the result of a qualitative test of protein performed as a part of clinical laboratory tests will be used).

Table 1.3-2 Allowable Time Windows for Postdose Examinations/Assessments

Item	Time Point		Allowable Window
Plasma drug concentration (* for early completers)	Day 1	Predose and before breakfast	Within 2 h predose
		2, 4, 6, and 8 h postdose	Specified time ± 20 min
	Day 2	24 h after Day 1 dosing (predose and before breakfast on Day 2)	Specified time −2 h and predose
	Day 7 and Day 14	24 h after Day 6 or Day 13 dosing (predose and before breakfast on Day 7 or Day 14)	Specified time −2 h and predose
		2, 4, 6, and 8 h postdose	Specified time ± 20 min
	Day 8	24 h after Day 7 dosing (predose and before breakfast on Day 8)	Specified time −2 h and predose
	Day 12	24 h after Day 11 dosing (predose and before breakfast on Day 12)	Specified time −2 h and predose
	Day 15 (EOT examination)	24 h after Day 14 dosing (or final IMP administration*) (before breakfast)	Specified time −2 h
	Day 15 (EOT examination)	32 h after Day 14 dosing (or final IMP administration*)	Specified time ± 90 min
	Day 16 (post-treatment examination)	48 h after Day 14 dosing (or final IMP administration*)	Specified time ± 2 h
Serum electrolyte (sodium, potassium) concentrations, serum osmolality	Day 1 and Day 7	Predose and before breakfast	Within 2 h predose
		4-6 h postdose	–
		8-12 h postdose	–
	Day 2, Day 3, Day 4, Day 5, Day 6, Day 8, Day 10, Day 12, and Day 14	Predose and before breakfast	Within 2 h predose
	Day 2	8 h after Day 2 dosing	Specified time ± 1 h
Biomarker sample storage (plasma, urine)	Day 1	Predose and before breakfast	Within 2 h predose
	Day 1 and Day 7	4 h postdose	Specified time ± 30 min
12-Lead ECG (central)	Day 1	Predose	After wake-up and before dosing
		2-4 h postdose	–
Urine volume/fluid intake/fluid balance in a time point set	Day −1	0-4, 4-8, 8-12, and 12-24 h after breakfast	± 30 min[a]
	Day 1, Day 7, and Day 14	0-4, 4-8, 8-12, and 12-24 h postdose	
	Day 15 (EOT examination)	24-28, 28-32, 32-36, and 36-48 h after Day 14 dosing	

[a]Any allowable window will not be applied to the starting time points of 0 hours after breakfast and 0 hours postdose.

Detailed procedures for the following visits shown in Table 1.3-1 are indicated.

Examinations/assessments will be conducted and recorded as specified in Section 8.1, Section 8.2, Section 8.3, Section 8.4, Section 8.5, Section 8.6, Section 8.7, and Section 8.8.

1.3.1 Informed Consent

Informed consent will be voluntary obtained from all subjects. See Section 10.1.2.

The date of informed consent will be documented in the electronic case report form (eCRF).

1.3.2 Screening

After acquisition of a subject's informed consent, the investigator or subinvestigator will assign a unique subject identifier (ID) number to the subject in accordance with Section 5.1. The date of informed consent and the subject ID number will be recorded in the source documents and eCRF, and the subject will be entered in the IWRS. The IWRS operations will be specified in a separate written procedure, as a system for controlling the enrollment status of subjects.

After acquisition of a subject's informed consent, the following investigations and examinations will be performed as a screening examination within 7 to 4 days before the start of treatment (Day −7 to Day −4) to determine the subject's eligibility for the trial. The results of eligibility assessment will be recorded in the source documents and eCRF.

[Examination and Investigation Items]

- Demographics (date of investigation, date of birth, sex, country in which the trial is being conducted, race, ethnicity, name of underlying disease, type of heart failure, presence/absence and type of arrhythmia, presence/absence of a pacemaker, presence/absence of an implantable cardioverter defibrillator, complications, classification of the complications, medical history [within the past 5 years prior to informed consent]), and classification of the disease underlying CHF
- Results of the eligibility assessment
- Serum electrolyte (sodium, potassium) concentrations, and serum osmolality
- Height (measured to one decimal place in cm; heights measured to more than one decimal place will be rounded to one decimal place.)
- Body weight
- BMI (Formula: BMI = body weight [kg] / height $[m]^2$. BMI will be calculated based on the height and body weight at screening. The first decimal place will be rounded up.)

- Congestive findings (lower limb edema, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound)
- Chest X-ray [Note)] (pulmonary congestion)
- Clinical laboratory tests
- Physical examination
- Vital signs (systolic and diastolic blood pressures, pulse rate, and body temperature)
- 12-Lead ECG (central)
- Check on concomitant medications/therapies
- Adverse events
- Presence/absence of the childbearing potential
- Urine pregnancy test (only for female subjects of childbearing potential; if the test result is positive, a serum pregnancy test will be performed.)

Note) If a chest X-ray was performed in a medical examination before trial participation, the state of pulmonary congestion may be evaluated based on the image obtained in that medical examination (within 14 days prior to informed consent), rather than performing a chest X-ray during the screening examination.

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

The investigator or subinvestigator will perform the following examinations and investigations to determine whether to proceed to the treatment period. Regardless of the usage of diuretics before the run-in period, the dose and dosage regimen of diuretic treatment at the start of the run-in period (Day −3) should not be changed until the end of the post-treatment examination. Hospitalization information will be recorded in the eCRF.

1) Before Breakfast
   - Body weight
   - Vital signs (systolic and diastolic blood pressures, pulse rate, and body temperature)

2) After Breakfast

   Subjects will be instructed to urinate completely after breakfast, and measurement of urine volume and fluid intake will be started to evaluate the items shown below. On Day −1, urine volume in a time point set, fluid intake in a time point set, and fluid balance in a time point set (at the times specified in Table 1.3-2) will also be evaluated.
   - Daily urine volume, daily fluid intake, and daily fluid balance (difference between daily fluid intake and daily urine volume)

- Urine volume in a time point set, fluid intake in a time point set, and fluid balance in a time point set (at the times specified in Table 1.3-2) (on Day −1 only)
- Daily urine osmolality and daily urine electrolyte (sodium, potassium) concentrations (on Day −3 and Day −2)
- Urine osmolality in a time point set, urine electrolyte (sodium, potassium) concentrations in a time point set, and urine aquaporin 2 concentration in a time point set (on Day −1 only)

3) At a Feasible Time on Each Evaluation Day
   - Check on the use of concomitant diuretics
   - Congestive findings (lower limb edema, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound)
   - Physical examination
   - Check on concomitant medications/therapies
   - Adverse events
   - Chest X-ray (cardiothoracic ratio and pulmonary congestion) (once during the run-in period)
   - NYHA Functional Classification (once during the run-in period)
   - 12-Lead ECG (central) (once during the run-in period)
   - [redacted]

1.3.4 Randomization and Proceeding to the Treatment Period

1) Determination of Whether to Proceed to the Treatment Period

   The investigator or subinvestigator will evaluate the use of concomitant diuretics, body weight, and congestive findings during the run-in period, confirm that all of the inclusion criteria (run-in period) are met, and enter the confirmation results in the IWRS. The results of eligibility assessment will be recorded in the source documents and eCRF.

2) Assignment of IMP Treatment to Subjects

   Subjects who meet all of the inclusion criteria (run-in period) will be randomized to one of the 5 groups shown below to receive the IMP in a double-blind manner. In principle, assignment will be performed on Day 1 (Assignment on Day −1 is acceptable if unavoidable. When assignment is performed on Day −1, it should be reconfirmed on Day 1 that the inclusion criteria for concomitant diuretics are met). The investigator or subinvestigator will check the randomization number assigned in the IWRS. The date of randomization, randomization number, and IMP number will be recorded in the eCRF.

- OPC-131461 1-mg group
- OPC-131461 2-mg group
- OPC-131461 5-mg group
- OPC-131461 10-mg group
- Placebo group

1.3.5 Treatment Period (Day 1)

The investigator or subinvestigator will perform the following examinations and investigations.

1) Before Breakfast and IMP Administration
   - Plasma drug concentration (at the time specified in Table 1.3-2)
   - Serum electrolyte (sodium, potassium) concentrations and serum osmolality (at the time specified in Table 1.3-2)
   - Pharmacodynamic laboratory tests (serum cystatin C concentration, serum creatinine concentration, plasma AVP concentration, plasma renin activity, plasma aldosterone concentration, plasma BNP concentration, serum troponin I concentration, and serum NT-proBNP concentration)
   - [redacted]
   - Clinical laboratory tests
   - Body weight
   - Vital signs (systolic and diastolic blood pressures, pulse rate, and body temperature)
   - Blood sampling and urine collection for storage of biomarker samples (optional) (at the time specified in Table 1.3-2)

2) Before IMP Administration
   - 12-Lead ECG (central) (at the time specified in Table 1.3-2)
   - Blood sampling for DNA storage (optional)

3) After Breakfast

   Subjects will be instructed to urinate completely after breakfast and by the time immediately before administration, and measurement of urine volume and fluid intake will be started after complete urination immediately before administration, which will be set as the starting time point to evaluate the items shown below.
   - Urine volume in a time point set, fluid intake in a time point set, and fluid balance in a time point set (at the times specified in Table 1.3-2)
   - Urine osmolality in a time point set and urine electrolyte (sodium, potassium) concentrations in a time point set

4) IMP Administration

After confirming that a subject meets all of the inclusion criteria and do not fall under any of the exclusion criteria, the investigator or subinvestigator will instruct the subject to take the IMP. The investigator or subinvestigator will confirm that the subject has taken the IMP completely, and record the date and time of administration and the dose in the source documents and eCRF.

- Status of IMP administration

5) After IMP Administration

- Plasma drug concentration (at the time specified in Table 1.3-2)
- Serum electrolyte (sodium, potassium) concentrations and serum osmolality (at the time specified in Table 1.3-2)
- 12-Lead ECG (central) (at the time specified in Table 1.3-2)
- Blood sampling and urine collection for storage of biomarker samples (optional) (at the time specified in Table 1.3-2)
- Urine volume in a time point set, fluid intake in a time point set, and fluid balance in a time point set (at the times specified in Table 1.3-2)
- Urine osmolality in a time point set and urine electrolyte (sodium, potassium) concentrations in a time point set

6) At a Feasible Time after IMP Administration

- Congestive findings (lower limb edema, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound)

7) At a Feasible Time

- Check on the use of concomitant diuretics
- Adverse events
- Physical examination
- Check on concomitant medications/therapies

1.3.6 Treatment Period (Day 2)

The investigator or subinvestigator will perform the following examinations and investigations.

1) Before Breakfast and IMP Administration

- Plasma drug concentration (at the time specified in Table 1.3-2)
- Serum electrolyte (sodium, potassium) concentrations and serum osmolality (at the time specified in Table 1.3-2)

- Body weight
- Vital signs (systolic and diastolic blood pressures, pulse rate, and body temperature)

2) After Breakfast

   Subjects will be instructed to urinate completely after breakfast and by the time immediately before administration, and measurement of urine volume and fluid intake will be started after complete urination immediately before administration, which will be set as the starting time point to evaluate the items shown below.

   - Daily urine volume, daily fluid intake, and daily fluid balance
   - Daily urine osmolality and daily urine electrolyte (sodium, potassium) concentrations

3) IMP Administration

   The investigator or subinvestigator will confirm that the subject has taken the IMP completely, and record the date and time of administration and the dose in the source documents and eCRF.

   - Status of IMP administration

4) After IMP Administration

   - Serum electrolyte (sodium, potassium) concentrations and serum osmolality (at the time specified in Table 1.3-2)

5) At a Feasible Time after IMP Administration

   - Congestive findings (lower limb edema, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound)

6) At a Feasible Time

   - Check on the use of concomitant diuretics
   - Adverse events
   - Physical examination
   - Check on concomitant medications/therapies

1.3.7 Treatment Period (Day 3 and Day 4)

The investigator or subinvestigator will perform the following examinations and investigations.

1) Before Breakfast and IMP Administration
   - Serum electrolyte (sodium, potassium) concentrations and serum osmolality (at the time specified in Table 1.3-2)
   - Body weight
   - Vital signs (systolic and diastolic blood pressures, pulse rate, and body temperature)

2) After Breakfast

   Subjects will be instructed to urinate completely after breakfast and by the time immediately before administration, and measurement of urine volume and fluid intake will be started after complete urination immediately before administration, which will be set as the starting time point to evaluate the items shown below.
   - Daily urine volume, daily fluid intake, and daily fluid balance
   - Daily urine osmolality and daily urine electrolyte (sodium, potassium) concentrations

3) IMP Administration

   The investigator or subinvestigator will confirm that the subject has taken the IMP completely, and record the date and time of administration and the dose in the source documents and eCRF.
   - Status of IMP administration

4) At a Feasible Time after IMP Administration
   - Congestive findings (lower limb edema, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound)

5) At a Feasible Time
   - Check on the use of concomitant diuretics
   - 12-Lead ECG (central) (once on Day 3 or Day 4)
   - Adverse events
   - Physical examination
   - Check on concomitant medications/therapies

1.3.8 Treatment Period (Day 5)

The investigator or subinvestigator will perform the following examinations and investigations.

1) Before Breakfast and IMP Administration
   - Serum electrolyte (sodium, potassium) concentrations and serum osmolality (at the time specified in Table 1.3-2)
   - Body weight
   - Vital signs (systolic and diastolic blood pressures, pulse rate, and body temperature)

2) After Breakfast

   Subjects will be instructed to urinate completely after breakfast and by the time immediately before administration, and measurement of urine volume and fluid intake will be started after complete urination immediately before administration, which will be set as the starting time point to evaluate the items shown below.
   - Daily urine volume, daily fluid intake, and daily fluid balance
   - Daily urine osmolality and daily urine electrolyte (sodium, potassium) concentrations

3) IMP Administration

   The investigator or subinvestigator will confirm that the subject has taken the IMP completely, and record the date and time of administration and the dose in the source documents and eCRF.
   - Status of IMP administration

4) At a Feasible Time after IMP Administration
   - Congestive findings (lower limb edema, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound)

5) At a Feasible Time
   - Check on the use of concomitant diuretics
   - Adverse events
   - Physical examination
   - Check on concomitant medications/therapies

1.3.9 Treatment Period (Day 6)

The investigator or subinvestigator will perform the following examinations and investigations.

1) Before Breakfast and IMP Administration
   - Serum electrolyte (sodium, potassium) concentrations and serum osmolality (at the time specified in Table 1.3-2)

- Body weight
- Vital signs (systolic and diastolic blood pressures, pulse rate, and body temperature)

2) After Breakfast

Subjects will be instructed to urinate completely after breakfast and by the time immediately before administration, and measurement of urine volume and fluid intake will be started after complete urination immediately before administration, which will be set as the starting time point to evaluate the items shown below.

- Daily urine volume, daily fluid intake, and daily fluid balance
- Daily urine osmolality and daily urine electrolyte (sodium, potassium) concentrations

3) IMP Administration

The investigator or subinvestigator will confirm that the subject has taken the IMP completely, and record the date and time of administration and the dose in the source documents and eCRF.

- Status of IMP administration

4) At a Feasible Time after IMP Administration

- Congestive findings (lower limb edema, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound)

5) At a Feasible Time

- Check on the use of concomitant diuretics
- Adverse events
- Physical examination
- Check on concomitant medications/therapies

1.3.10 Treatment Period (Day 7)

The investigator or subinvestigator will perform the following examinations and investigations.

1) Before Breakfast and IMP Administration

- Plasma drug concentration (at the time specified in Table 1.3-2)
- Serum electrolyte (sodium, potassium) concentrations and serum osmolality (at the time specified in Table 1.3-2)
- Body weight

- Vital signs (systolic and diastolic blood pressures, pulse rate, and body temperature)

2) After Breakfast

Subjects will be instructed to urinate completely after breakfast and by the time immediately before administration, and measurement of urine volume and fluid intake will be started after complete urination immediately before administration, which will be set as the starting time point to evaluate the items shown below.

- Urine volume in a time point set, fluid intake in a time point set, and fluid balance in a time point set (at the times specified in Table 1.3-2)
- Urine osmolality in a time point set and urine electrolyte (sodium, potassium) concentrations in a time point set

3) IMP Administration

The investigator or subinvestigator will confirm that the subject has taken the IMP completely, and record the date and time of administration and the dose in the source documents and eCRF.

- Status of IMP administration

4) After IMP Administration

- Plasma drug concentration (at the time specified in Table 1.3-2)
- Serum electrolyte (sodium, potassium) concentrations and serum osmolality (at the time specified in Table 1.3-2)
- Blood sampling and urine collection for storage of biomarker samples (optional) (at the time specified in Table 1.3-2)
- Urine volume in a time point set, fluid intake in a time point set, and fluid balance in a time point set (at the times specified in Table 1.3-2)
- Urine osmolality in a time point set and urine electrolyte (sodium, potassium) concentrations in a time point set

5) At a Feasible Time after IMP Administration

- Congestive findings (lower limb edema, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound)
- Chest X-ray (cardiothoracic ratio and pulmonary congestion)
- NYHA Functional Classification
- 12-Lead ECG (central)

6) At a Feasible Time

- Check on the use of concomitant diuretics
- Adverse events

- Physical examination
- Check on concomitant medications/therapies

1.3.11 Treatment Period (Day 8)

The investigator or subinvestigator will perform the following examinations and investigations.

1) Before Breakfast and IMP Administration
   - Plasma drug concentration (at the time specified in Table 1.3-2)
   - Serum electrolyte (sodium, potassium) concentrations and serum osmolality (at the time specified in Table 1.3-2)
   - Pharmacodynamic laboratory tests (serum cystatin C concentration, serum creatinine concentration, plasma AVP concentration, plasma renin activity, plasma aldosterone concentration, plasma BNP concentration, serum troponin I concentration, and serum NT-proBNP concentration)
   - [redacted]
   - Clinical laboratory tests
   - Body weight
   - Vital signs (systolic and diastolic blood pressures, pulse rate, and body temperature)

2) After Breakfast

   Subjects will be instructed to urinate completely after breakfast and by the time immediately before administration, and measurement of urine volume and fluid intake will be started after complete urination immediately before administration, which will be set as the starting time point to evaluate the items shown below.
   - Daily urine volume, daily fluid intake, and daily fluid balance
   - Daily urine osmolality and daily urine electrolyte (sodium, potassium) concentrations

3) IMP Administration

   The investigator or subinvestigator will confirm that the subject has taken the IMP completely, and record the date and time of administration and the dose in the source documents and eCRF.
   - Status of IMP administration

4) At a Feasible Time after IMP Administration
   - Congestive findings (lower limb edema, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound)

5) At a Feasible Time
   - Check on the use of concomitant diuretics
   - Adverse events
   - Physical examination
   - Check on concomitant medications/therapies

1.3.12 Treatment Period (Day 9 and Day 11)

The investigator or subinvestigator will perform the following examinations and investigations.

1) Before Breakfast and IMP Administration
   - Body weight
   - Vital signs (systolic and diastolic blood pressures, pulse rate, and body temperature)

2) After Breakfast

   Subjects will be instructed to urinate completely after breakfast and by the time immediately before administration, and measurement of urine volume and fluid intake will be started after complete urination immediately before administration, which will be set as the starting time point to evaluate the items shown below.
   - Daily urine volume, daily fluid intake, and daily fluid balance
   - Daily urine osmolality and daily urine electrolyte (sodium, potassium) concentrations

3) IMP Administration

   The investigator or subinvestigator will confirm that the subject has taken the IMP completely, and record the date and time of administration and the dose in the source documents and eCRF.
   - Status of IMP administration

4) At a Feasible Time after IMP Administration
   - Congestive findings (lower limb edema, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound)

5) At a Feasible Time
   - Check on the use of concomitant diuretics
   - Adverse events
   - Physical examination
   - Check on concomitant medications/therapies

1.3.13 Treatment Period (Day 10)

The investigator or subinvestigator will perform the following examinations and investigations.

1) Before Breakfast and IMP Administration
   - Serum electrolyte (sodium, potassium) concentrations and serum osmolality (at the time specified in Table 1.3-2)
   - Body weight
   - Vital signs (systolic and diastolic blood pressures, pulse rate, and body temperature)

2) After Breakfast

   Subjects will be instructed to urinate completely after breakfast and by the time immediately before administration, and measurement of urine volume and fluid intake will be started after complete urination immediately before administration, which will be set as the starting time point to evaluate the items shown below.
   - Daily urine volume, daily fluid intake, and daily fluid balance
   - Daily urine osmolality and daily urine electrolyte (sodium, potassium) concentrations

3) IMP Administration

   The investigator or subinvestigator will confirm that the subject has taken the IMP completely, and record the date and time of administration and the dose in the source documents and eCRF.
   - Status of IMP administration

4) At a Feasible Time after IMP Administration
   - Congestive findings (lower limb edema, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound)

5) At a Feasible Time
   - Check on the use of concomitant diuretics
   - Adverse events
   - Physical examination
   - Check on concomitant medications/therapies

1.3.14 Treatment Period (Day 12)

The investigator or subinvestigator will perform the following examinations and investigations.

1) Before Breakfast and IMP Administration
   - Plasma drug concentration (at the time specified in Table 1.3-2)
   - Serum electrolyte (sodium, potassium) concentrations and serum osmolality (at the time specified in Table 1.3-2)
   - Body weight
   - Vital signs (systolic and diastolic blood pressures, pulse rate, and body temperature)

2) After Breakfast

   Subjects will be instructed to urinate completely after breakfast and by the time immediately before administration, and measurement of urine volume and fluid intake will be started after complete urination immediately before administration, which will be set as the starting time point to evaluate the items shown below.
   - Daily urine volume, daily fluid intake, and daily fluid balance
   - Daily urine osmolality and daily urine electrolyte (sodium, potassium) concentrations

3) IMP Administration

   The investigator or subinvestigator will confirm that the subject has taken the IMP completely, and record the date and time of administration and the dose in the source documents and eCRF.
   - Status of IMP administration

4) At a Feasible Time after IMP Administration
   - Congestive findings (lower limb edema, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound)

5) At a Feasible Time
   - Check on the use of concomitant diuretics
   - Adverse events
   - Physical examination
   - Check on concomitant medications/therapies

1.3.15 Treatment Period (Day 13)

The investigator or subinvestigator will perform the following examinations and investigations.

1) Before Breakfast and IMP Administration
   - Body weight
   - Vital signs (systolic and diastolic blood pressures, pulse rate, and body temperature)

2) After Breakfast

   Subjects will be instructed to urinate completely after breakfast and by the time immediately before administration, and measurement of urine volume and fluid intake will be started after complete urination immediately before administration, which will be set as the starting time point to evaluate the items shown below.
   - Daily urine volume, daily fluid intake, and daily fluid balance
   - Daily urine osmolality and daily urine electrolyte (sodium, potassium) concentrations

3) IMP Administration

   The investigator or subinvestigator will confirm that the subject has taken the IMP completely, and record the date and time of administration and the dose in the source documents and eCRF.
   - Status of IMP administration

4) At a Feasible Time after IMP Administration
   - Congestive findings (lower limb edema, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound)

5) At a Feasible Time
   - Check on the use of concomitant diuretics
   - Adverse events
   - Physical examination
   - Check on concomitant medications/therapies

1.3.16 Treatment Period (Day 14)

The investigator or subinvestigator will perform the following examinations and investigations.

1) Before Breakfast and IMP Administration
   - Plasma drug concentration (at the time specified in Table 1.3-2)
   - Serum electrolyte (sodium, potassium) concentrations and serum osmolality (at the time specified in Table 1.3-2)
   - Body weight
   - Vital signs (systolic and diastolic blood pressures, pulse rate, and body temperature)

2) After Breakfast

   Subjects will be instructed to urinate completely after breakfast and by the time immediately before administration, and measurement of urine volume and fluid intake will be started after complete urination immediately before administration, which will be set as the starting time point to evaluate the items shown below. Urine volume in a time point set, fluid intake in a time point set, and fluid balance in a time point set (at the times specified in Table 1.3-2) will also be evaluated.
   - Urine volume in a time point set, fluid intake in a time point set, and fluid balance in a time point set (at the times specified in Table 1.3-2)
   - Urine osmolality in a time point set, urine electrolyte (sodium, potassium) concentrations in a time point set, and urine aquaporin 2 concentration in a time point set

3) IMP Administration

   The investigator or subinvestigator will confirm that the subject has taken the IMP completely, and record the date and time of administration and the dose in the source documents and eCRF.
   - Status of IMP administration

4) After IMP Administration
   - Plasma drug concentration (at the time specified in Table 1.3-2)
   - Urine volume in a time point set, fluid intake in a time point set, and fluid balance in a time point set (at the times specified in Table 1.3-2)
   - Urine osmolality in a time point set, urine electrolyte (sodium, potassium) concentrations in a time point set, and urine aquaporin 2 concentration in a time point set

5) At a Feasible Time after IMP Administration
   - Congestive findings (lower limb edema, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound)

6) At a Feasible Time
   - Check on the use of concomitant diuretics
   - Adverse events
   - Physical examination
   - Check on concomitant medications/therapies

1.3.17 Treatment Period (End of Treatment Examination on Day 15 or Withdrawal Examination: the Day after the Final IMP Administration)

The investigator or subinvestigator will perform the following examinations and investigations on the day after the final IMP administration or at discontinuation. Completion of the EOT examination or withdrawal examination will be entered in the IWRS.

1) Before Breakfast
   - Plasma drug concentration (at the time specified in Table 1.3-2; only for completers and early completers)
   - Serum electrolyte (sodium, potassium) concentrations, and serum osmolality
   - Pharmacodynamic laboratory tests (serum cystatin C concentration, serum creatinine concentration, plasma AVP concentration, plasma renin activity, plasma aldosterone concentration, plasma BNP concentration, serum troponin I concentration, and serum NT-proBNP concentration)
   - [redacted]
   - Clinical laboratory tests
   - Body weight
   - Vital signs (systolic and diastolic blood pressures, pulse rate, and body temperature)

2) After Breakfast
   - Plasma drug concentration (at the time specified in Table 1.3-2; only for completers and early completers)
     Subjects will be instructed to urinate completely after breakfast, and measurement of urine volume and fluid intake will be started after complete urination, which will be set as the starting time point to evaluate the items shown below.
   - Daily urine volume, daily fluid intake, and daily fluid balance (only for early completers and withdrawals)
   - Daily urine osmolality and daily urine electrolyte (sodium, potassium) concentrations (only for early completers and withdrawals)

- Urine volume in a time point set, fluid intake in a time point set, and fluid balance in a time point set (at the times specified in Table 1.3-2; only for completers)
- Urine osmolality in a time point set, and urine electrolyte (sodium, potassium) concentrations in a time point set (only for completers)

3) At a Feasible Time
   - Check on the use of concomitant diuretics
   - Congestive findings (lower limb edema, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound)
   - Chest X-ray (cardiothoracic ratio and pulmonary congestion)
   - NYHA Functional Classification
   - 12-Lead ECG (central)
   - Adverse events
   - Physical examination
   - Check on concomitant medications/therapies
   - Plasma drug concentration (only for withdrawals)
   - [redacted]

1.3.18 Post-treatment Observation Period (Post-treatment Examination on Day 16: 2 Days after the Final IMP Administration)

The investigator or subinvestigator will perform the following examinations and investigations 2 days after the final IMP administration.

1) At a Specified Time
   - Plasma drug concentration (at the time specified in Table 1.3-2; only for completers and early completers)

2) Before Breakfast
   - Serum electrolyte (sodium, potassium) concentrations, and serum osmolality
   - Clinical laboratory tests
   - Body weight
   - Vital signs (systolic and diastolic blood pressures, pulse rate, and body temperature)

3) After Breakfast

Subjects will be instructed to urinate completely after breakfast, and measurement of urine volume and fluid intake will be ended when the complete urination after breakfast is finished, which will be set as the ending time point to evaluate the items shown below.

- Daily urine volume, daily fluid intake, and daily fluid balance (only for early completers and withdrawals)
- Daily urine osmolality and daily urine electrolyte (sodium, potassium) concentrations (only for early completers and withdrawals)
- Urine volume in a time point set, fluid intake in a time point set, and fluid balance in a time point set (at the times specified in Table 1.3-2; only for completers)
- Urine osmolality in a time point set, and urine electrolyte (sodium, potassium) concentrations in a time point set (only for completers)

4) At a Feasible Time

- Check on the use of concomitant diuretics
- Congestive findings (lower limb edema, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound)
- 12-Lead ECG (central)
- Adverse events
- Physical examination
- Check on concomitant medications/therapies
- [redacted]

1.3.19 Follow-up Examination (Day 24 to Day 28: 10 to 14 Days after the Final IMP Administration)

The investigator or subinvestigator will perform the following examinations and investigations between 10 and 14 days after the final IMP administration. Subjects who have been discharged will undergo the examinations and investigations on an outpatient basis. Discharge information will be recorded in the eCRF.

1) Before Breakfast

- Serum electrolyte (sodium, potassium) concentrations, and serum osmolality
- [redacted]
- Clinical laboratory tests
- Body weight

- Vital signs (systolic and diastolic blood pressures, pulse rate, and body temperature)

2) At a Feasible Time
   - Plasma drug concentration (only for completers and early completers)
   - Congestive findings (lower limb edema, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound)
   - 12-Lead ECG (central)
   - Adverse events
   - Physical examination
   - Check on the use of concomitant medications/therapies
   - Urine pregnancy test (only for female subjects of childbearing potential; if the test result is positive, a serum pregnancy test will be performed.)

2 Introduction

OPC-131461 is a new orally available vasopressin antagonist with vasopressin V_{1a} and V_2 receptor dual antagonism. As OPC-131461 is expected to become a treatment for cardiac edema, etc, Otsuka Pharmaceutical Co., Ltd. (hereinafter, Otsuka) decided to begin the clinical development of OPC-131461.

Refer to the current OPC-131461 Investigator's Brochure (IB) for more detailed information.

2.1 Trial Rationale

In patients with congestive heart failure (CHF), congestive edematous symptoms secondary to heart failure such as jugular venous distension, lower limb edema, and hepatomegaly are observed. Diuretics (mainly loop diuretics) are commonly used to reduce edematous symptoms, but Samsca® (tolvaptan) is recommended to be used for the improvement of volume overload when adequate response is not obtained despite having received the conventional diuretics.[1,2] While widely used in clinical practice, tolvaptan is likely to induce adverse reactions due to its pharmacological action in the early stage of treatment. Particularly, hypernatremia-related adverse reactions (eg, hypernatremia and increased serum sodium concentrations) may lead to serious adverse reactions such as disturbed consciousness and osmotic demyelination syndrome. When using tolvaptan, healthcare professionals are required to take additional measures in order to ensure the safety of patients, including hospitalization of patients to begin or resume tolvaptan treatment and frequent monitoring of serum sodium concentrations particularly on the day that tolvaptan treatment is started or resumed. This is a challenge of tolvaptan compared to other conventional diuretics.

OPC-131461 was studied in a phase 1, single and multiple dose clinical trial of OPC-131461 suspension in healthy adult male subjects (Protocol No. 351-102-00001; hereinafter referred to as "Japanese phase 1 single and multiple dose trial"), the results of which demonstrated that OPC-131461 suspension was safe and tolerable when orally administered at 5 to 320 mg as a single dose or at 5, 40, and 100 mg as multiple doses for 14 days. OPC-131461 was also confirmed to be antagonistic to vasopressin V_2 receptors as seen in tolvaptan and have a longer half-life than tolvaptan, with a slow increase in the plasma drug concentration to reach the steady state. These findings indicate that OPC-131461 can be considered to become a novel aquaretic in patients with CHF that can reduce pharmacology-related adverse reactions that likely occur early in treatment, which is a challenge of tolvaptan, by using the dose at which the aquaretic effect is

exerted more slowly at the early stage of treatment compared to tolvaptan and is expected to adequately reduce body weight and improve congestive findings by continued treatment even though the aquaretic effect at the early stage of treatment is slower than tolvaptan. On the other hand, there is no clinical experience with OPC-131461 in patients with CHF. Therefore, Otsuka has planned a Japanese phase 2 dose-ranging trial (hereinafter referred to as "the trial") to investigate the dose response in respect of weight decrease following repeated oral administration of OPC-131461 at 1, 2, 5, and 10 mg or placebo in patients with CHF with volume overload despite having received diuretics other than vasopressin antagonists.

In conclusion, the conduct of the trial can be justified from scientific and ethical standpoints.

2.2 Background

OPC-131461 is a new orally available vasopressin V_{1a} and V_2 receptor dual antagonist developed by Otsuka. Samsca® (tolvaptan), a V_2 receptor antagonist as is OPC-131461, was first granted marketing approval as an oral aquaretic agent in Japan in October 2010, and it has proved to be a useful treatment for heart failure patients with volume overload despite having received the conventional diuretics. Although tolvaptan is the only vasopressin receptor antagonist orally available for the treatment of volume overload secondary to heart failure, there are challenges in clinical practice that treatment of tolvaptan requires to be started or resumed under hospitalization since hypernatremia-related adverse reactions may occur and lead to serious adverse reactions due to the potent aquaretic effect at the early stage of starting the treatment and that it particularly requires a frequent measurement of serum sodium concentration on the day of start or resumption of administration. A vasopressin receptor antagonist that resolves those challenges is called for by medical institutions.

[redacted]

[redacted]

OPC-131461 may be a solution to the challenges of tolvaptan when used at the dose at which the aquaretic effect is exerted more slowly than tolvaptan in the early stage of treatment to prevent a rapid increase in serum sodium concentrations and thus improve volume overload in a safer manner in patients with CHF.

Based on the above, Otsuka has planned the trial to evaluate the efficacy and safety of OPC-131461 tablet in patients with CHF.

2.2.1 Nonclinical Data

[redacted]

[redacted]

[redacted]

Please refer to the current version of the OPC-131461 IB for more detailed information on the results of nonclinical studies.

2.2.2 Clinical Data

1) Phase 1 Single and Multiple Oral Dose Trial of OPC-13146 Suspension in Healthy Adult Male Subjects (Protocol No. 351-102-00001, Japan)

   This trial consisted of Part A in which OPC-131461 suspension at 5, 10, 20, 40, 80, 160, and 320 mg was orally administered as a single dose and Part B in which OPC-131461 suspension at 5, 40, and 100 mg was orally administered as multiple doses for 14 days to evaluate the safety, tolerability, PK, and pharmacodynamics (PD) of oral OPC-131461 suspension in healthy adult male subjects.

a) Part A (Single Oral Administration)

Of 56 healthy adult male subjects enrolled, 42 subjects (6 subjects/group) received a single oral administration of OPC-131461 suspension at 5, 10, 20, 40, 80, 160, and 320 mg, and 14 control subjects (2 subjects/group) received a single oral administration of placebo.

The maximum (peak) plasma concentration of the drug (C_{max}), area under the concentration-time curve from time zero to infinity (AUC_{∞}), and area under the concentration-time curve calculated to the last observable concentration at time t (AUC_t) of OPC-131461 increased dose-dependently in subjects treated with a single oral dose of OPC-131461 suspension at 5 to 320 mg. The median t_{max} was 2.00 to 4.00 hours and the mean $t_{1/2,z}$ was 20.9 to 29.8 hours. The daily urine volume increased dose-dependently from baseline in all treatment groups, and OPC-131461 at 5 mg was associated with a daily urine volume equivalent to that after administration of tolvaptan at 15 mg (Protocol No. 156-00-001). Following OPC-131461 administration, the percent of inhibition of AVP-induced platelet aggregation increased from predose in each active group or placebo, with a marked increase at 20 mg or higher.

Seventy-five adverse events (AEs) occurred in 33 of 42 OPC-131461-treated subjects (78.6%) and 3 AEs in 2 of 14 placebo-treated subjects (14.3%). The majority of AEs, except for 6 events in OPC-131461-treated subjects and 1 event in placebo-treated subjects, were judged to be related to OPC-131461. All events were mild or moderate in severity, with no severe events reported. The AEs with a higher incidence were polyuria (29/42 subjects) and thirst (23/42 subjects). Among AEs considered to be related to the pharmacology of the investigational medicinal product (IMP), 9 events of orthostatic hypotension or blood pressure orthostatic decreased were reported in 8 of 42 OPC-131461-treated subjects and 2 such events were reported in 2 of 14 placebo-treated subjects. All of these events were mild in severity and resolved within 24 hours of onset. All the events were judged to be related to OPC-131461 with the exception of 1 event that occurred in 1 subject the day after single administration of OPC-131461 at 5 mg. Two AEs leading to trial discontinuation (hypernatraemia and orthostatic hypotension) were reported in 2 subjects following single oral administration at the highest dose of 320 mg. Both events were judged to be related to OPC-131461, however, they were mild in severity and resolved within 24 hours of onset. Adverse reactions reported in more than 1 subject in any treatment group after single oral administration of OPC-131461 suspension at 5 to 320 mg are summarized in Table 2.2.2-1.

Table 2.2.2-1 Adverse Reactions Reported in more than 1 Subject in Any Treatment Group after Single Oral Administration of OPC-131461 Suspension at 5 to 320 mg

	OPC-131461								Placebo
Preferred Term	5 mg (N = 6) n (%)	10 mg (N = 6) n (%)	20 mg (N = 6) n (%)	40 mg (N = 6) n (%)	80 mg (N = 6) n (%)	160 mg (N = 6) n (%)	320 mg (N = 6) n (%)	Total (N = 42) n (%)	(N = 14) n (%)
Thirst	0 (0.0)	1 (16.7)	1 (16.7)	4 (66.7)	6 (100.0)	5 (83.3)	6 (100.0)	23 (54.8)	0 (0.0)
Polyuria	0 (0.0)	1 (16.7)	4 (66.7)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	29 (69.0)	0 (0.0)
Orthostatic hypotension	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (16.7)	2 (33.3)	4 (9.5)	2 (14.3)

b) Part B (Repeated Oral Administration)

Of 26 healthy adult male subjects enrolled, 5, 6, and 6 subjects received 14-day repeated oral administration of OPC-131461 suspension at respectively 5, 40, and 100 mg and 9 control subjects (3 subjects/group) received 14-day repeated oral administration of placebo.

The C_{max} and area under the concentration-time curve from time zero to 24 hours (AUC_{24h}) of OPC-131461 increased dose-dependently in subjects treated with multiple oral doses of OPC-131461 suspension at 5, 40, and 100 mg. The accumulation ratio for C_{max} and AUC_{24h} on Day 14 versus Day 1 at 5, 40, and 100 mg was respectively 1.64, 0.915, and 0.731, and respectively 1.60, 0.796, and 0.625. Fourteen days of oral administration of OPC-131461 at 5 mg resulted in approximately 1.6-fold accumulation of C_{max} and AUC_{24h}, whereas at 40 and 100 mg, accumulation of C_{max} and AUC_{24h} decreased dose-dependently. The median t_{max} was 1.50 to 3.00 hours and the mean $t_{1/2,z}$ was 18.5 to 28.4 hours. The daily urine volume increased dose-dependently from baseline in all treatment groups and almost returned to the baseline urine volume 2 days after the final IMP administration. Following OPC-131461 administration, the percent of inhibition of AVP-induced platelet aggregation increased from predose in each active group or placebo.

Sixty-two AEs occurred in 15 of 17 OPC-131461-treated subjects (88.2%) and 4 AEs in 3 of 9 placebo-treated subjects (33.3%). The majority of AEs, except for 8 events in 6 OPC-131461-treated subjects and 1 event in one placebo-treated subject, were judged to be related to OPC-131461. All events were mild or moderate in severity, with no severe events reported. The AEs with a higher incidence were polyuria (13/17 subjects) and thirst (11/17 subjects). Among AEs considered to be related to the pharmacology of the IMP, 22 events of orthostatic hypotension or blood pressure orthostatic decreased were reported in 7 of 17 OPC-131461-treated subjects and 3 such events were reported in 3 of 9 placebo-treated subjects. All of these events were mild in severity and judged to be related to OPC-131461. Two events in the 100 mg group took 3 days to resolve and all the other events resolved within approximately 24 hours of onset. In the 40 mg group, 2 AEs leading to treatment discontinuation (hypernatraemia and tonsillitis) were reported in

2 subjects. The event of hypernatraemia was judged to be related to OPC-131461 and was mild in severity and resolved within 24 hours after treatment discontinuation. The event of tonsillitis was judged to be unrelated to OPC-131461 and was moderate in severity and resolved 6 days after onset. Adverse reactions reported in more than 1 subject in any treatment group after repeated oral administration of OPC-131461 suspension at 5, 40, and 100 mg are summarized in Table 2.2.2-2.

Table 2.2.2-2 Adverse Reactions Reported in more than 1 Subject in Any Treatment Group after Repeated Oral Administration of OPC-131461 Suspension at 5, 40, and 100 mg

	OPC-131461				Placebo
Preferred Term	5 mg (N = 5) n (%)	40 mg (N = 6) n (%)	100 mg (N = 6) n (%)	Total (N = 17) n (%)	(N = 9) n (%)
Thirst	1 (20.0)	6 (100.0)	4 (66.7)	11 (64.7)	0 (0.0)
Blood pressure orthostatic decreased	2 (40.0)	0 (0.0)	2 (33.3)	4 (23.5)	1 (11.1)
Headache	0 (0.0)	2 (33.3)	0 (0.0)	2 (11.8)	0 (0.0)
Polyuria	1 (20.0)	6 (100.0)	6 (100.0)	13 (76.5)	0 (0.0)
Orthostatic hypotension	1 (20.0)	1 (16.7)	2 (33.3)	4 (23.5)	2 (22.2)

No serious adverse events (SAEs) including death were reported in any treatment group in Parts A and B. In addition, there were no clinically significant findings or abnormalities in prothrombin time-international normalized ratio (PT-INR) or activated partial thromboplastin time (APTT) for assessment of bleeding/bleeding tendency or in 12-lead ECG.

In conclusion, OPC-131461 suspension was safe and tolerable when administered as a single oral dose of 5 to 320 mg or as multiple oral doses of 5, 40, and 100 mg for 14 days.

2) Phase 1 Relative Bioavailability and Food Effect Trial of OPC-131461 in Healthy Adult Male Subjects (Protocol No. 351-102-00002, Japan)

In this 2-group, 2-period crossover trial, healthy adult male subjects received single oral administration of OPC-131461 suspension at 20 mg or four OPC-131461 5-mg tablets in the relative BA part and the food effect part. Preliminary PK and safety results were available when the original version of this protocol was finalized.

No SAEs including death were reported in any treatment group.

a) Relative BA part

A total of 8 healthy adult male subjects (4 in the suspension-first group and 4 in the tablet-first group) orally received OPC-131461 suspension or OPC-131461 tablets to investigate the PK of both formulations.

The geometric mean ratio for C_{max} and area under the concentration-time curve (AUC) after OPC-131461 tablet (5 mg) administration at 20 mg versus OPC-131461 suspension administration at 20 mg was respectively 0.89 and 1.01. The median t_{max} after OPC-131461 suspension administration at 20 mg and after OPC-131461 tablet (5 mg) administration at 20 mg was respectively 2.50 and 3.50 hours and the mean $t_{1/2,z}$ was respectively 24.0 and 23.7 hours.

The AEs with a higher incidence were polyuria and thirst. All these events were mild in severity, judged to be related to OPC-131461, and resolved. Apart from polyuria and thirst, no other AEs probably related to the pharmacology of the IMP were reported.

b) Food effect part

A total of 8 healthy adult male subjects (4 in the tablet fasting-state-first group and 4 in the tablet fed-state-first group) orally received OPC-131461 5-mg tablets to investigate the effect of food (high-fat meal) on the PK of OPC-131461.

The C_{max} and AUC after administration of OPC-131461 5-mg tablets at 20 mg in the fed state were respectively 1.20 and 1.14 times those after administration in the fasting state. The median t_{max} was 3.50 hours and the mean $t_{1/2,z}$ was 24.7 hours regardless of whether OPC-131461 5-mg tablets at 20 mg were administered in the fed state or in the fasting state.

The AEs with a higher incidence were polyuria and thirst. All these events were mild in severity, judged to be related to OPC-131461, and resolved. Apart from polyuria and thirst, no other AEs probably related to the pharmacology of the IMP were reported.

Please refer to the current version of the OPC-131461 IB for more detailed information on the results of clinical trials.

2.3 Known and Potential Risks and Benefits

Although there is no clinical experience of OPC-131461 in patients with CHF, a Japanese phase 1 single and multiple dose trial in healthy adult male subjects has demonstrated that OPC-131461 possesses vasopressin V_2 receptor antagonism as observed with tolvaptan, indicating that OPC-131461 may offer similar benefits to those of tolvaptan. Tolvaptan is effective in reducing body weight and improving cardiac edema-related findings (jugular venous distension, hepatomegaly, and lower limb edema) in patients with CHF.

Potential risks of treatment with OPC-131461 in patients with CHF were indicated by several results from safety pharmacology and toxicity studies in rats and dogs (see the current version of IB for detailed information) as well as changes that may occur in association with the pharmacology of OPC-131461, including hypotension, bleeding, increased serum sodium concentration, polyuria, thirst, and dehydration/hypovolemia. Events associated with the pharmacological action of OPC-131461 were observed in a Japanese phase 1 single and multiple dose trial of OPC-131461 suspension in healthy adult male subjects and a Japanese phase 1 relative bioavailability and food effect trial of OPC-131461 tablet, which were conducted to date. Additional information on these trials is provided in Section 2.2.2. The adverse reactions reported in these trials may also occur in patients with CHF and it is recommended to closely monitor the subjects of the present trial and allow them to drink water without restriction.

It has been confirmed that OPC-131461 tablet has similar oral absorbability to that of OPC-131461 suspension and is associated with only a minor food effect. Given these findings, the potential risks of OPC-131461 tablet are comparable to those of OPC-131461 suspension.

Trial sites will receive updated versions of the IB, when available, and trial sites should refer to the most current version as needed.

3 Objectives and Endpoints

The objectives and endpoints of this trial are shown in Table 3-1.

Table 3-1 Trial Objectives and Endpoints

Objectives	Endpoints
Primary Objectives: To investigate the dose response in respect of weight decrease following repeated oral administration of OPC-131461 at 1, 2, 5, and 10 mg or placebo in patients with CHF with volume overload despite having received diuretics other than vasopressin antagonists	Primary Efficacy Endpoint: Change in body weight from baseline to last assessment time point (the day after investigational medicinal product [IMP] administration) by Day 8 Secondary Efficacy Endpoints: Change in body weight from baseline to last assessment time point (the day after IMP administration) by Day 15 Percent change in body weight from baseline to last assessment time point (the day after IMP administration) by Day 8 Percent change in body weight from baseline to last assessment time point (the day after IMP administration) by Day 15 Improvement of or change in congestive findings (lower limb edema, pulmonary congestion, jugular venous distension, hepatomegaly, cardiothoracic ratio, pulmonary rales, and cardiac third sound) from baseline to last assessment time point (the day of IMP administration) by Day 7 Improvement of or change in congestive findings (lower limb edema, pulmonary congestion, jugular venous distension, hepatomegaly, cardiothoracic ratio, pulmonary rales, and cardiac third sound) from baseline to last assessment time point (the day after IMP administration) by Day 15 Congestive findings (lower limb edema, pulmonary congestion, jugular venous distension, hepatomegaly, cardiothoracic ratio, pulmonary rales, and cardiac third sound), time to resolution of congestive findings, and the New York Heart Association (NYHA) Functional Classification
Secondary Objectives: To confirm the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of OPC-131461 versus placebo in patients with CHF with volume overload despite having received diuretics other than vasopressin antagonists	Safety: Adverse events (AEs), clinical laboratory test values, physical examination findings, vital signs, and 12-lead electrocardiogram (ECG) Pharmacodynamic endpoint: Serum osmolality, serum electrolyte (sodium, potassium) concentrations, serum troponin I

Table 3-1 Trial Objectives and Endpoints	
Objectives	**Endpoints**
	concentration, serum N-terminal pro-brain natriuretic peptide (NT-proBNP) concentration, serum creatinine concentration, serum cystatin C concentration, estimated glomerular filtration rate (estimated glomerular filtration rate using the creatinine [eGFRcre], estimated glomerular filtration rate using the cystatin C [eGFRcys]), plasma arginine vasopressin (AVP) concentration, plasma brain natriuretic peptide (BNP) concentration, plasma renin activity, and plasma aldosterone concentration Daily urine volume/fluid intake/fluid balance Urine volume/fluid intake/fluid balance in a time point set Urine volume/fluid intake/fluid balance per hour Urine osmolality, urine sodium excretion, urine potassium excretion, urine aquaporin 2 concentration, and free water clearance Pharmacokinetic endpoint: Plasma concentrations and PK parameters of OPC-131461 and its metabolites
Exploratory Objective: To conduct an exploratory investigation of OPC-131461 compared to placebo.	Exploratory endpoint: [redacted]

Section 9.4 describes the statistical analysis of the endpoints.

4 Trial Design

4.1 Type/Design of Trial

In this multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging trial, 155 patients with CHF with volume overload, despite having received diuretics other than vasopressin antagonists, will be randomized to receive OPC-131461 1 mg, 2 mg, 5 mg, or 10 mg, or placebo (31 subjects/group) to investigate the dose response of OPC-131461 in respect of change in body weight from baseline at completion of 14 days of repeated oral administration. The trial design schematics is shown in Figure 1.2-1.

The trial comprises the screening period, run-in period, treatment period, post-treatment observation period, and follow-up period. Subjects must be hospitalized from the day

before the run-in period through the end of post-treatment examination. Once the post-treatment examination is finished, outpatient visits will be permitted.

After obtaining written informed consent from patients, the investigator or subinvestigator will perform the screening examination, determine eligibility of patients, and enroll eligible patients in the trial. Day 1 is defined as the day when the first dose of IMP is administered. The dose and regimen of any concomitant diuretics must remain unchanged from Day −3 in the run-in period through the end of the post-treatment examination. The use of diuretics, changes in body weight, and presence or absence of congestive findings during the run-in period will be assessed, and only subjects who meet the inclusion criteria for proceeding to the treatment period will be randomized to one of the treatment groups and then proceed to the treatment period.

The investigator or subinvestigator will allocate the IMP to subjects in a double-blinded fashion using the interactive web response system (IWRS) and then administer the IMP to them. Each subject will receive one of the following combinations in accordance with his or her assigned treatment group: only OPC-131461 tablets (1-mg or 5-mg tablets), OPC-131461 tablet (1-mg or 5-mg tablets) plus placebo tablet, or only placebo tablets.

During the treatment period, subjects will orally receive the IMP once daily for 14 days.

However, the treatment will be terminated before completing 14 days of treatment, if the investigator or subinvestigator judges that no further improvement of volume overload is necessary in a case that all congestive findings present at baseline are resolved or in other cases. Subjects who complete the trial or who discontinue the trial after receiving the IMP will undergo the end-of-treatment (EOT) examination on the day after the final IMP administration, post-treatment examination 2 days after the final IMP administration, and follow-up examination 10 to 14 days after the final IMP administration. Subjects will also be followed up for AEs, as necessary.

All subjects should undergo EOT/withdrawal examination, post-treatment observation, and follow-up after the final IMP administration even if the actual treatment duration is less than 14 days as specified in the protocol.

The trial duration for each subject is from informed consent to the end of the follow-up examination.

4.2 Scientific Rationale for Trial Design

The subjects of this trial are patients with CHF who have volume overload despite treatment with diuretics other than vasopressin receptor antagonists. This is the same condition as that of the target patients for whom tolvaptan has been approved for

marketing. To compare the efficacy, safety, and pharmacological characteristics of OPC-131461 to those of tolvaptan 15 mg for characterization, the designs of a phase 3 confirmatory trial (protocol No. 156-06-002) and clinical pharmacology trial (protocol No. 156-06-004) of tolvaptan were used as references. For this trial, it is appropriate to use placebo as a comparator to investigate the dose-response relationship of OPC-131461 in patients with CHF. Subjects are to be hospitalized to ensure safety and the appropriate evaluation of OPC-131461.

To investigate the dose response of OPC-131461 with respect to weight decrease and improvement of congestive findings, a 15-day treatment period is required, including a 14-day dosing period and the protocol-specified EOT examination on the day after the final IMP administration. For the rationale for the dosing period, see Section 4.3.

As a period required for the evaluation of OPC-131461, the post-treatment observation period is scheduled for 2 days after the final IMP administration. Because prolonged hospitalization is considered to be clinically unfavorable, subjects may be discharged when the post-treatment examination indicates no safety concerns. As for the follow-up period, the follow-up examination is scheduled on a day between 10 and 14 days after the final IMP administration in the trial. [redacted] Therefore, a follow-up examination on a day between 10 and 14 days after the final IMP administration is adequate as a safety observation period.

Based on the above, the trial design has been judged to be scientifically and ethically justifiable.

4.3 Dosing Rationale

- Dosage regimen: Oral administration once daily
- Dose: OPC-131461 at 1 mg/day, 2 mg/day, 5 mg/day, 10 mg/day, or 0 mg
- Treatment duration: 14 days (However, the treatment will be terminated before completing 14 days of treatment, if the investigator or subinvestigator judges that no further improvement of volume overload is necessary in a case that any of congestive findings [lower limb edema, pulmonary congestion, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound] were resolved or in other cases.)

Rationale

[redacted]

4.4 End of Trial Definition

The end-of-trial date is defined as the last date of trial contact, or the date of final contact attempt as recorded on the post-treatment follow-up electronic case report form (eCRF) page for the last subject completing or withdrawing from the trial.

4.5 Definition of Completed Subjects

The treatment period is defined as the period during which subjects are evaluated for the primary and/or secondary objectives of the trial, irrespective of whether or not the subjects actually take all doses of the IMP. Subjects who complete the 14-day treatment and the evaluation at the last scheduled visit during the treatment period are defined as trial completers. Subjects who terminate treatment before completing 14 days of

treatment, because the investigator or subinvestigator judges that no further improvement of volume overload is necessary in a case that all congestive findings (lower limb edema, pulmonary congestion, jugular venous distension, hepatomegaly, pulmonary rales, or cardiac third sound) present at baseline are resolved or in other cases, and who undergo the evaluation at the last scheduled visit during the treatment period are defined as early completers. For the purposes of this trial, early completers will also be considered as trial completers. Subjects who fall under the conditions in Section 7.3.2 are defined as withdrawals. All subjects will undergo the EOT/withdrawal examination, post-treatment examination, and follow-up examination.

5 Trial Population

A total of 155 Japanese male and female subjects (31 subjects each in 5 groups; the target number of subjects who will begin the trial treatment) who are between the ages of 18 and 89 years, inclusive at the time of informed consent, and who are suffering from CHF with volume overload (lower limb edema, pulmonary congestion, or jugular venous distension) despite having received diuretics other than vasopressin receptor antagonists will be enrolled in the trial.

5.1 Subject Selection and Numbering

Subjects will be assigned a unique subject identifier (ID; site number [3 digits] + subject number [‘S’ + 5 digits]) upon providing written consent. The site numbers will be designated by the sponsor. The subject numbers will be assigned serially from S00001 in the order of informed consent at each site. Each site will prepare and retain a list of all subjects who have given consent and their subject ID numbers.

5.2 Eligibility Criteria

Eligibility criteria exceptions, by either the investigator or the subinvestigator, will not be permitted in this trial.

5.2.1 Inclusion Criteria

Subjects are required to meet the following inclusion criteria when assessed:

5.2.1.1 Screening Period

Subjects who meet all of the following inclusion criteria (screening period) will be selected.

1)	Subjects with CHF with any of lower limb edema, pulmonary congestion, or jugular venous distension due to volume overload. Subjects with pulmonary congestion confirmed by a chest X-ray taken within 14 days before informed consent may be included.
2)	Subjects undergoing any of the following diuretic therapies (including subjects scheduled to begin such therapy during the run-in period) • Loop diuretics at a dosage equivalent to 40 mg/day or more of furosemide tablet/fine granule • Concomitant administration of a loop diuretic and a thiazide diuretic (including similar drugs) at any doses • Concomitant administration of a loop diuretic and a mineralocorticoid receptor antagonist or potassium-sparing diuretic at any doses Note: The type and dosages of concomitant diuretics are specified as follows: c) Loop diuretics at a dosage equivalent to 40 mg/day or more of furosemide tablet/fine granule Bumetanide tablet, 1 mg; azosemide tablet, 60 mg; and torasemide tablet, 8 mg d) Thiazide diuretics (including similar drugs) Hydrochlorothiazide tablet, trichlormethiazide tablet, benzylhydrochlorothiazide tablet, and mefruside tablet e) Mineralocorticoid receptor antagonists or potassium-sparing diuretics Spironolactone tablet/fine granule and triamterene capsules
3)	Males or females between the ages of 18 and 89 years inclusive (at the time of informed consent)
4)	Subjects who were currently hospitalized or who are able to be hospitalized from the day before the run-in period (Day −4) until the end of the post-treatment examination (Day 16)
5)	Subjects who are able to take oral medications
6)	Subjects capable of providing written informed consent prior to the initiation of any trial-related procedures and capable, in the opinion of the investigator or subinvestigator, of complying with all the requirements of the trial.

Rationale for Inclusion Criteria (Screening Period)

1) Volume overload is manifested as lower limb edema, pulmonary congestion, and jugular venous distension and also as hepatomegaly and cardiac third sound, but lower limb edema, pulmonary congestion, and jugular venous distension are set as the criterion because they are less susceptible to other factors and were actually observed in many patients who participated in a phase 3 tolvaptan confirmatory trial in CHF subjects (156-06-002) and a clinical pharmacology trial in CHF subjects (Protocol No. 156-06-004).
2) The criterion is set to select subjects who have volume overload despite having received diuretics other than vasopressin antagonists.
3) The lower age limit is specified to select subjects who are legally competent to provide consent and the upper age limit is set at 89 years based on the fact that cardiac edema commonly affects the elderly and in consideration of subject safety.
4) Subjects who are able to be hospitalized will be selected to ensure accurate evaluation and in consideration of subject safety.
5) OPC-131461 used in the trial is a tablet formulation.
6) The criterion is set to ensure ethically appropriate conduct of a clinical trial.

5.2.1.2 Run-in Period

Subjects who meet all of the following inclusion criteria (run-in period) will proceed to the treatment period.

7)	Subjects with lower limb edema, jugular venous distension (on Day −1 in the run-in period), or pulmonary congestion (by chest X-ray in the run-in period)
8)	Subjects who received diuretics without any change in the dose or regimen during the run-in period
9)	Subjects whose body weight changed by no more than 1.0 kg in 2 days before trial treatment begins (ie, between Day −2 and Day −1 in the run-in period)

Rationale for Inclusion Criteria (Run-in Period)

7) The criterion is set to select subjects with volume overload as these findings are commonly observed in patients with volume overload.
8) The criterion is set to select subjects who have volume overload despite having received diuretics other than vasopressin antagonists.
9) Volume overload needs to be stable to enable efficacy evaluation of OPC-131461.

5.2.2 Exclusion Criteria

Subjects who meet any of the following exclusion criteria in the screening period will be excluded.

1)	Subjects with acute heart failure
2)	Subjects with an assisted circulation device
3)	Subjects with any of the following diseases, complications, or symptoms: • Suspected decrease in the circulating blood volume • Hypertrophic cardiomyopathy (other than the dilated phase) • Cardiac valve disease with significant valve stenosis • Hepatic encephalopathy with difficulty in adequate hydration
4)	Subjects with acute myocardial infarction occurred within 30 days before screening examination
5)	Subjects with confirmed active myocarditis or amyloid cardiomyopathy
6)	Subjects with any of the following diseases, complications, or symptoms: • Uncontrolled diabetes mellitus • Anuria • Urinary excretion disorders due to urinary stenosis, urinary calculus, tumor
7)	Subjects with any of the following medical histories: • Occurrence of sustained ventricular tachycardia or ventricular fibrillation within 30 days prior to screening examination in subjects not using an implantable cardioverter defibrillator • Occurrence of a cerebrovascular disorder within 6 months prior to screening examination (excluding asymptomatic cerebral infarction) • History of hypersensitivity or idiosyncratic reaction to benzazepines (tolvaptan sodium phosphate, tolvaptan, mozavaptan hydrochloride, and benazepril hydrochloride)
8)	Subjects who have undergone surgical gastrectomy or small intestine resection

9)	Morbidly obese subjects with the body mass index (BMI = body weight [kg] / height [m]^2) of more than 35 kg/m^2
10)	Subjects with supine systolic blood pressure of less than 90 mmHg
11)	Subjects with any of the following clinical laboratory abnormalities: • Total bilirubin > 3.0 mg/dL • Serum creatinine > 3.0 mg/dL • Serum sodium < 125 mEq/L, serum sodium > 147 mEq/L • Serum potassium > 5.5 mEq/L
12)	Subjects with prior or concurrent hepatic impairment (including subjects with aspartate aminotransferase [AST] or alanine aminotransferase [ALT] greater than 3 times the upper limit of reference range at screening examination)
13)	(Removed due to deletion in Protocol Amendment 3)
14)	Subjects who cannot sense thirst or who have difficulty in ingesting water
15)	Females who are breastfeeding or have a positive pregnancy test before trial treatment begins
16)	Sexually active males of reproductive potential or sexually active females of childbearing potential who do not agree to practice 2 different methods of birth control or remain fully abstinent during the trial and for 90 days (males) or for 180 days (females) after the final administration of IMP. If employing birth control, 2 of the following methods must be used: vasectomy, tubal ligation, intrauterine device (IUD), birth control pill, and condom (all of these methods are approved or certified in Japan)
17)	Subjects who used any of the following drugs/foods/beverages/supplements at and after the specified time point 
18)	Subjects who, in the opinion of the investigator or subinvestigator, are inappropriate for inclusion in the trial for any other reason

Drug, Food, Beverage, Supplement	Timing
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Rationale for Exclusion Criteria

1) Rapid symptom onset or worsening of symptoms may complicate the conduct of the trial.
2) An assisted circulation device may affect efficacy and safety evaluations.
3) Treatment that induces excessive diuresis may be unfavorable in such subjects.
4) and 5) In consideration of safety.
6) In consideration of safety and no adequate diuretic effect is expected in such subjects.
7) In consideration of safety.
8) This surgical history may affect efficacy and safety evaluations.
9) Morbid obesity may complicate efficacy evaluation.
10) Diuresis may decrease blood pressure.
11) to 14) In consideration of safety.
15) and 16) In consideration of general safety and ethical issues.
17) These medications may affect efficacy and safety evaluations.
18) In consideration of general safety and ethical issues.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

If diet therapy (salt restriction) is used, the amount of salt in meals should not be changed from the start of the run-in period to the end of the post-treatment examination. For prohibited concomitant foods, beverages, and supplements, see Section 6.5.1.

5.3.2 Caffeine, Alcohol, and Tobacco

Consumption of caffeine, alcohol, and tobacco will be prohibited from the start of the run-in period to the end of the post-treatment examination.

5.3.3 Activity

Not applicable.

5.4 Screen Failures

A screen failure is a subject from whom informed consent is obtained and is documented in writing (ie, the subject signs an informed consent form [ICF]), but who is not randomized or assigned to the trial treatment(s). All AEs must be reported after subject informed consent has been obtained, including screening failures due to AEs, irrespective of IMP administration.

Subjects who sign an ICF but are not assigned to the trial treatment(s) may be rescreened once. If the screening examination is repeated, a new informed consent will be obtained, and a new subject ID number will be assigned beforehand.

If the subject meets the definition of a screen failure in this trial, the following information will be recorded in the source documents and eCRF:

- Date of informed consent
- Visit date (date of screening examination)
- Demographics (collection date, birth date, sex, race, ethnicity, country where the trial was conducted)
- Result of eligibility assessment
- Screen failure date
- Reason for screen failure
- Adverse events

6 Trial Treatments

The trial treatments in this trial are the IMPs (OPC-131461 tablets 1-mg and 5-mg) and matching placebo tablets.

6.1 Trial Treatments Administered

The dose and drugs to use in each treatment group are shown in Table 6.1-1.

The investigator or subinvestigator will orally administer 2 tablets of OPC-131461 tablet 1-mg, OPC-131461 tablet 5-mg, or placebo tablet with water, immediately after completion of urination for urine volume measurement after breakfast once daily for 14 days. The dosing time on and after Day 2 will be within 20 minutes before or after the dosing time on Day 1. Administration should be performed even if the subject does not have breakfast at all.

After confirming that the subject has taken the drug completely, the date and time of administration, dose, presence/absence of breakfast, and time of completion of breakfast will be recorded in the source documents and eCRF.

Table 6.1-1 Dose and Drugs to Use for Each Treatment Group		
Group Name	**Dose**	**Drugs to Use**
OPC-131461 1-mg group	1 mg/day	OPC-131461 tablet 1-mg × 1, placebo tablet × 1
OPC-131461 2-mg group	2 mg/day	OPC-131461 tablet 1-mg × 2
OPC-131461 5-mg group	5 mg/day	OPC-131461 tablet 5-mg × 1, placebo tablet × 1
OPC-131461 10-mg group	10 mg/day	OPC-131461 tablet 5-mg × 2
Placebo group	0 mg/day	Placebo tablet × 2

For the dosage regimen and treatment period (including the follow-up period after completion of IMP administration) for each treatment group, see Section 4.1.

6.1.1 Medical Devices

Not applicable.

6.2 Management of Investigational Medicinal Product

For full details on IMP management, please refer to the OPC-131461 IB and a separate procedure specifying the IMP management.

6.2.1 Packaging and Labeling

Investigational medicinal product will be provided by the sponsor or designated agent to the IMP manager. The IMP will be supplied in packaging boxes. Each packaging box used in the dosing period will be labeled to clearly disclose the subject ID number, compound ID, trial number, sponsor's name and address, route of administration, and appropriate precautionary statements.

6.2.2 Storage

The IMP will be stored in a securely locked cabinet or enclosure. Access will be limited to the IMP manager.

The IMP will be stored according to the conditions indicated on the IMP label.

The trial site staff will maintain a temperature log in the IMP storage area by recording the temperature.

6.2.3 Accountability

The IMP manager must maintain an inventory record of IMP (investigational or placebo tablet) received, dispensed, administered, and returned. The IMP manager must not provide the IMP to any subject not participating in this trial.

6.2.4 Returns and Destruction

Upon completion or termination of the trial, unused IMP and partially-used IMP must be returned to the sponsor or a designated agent. All IMP returned to the sponsor must be accompanied by the appropriate documentation and be clearly 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 used IMP containers, unused IMP, and partially-used IMP.

6.2.5 Reporting of Product Quality Complaints

A Product Quality Complaint (PQC) is any written, electronic, or oral communication provided by a healthcare professional, consumer, subject, medical representative, regulatory agency, Partner, or other third party that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a Medical Device or Medicinal Product or a falsified, tampered, or diverted product after it is released for distribution to a clinical trial. 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 or empty blisters)
- Product defects (eg, odor, chipped, broken, embossing illegible)
- Loss or theft of the product

6.2.5.1 Eliciting and Reporting Product Quality Complaints

The investigator/subinvestigator or designee must record each PQC 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) via e-mail [redacted] or IWRS of the information described in Section 6.2.5.2 immediately after becoming aware of the PQC.

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

6.2.5.2 Information Required for Purposes of Reporting Product Quality Complaints

- Description of complaint
- Reporter identification (eg, subject, investigator/subinvestigator, site, etc.)
- Reporter contact information (eg, address, phone number, e-mail address)
- ID of material (product/compound name, IMP number)
- Clinical protocol reference (number and/or trial name)
- Dosage form/strength (if known)
- Pictures of complaint sample (if available)
- Availability of complaint sample for return

6.2.5.3 Return Process When Product Quality Complaints Are Received

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

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

6.2.5.4 Assessment/Evaluation

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

6.2.6 Investigational Medicinal Product Reserve Sample Requirements

Not applicable.

6.3 Measures to Minimize/Avoid Bias

Subjects who meet the criteria for proceeding to the treatment period will be randomized at a ratio of 1:1:1:1:1 with the IWRS (placebo group: OPC-131461 1-mg group: OPC-131461 2-mg group: OPC-131461 5-mg group: OPC-131461 10-mg group). Details on treatment assignment to subjects will be shown in a separate written assignment confirmation. Neither the subjects nor the investigator/subinvestigator will be informed of the treatment assignment codes. Trial-related parties of the sponsor including contract research organizations (excluding bioanalytical laboratories and unblinded analytical organizations) will also be unaware of the treatment assignment codes.

The indistinguishability of trial treatment will be confirmed by the allocation manager and the IMP packager prior to the start of the trial. A randomization table will be securely stored until unblinding after all eCRFs and databases have been locked.

Measurements of serum osmolality, plasma AVP concentration, urine osmolality, urine sodium concentration, and urine potassium concentration may unblind the trial treatments, while measurements of urine aquaporin 2 concentration may lead to an evaluation bias. Therefore, measurement results from laboratories will not be disclosed until unblinding. These measurements during the trial will be performed at specified laboratories, and will not be performed at local laboratories.

Measurement of plasma drug concentration will be performed at a specific bioanalytical laboratory other than the trial site, and measurement results that can identify the subjects will not be disclosed to trial-related parties (excluding unblinded analytical organizations) until unblinding. When the sponsor receives the results of the PK analysis (descriptive statistics of the major PK parameters) from an unblinded analytical organization before unblinding, the results will not include individual data to keep the assigned trial treatments blinded.

Procedures for breaking the blind are described in Section 8.8.7.

6.4 Subject Compliance

The subjects will be under the control of the investigator or subinvestigator during the trial. The investigator or subinvestigator will instruct them to:

- Administer the IMP and concomitant diuretics at the specified dose according to the specified dosage regimen;
- Adhere to the prespecified schedule during the trial;
- Never use the prohibited concomitant medications (see Section 6.5.1);
- Never change the dose or dosage regimen of restricted concomitant medications (see Section 6.5.3); and,
- Never disclose information obtained through participation in this trial to any third party.

6.5 Concomitant Medications and Therapies

The investigator or subinvestigator will record all concomitant medications (including prescription medications, over-the-counter medications, herbal remedies, etc.) and other concomitant therapies from the date of signing a written informed consent until the end of the trial (defined as the date of last contact or the date of the final contact attempt) in the eCRF.

For concomitant medications, the drug name, indication, dosage per administration, frequency, route of administration, and start and end dates of treatment will be recorded

in the eCRF. For concomitant therapies (including salt restriction), the name of the therapy, purpose, and start and end dates of treatment will be recorded in the eCRF.

6.5.1 Prohibited Medications and Therapies

[redacted]

[redacted]

[redacted]

[redacted]

6.5.2 Medications Requiring Caution for Concomitant Use

[redacted]

6.5.3 Restricted Medications and Therapies

[redacted]

[redacted]

[redacted]

6.5.4 Rescue Medications

Not applicable.

6.6 Intervention After the End of the Trial

Not applicable.

7 Stopping Rules, Withdrawal Criteria, and Procedures

7.1 Entire Trial or Treatment

If the sponsor decides to terminate or suspend 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.

7.2 Individual Site

Individual trial site participation may be discontinued by the sponsor, the investigator, or the institutional review board (IRB) if judged to be necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and Good Clinical Practice (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.

7.3 Individual Subject Discontinuation

7.3.1 Treatment Interruption

Not applicable.

7.3.2 Treatment Discontinuation

After treatment assignment, a subject may stop treatment permanently for a variety of reasons. Treatment discontinuations may be initiated by a subject who is not satisfied with treatment or may become medically necessary due to AEs, required treatment with a disallowed medication or therapy, or other issues, as determined by the investigator or subinvestigator. In any cases, 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 7.3.5. Subjects withdrawn from the trial after receiving the IMP will be encouraged to undergo all of the EOT/withdrawal examination, post-treatment examination, and follow-up examination.

As per the protocol, subjects who terminate treatment before completing the 14 days of the treatment period because the investigator or subinvestigator judges that no further improvement of volume overload is necessary in a case that all congestive findings (lower limb edema, pulmonary congestion, jugular venous distension, hepatomegaly, pulmonary rales, or cardiac third sound) present at baseline are resolved or in other cases will undergo the EOT/withdrawal examination, post-treatment examination, and follow-up examination at the specified timing following the final IMP administration of each early completer.

The EOT/withdrawal examination, post-treatment examination, and follow-up examination will be conducted in accordance with Section 1.3.17, Section 1.3.18, and Section 1.3.19, respectively.

7.3.3 Documenting Reasons for Treatment Discontinuation

Every subject has the right to withdraw from the trial and the investigator or subinvestigator can also discontinue a subject's participation in the trial at any time if medically necessary. In addition, subjects who meet any of the following criteria must be withdrawn from the trial. Only one main reason for discontinuation should be recorded in the eCRF.

1) Adverse event-related reasons:
- Subject decides to discontinue because of annoyance or discomfort due to a nonserious AE which is not otherwise determined to be an undue hazard
- Continuing IMP places the subject at undue risk as determined by the investigator or subinvestigator (eg, a safety concern that is possibly, probably, or likely related to IMP)
  - SAE
  - Other potentially IMP-related safety concerns or AEs

2) Withdrawal by subject
3) Protocol deviation
- Enrolled in the trial without meeting the inclusion criteria or with falling under the exclusion criteria
- Continued to participate in the trial after falling under the withdrawal criteria during the trial
- Inappropriate dose and/or regimen of IMP
- Noncompliance with prohibited concomitant medications/therapies or restricted concomitant medications/therapies

4) Protocol-specific withdrawal criterion met
- Local or central clinical laboratory value (AST or ALT) ≥ 3 × upper limit of normal (ULN)
- ≥ 12 mEq/L increase from baseline in local serum sodium concentration within 24 hours after IMP administration
- Local serum sodium concentration of ≥ 155 mEq/L during the treatment period

  *If these events are judged to be an AE, "adverse event" should be selected as the reason for discontinuation.

5) Death
6) Lost to follow-up
7) Pregnancy (see Section 10.3)
8) Study terminated by sponsor

9) Physician decision
10) Other

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. Follow-up procedures in Section 7.3.2 must be followed.

7.3.4 Withdrawal of Consent or Assent

Each subject has the right to withdraw their consent from further participation in the trial at any time without prejudice. Subjects can withdraw consent for use of data which has not previously been anonymously transferred into trial data sets collected as part of the trial and can only withdraw consent 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:

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

Withdrawal of consent is a critical trial event and, therefore, should be approached with the same degree of importance and care as is used in initially obtaining informed consent. The reasons for a subject's intended withdrawal need to be completely understood, documented, and managed to protect the rights of the subject and the integrity of the trial. A subject may initially express their desire to discontinue IMP administration, which is not equivalent to a complete withdrawal of consent for further participation (see

Section 7.3.2). A subject may, however, indicate that further trial participation is creating a burden on their work, school, or social schedule. Therefore, the investigator or subinvestigator should follow the procedures outlined in Section 7.3.3 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 methods of follow-up are considered to have completely withdrawn their consent to participate in the trial.

Details on the withdrawal of consent from the optional Future Biospecimen Research (FBR) substudy are provided in the ICF for the FBR.

7.3.5 Procedures to Encourage Continued Trial Participation

In all cases of impending IMP discontinuation or consent withdrawal, investigators or subinvestigators will be instructed to meet and discuss (without undue coercion) 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.

7.4 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted before the last day of observation, 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 site will make 3 documented attempts to contact the subject by telephone and in the event the site is unable to reach the subject by telephone, the site 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 was classified as "lost to follow-up," "Were you able to contact the subject?", "Date of contact/Date of final contact attempt," and "Contact method" will be recorded in the eCRF.

8 Trial Procedures

The assessments that are to be conducted during the trial are summarized in Table 1.3-1.

8.1 Efficacy Assessments

8.1.1 Body Weight

The investigator or subinvestigator will instruct subjects to urinate at least once after waking up, and measure body weight before breakfast using an appropriately calibrated scale after minimizing the effects of bowel movements and variations due to clothes. The presence/absence of a measurement, the date and time of the measurement, and the measured value (up to the first decimal place in kg units) will be recorded in the source documents and eCRF. If measured to the second or further decimal place, the measured value will be rounded off to the first decimal place.

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

The investigator or subinvestigator will examine the subjects for congestive findings including lower limb edema, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound to assess the presence/absence and severity of each of the symptoms using the methods shown below. The presence/absence of an examination, date and time of the assessment, and results of the assessment will be recorded in the source documents and eCRF.

1) Lower Limb Edema
   As a rule, the tibial margins or acrotarsia in a sitting position will be examined to assess the severity of edema according to the criteria in Table 8.1.2-1.

Table 8.1.2-1 Criteria for Assessment of Lower Limb Edema

	Severity	Criteria for Assessment
0	Absent	No pitting observed at all
1	Mild	Slight pitting observed
2	Moderate	Pitting observed
3	Severe	Apparent edema

2) Jugular Venous Distension
   The presence/absence of jugular venous distension will be investigated. For those in whom it is present, the height (cm) from the sternal angle to the highest point of pulsation of the internal jugular vein in a half-sitting position will be measured. The measured value will be recorded to one decimal place.

3) Hepatomegaly
   The presence/absence of liver palpable will be investigated. If palpable, its width (length [cm] from the costal arch on the right mammary gland line) will be measured. The measured value will be recorded to one decimal place.

4) Pulmonary Rales
   The presence or absence of pulmonary rales will be investigated by auscultation.

5) Cardiac Third Sound
   The presence or absence of cardiac third sound will be investigated by auscultation.

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

The investigator or subinvestigator will perform a chest X-ray, and record whether or not X-ray measurement is performed and date of chest X-ray in the source documents and eCRF. The cardiothoracic ratio and pulmonary congestion will be assessed using the methods shown below.

1) Cardiothoracic Ratio
   The cardiothoracic ratio will be measured, and the measured value will be recorded in the source documents and eCRF. The measured value will be rounded to one decimal place for recording.

2) Pulmonary Congestion
   The severity of pulmonary congestion will be determined according to the criteria in Table 8.1.3-1, and the determined severity will be recorded in the source documents and eCRF.

Table 8.1.3-1 Criteria for Assessment of Pulmonary Congestion

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

These criteria were created by modifying the criteria in the following article: Medical therapy of acute myocardial infarction by application of hemodynamic subsets (First of two parts).[5]

8.1.4 NYHA Functional Classification

The investigator or subinvestigator will make an assessment using the NYHA Functional Classification (Table 8.1.4-1).[1] The presence/absence of an assessment, date of assessment, and results of the assessment will be recorded in the source documents and eCRF.

Table 8.1.4-1 NYHA Functional Classification

Functional Capacity	
Class I	Patient has no limitation of physical activity due to heart disease. Ordinary physical activity does not cause fatigue, palpitations, dyspnea, or anginal pain.
Class II	Patient has slight limitation of physical activity due to heart disease, but comfortable in living his/her life with rest. Ordinary physical activity causes fatigue, palpitations, dyspnea, or anginal pain.
Class III	Patient has marked limitation of physical activity, but comfortable in living his/her life with rest. Less than ordinary activity causes fatigue, palpitations, dyspnea, or anginal pain.
Class IV	Patient is unable to carry on any physical activity without discomfort due to heart disease. Symptoms of heart failure or angina may be present, even at rest. Any physical activity worsens symptoms.

8.2 Pharmacokinetic Assessments

8.2.1 Pharmacokinetic Blood/Plasma Samples

1) Blood Sampling Time Points

   Blood samples for PK assessments will be collected at the time points presented in the schedule of assessments (Table 1.3-1) and in the allowable time windows for postdose examinations/assessments (Table 1.3-2). The presence/absence of blood sampling and the date and time of blood sampling will be recorded in the source documents and eCRF.

   Vital sign measurements or ECG will be performed prior to blood sampling for PK assessments, when they are scheduled at the same time.

2) Methods of Blood Sampling and Analysis

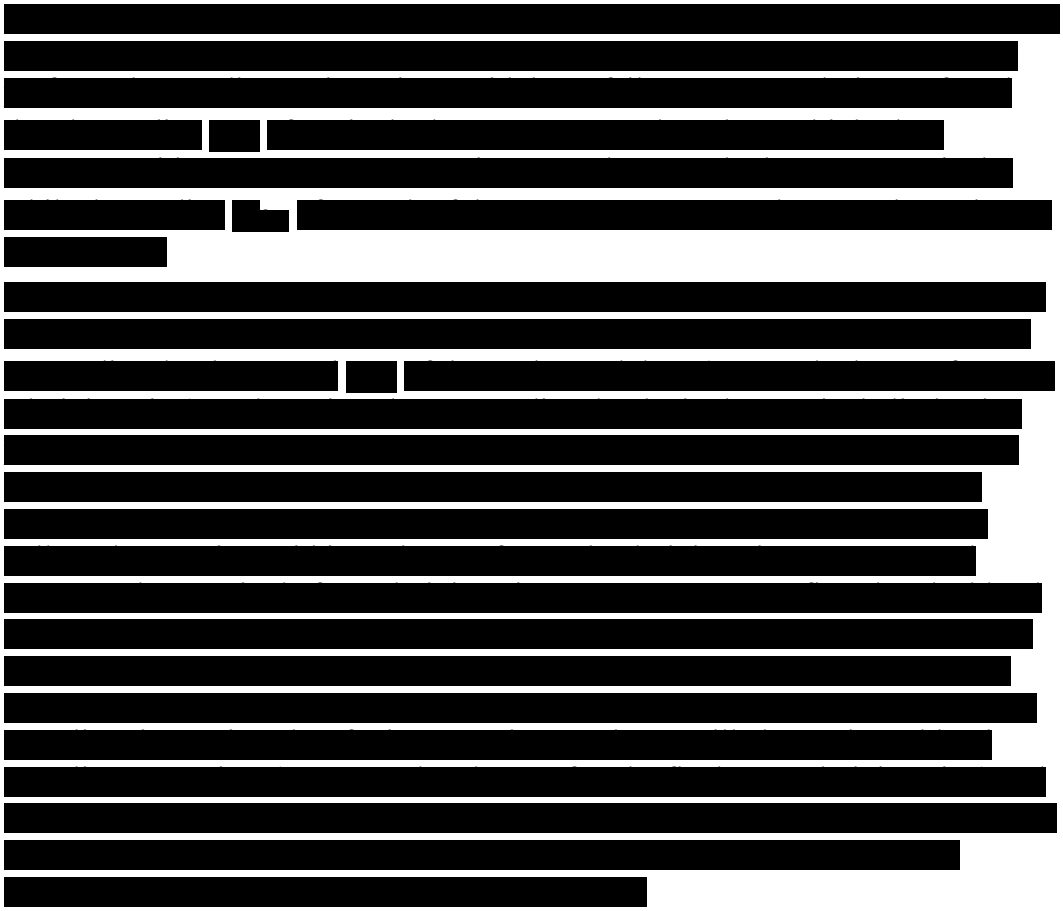
   Blood samples (2 mL) will be collected in vacutainers containing ethylenediaminetetraacetic acid (EDTA) and processed into plasma to measure concentrations of OPC-131461 and its metabolites (M35101 and M35103) by validated high performance liquid chromatography-tandem mass spectrometry. Analyses of metabolites not specified in the protocol may be performed, if necessary. Pharmacokinetic samples may be used for the investigation of a bioanalytical method, if needed.

   Plasma samples will be sent to the bioanalytical laboratory for analysis. The bioanalytical laboratory will measure the drug concentrations in samples from the

OPC-131461 groups only after recording the use of the randomization table. The contents of the randomization table should be strictly managed by the person responsible for measurement of drug concentrations, with no disclosure to any person other than those deemed necessary to execute the work. The results of drug concentration measurement will be securely stored by the bioanalytical laboratory. When electronic data on the results of drug concentration measurement are submitted to the sponsor before unblinding, information that can identify the subjects will be deleted beforehand. The bioanalytical laboratory will submit the electronic file containing the final data to the sponsor after unblinding. Recording the measurement results in the source documents or eCRF is not necessary.

Details on collection, handling, and shipment of samples are provided in the procedures separately prepared.

3) Rationale for the Blood Sampling Time Points



8.3 Pharmacodynamic Assessments

8.3.1 Urine Volume

8.3.1.1 Urine Volume in a Time Point Set

- Time points: Time points specified in the allowable time windows for the postdose examinations/assessments (Table 1.3-2)
- Method: In the run-in period, urine volume will be measured at each of the time points shown in Table 1.3-2, setting the time after complete urination after breakfast as the starting time point. In the treatment period (after the start of IMP administration on Day 1), urine volume will be measured at each of the time points shown in Table 1.3-2, setting the time after complete urination after breakfast and by the time immediately before administration as the starting point. For the start time and end time of each time point, an allowable time window of ± 30 minutes will be set. Subjects will be instructed to urinate completely at the end of each time point for the next urine accumulation. If urine volume in a time point set cannot be measured accurately for some reason (eg, some of urine samples have been discarded), the urine volume in the time point will not be measured and will be handled as missing data. The presence/absence of measurement, the start and end date and time of each time point, and urine volume in each time point will be recorded in the source documents and eCRF.

8.3.1.2 Daily Urine Volume

- Time points: Every day from Day −3 in the run-in period to Day 16 in the post-treatment observation period (2 days after the final IMP administration). However, the time points of measurement of urine volume in a time point set shown in Section 8.3.1.1 are excluded.
- Method: Daily urine volume will be measured, setting the period from the time after complete urination after breakfast (or complete urination after breakfast and by the time immediately before administration in the treatment period) to the time after complete urination after breakfast (or complete urination after breakfast and by the time immediately before administration in the treatment period) on the next day as 1 time point. If the daily urine volume cannot be measured accurately for some reason (eg, some of urine samples have been discarded), the daily urine volume on that day will not be measured and will instead be handled as missing data. The presence/absence of measurement, the start and end date and time of measurement, and the daily urine volume will be recorded in the source documents and eCRF.

8.3.2 Fluid Intake

- Time points: Fluid intake will be measured using the same start and end time as those of each measurement time point shown in Section 8.3.1.1 and Section 8.3.1.2.
- Method: The total amount of fluids contained in the specified meals and other fluids (beverages [juice, milk, tea, etc.], water, infusion solution, etc.) taken in each

specified interval will be measured. Fluid intake from the specified meals will be measured using the formula shown below. The water intake at the time of IMP administration will be included in the water intake after IMP administration.

Formula: Fluid intake from the specified meals = fluid contained in the specified meals × food intake (proportion)

- The presence/absence of measurement, the start and end date and time of measurement, and fluid intake in a time point set or daily fluid intake will be recorded in the source documents and eCRF.

8.3.3 Fluid Balance

Fluid balance will be calculated using the following formula: Daily fluid intake − daily urine volume; or Fluid intake in a time point set − urine volume in a time point set. Fluid balance will be calculated by the sponsor, and therefore, recording in the eCRF is not necessary.

8.3.4 Clinical Laboratory Tests for Pharmacodynamic Assessments

The samples listed in Table 8.3.4-1 will be collected at the time points presented in the schedule of assessments in Table 1.3-1. The presence/absence of measurement, the date and time of blood sampling, and the date and time of urine collection will be recorded in the source documents and eCRF. As for serum electrolyte (sodium, potassium) concentrations and serum creatinine concentrations, data obtained from a clinical laboratory test will be used if the time point of blood sampling for measurement is the same as the time point specified in Section 8.7.1. Details on collection, handling, and shipment of samples are provided in the procedures separately prepared. If urine volume in a time point set or daily urine volume cannot be measured accurately for some reason (eg, some of urine samples have been discarded), the urine electrolyte concentration, urine osmolality, and urine aquaporin 2 concentration in the time point or on the day will be handled as missing data without sending the samples to the laboratory.

All samples for central measurement will be sent to the central laboratory. Central measurements will be performed according to the procedure specified by the laboratory, and their results will be reported to the sponsor and investigator/subinvestigator. The electronic file containing the measurement results provided to the sponsor from the central laboratory will be used as a source document; therefore, recording in the eCRF is not necessary. To maintain blindness, the results of measurements of serum osmolality, plasma AVP concentration, urine osmolality, and urine electrolyte (sodium, potassium) concentrations will be kept undisclosed until unblinding at the end of the trial. The results of measurements of urine aquaporin 2 concentration will also be kept undisclosed until unblinding at the end of the trial, because an evaluation bias may occur. The

measurement results will be securely stored by the laboratory, reported to the investigator or subinvestigator after unblinding, and provided to the sponsor in an electronic file.

In order that the investigator or subinvestigator can quickly grasp the state of serum sodium and potassium concentration for subject safety, serum sodium and potassium concentrations will also be measured at each trial site during the treatment period, and the presence/absence of blood sampling, the date and time of blood sampling, and the measurement results will be recorded in the source documents and eCRF. If a local measurement of serum potassium concentration is found to exceed 5.5 mEq/L, a 12-lead ECG will be performed with reference to Section 8.7.4.

Daily urine sodium excretion or daily urine potassium excretion will be calculated by multiplying the urine sodium concentration or urine potassium concentration by the daily urine volume. Urine excretion will be calculated by the sponsor, and therefore, recording in the eCRF is not necessary.

Table 8.3.4-1 Pharmacodynamic Clinical Laboratory Assessments

Urine: Urine osmolality Urine electrolyte (sodium, potassium) concentrations Urine aquaporin 2 concentration	Serum: Serum osmolality Serum electrolyte (sodium, potassium) concentrations Serum cystatin C concentration Serum creatinine concentration Serum troponin I concentration Serum NT-proBNP concentration Plasma: Plasma AVP concentration Plasma renin activity Plasma aldosterone concentration Plasma BNP concentration

8.4 Pharmacogenomic Assessments

Not applicable.

8.5 Exploratory Assessments

8.5.1 [redacted]

[redacted]

[redacted]

[redacted]

8.5.2 [redacted]

[redacted]

8.6 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.7 Safety Assessments

Details pertaining to the definitions, collection, reporting, and follow-up of AEs are described in Section 8.8.

8.7.1 Clinical Laboratory Assessments

Clinical laboratory samples will be collected at the time points described in the schedule of assessments (Table 1.3-1) to perform the clinical laboratory assessments described in Section 10.2. The total volume of blood to be collected during the trial will be documented in the ICF.

All samples for central measurement will be sent to the central laboratory. Details on collection, handling, and shipping of samples are provided in the procedures separately

prepared. Central measurements will be performed according to the procedure specified by the laboratory, and their results will be reported to the sponsor and investigator/subinvestigator. The presence/absence of blood sampling/urine collection and the date and time of blood sampling/urine collection will be recorded in the source documents and eCRF. The electronic file containing the measurement results provided to the sponsor from the central laboratory will be used as a source document; therefore, recording in the eCRF is not necessary.

In order that the investigator or subinvestigator can quickly grasp the state of serum sodium and potassium concentration for subject safety, serum sodium and potassium concentrations will also be measured at each trial site during the treatment period, and the presence/absence of blood sampling, the date and time of blood sampling, and the measurement results will be recorded in the source documents and eCRF. If a local measurement of serum potassium concentration is found to exceed 5.5 mEq/L, a 12-lead ECG will be performed with reference to Section 8.7.4.

For FOCBP, a pregnancy test will be performed at the time of the screening examination with reference to Section 10.3, and the results must be obtained before IMP administration. A urine human chorionic gonadotropin (hCG) test will be performed using a pregnancy diagnostic reagent provided by the sponsor. If the result is unclear, a urine hCG test will be performed again. If the result of the urine test is positive, the investigator or subinvestigator will perform a serum test for confirmation. The investigator or subinvestigator will confirm the test result and record the presence/absence of a test, the date of the test, and the result of the test (positive or negative) in the source documents and eCRF.

8.7.2 Physical Examination

Physical examinations will be performed at the time points described in the schedule of assessments (Table 1.3-1).

Physical examinations include assessment of the head, ears, eyes, nose, pharynx, chest, abdomen, genitourinary tract, extremities, nerves, and skin and mucosae.

At screening, the presence/absence, date, and results of assessment will be recorded in the eCRF. At subsequent time points, the presence/absence and date of assessment only will be recorded in the eCRF and the results of assessment will be recorded in the source documents only. Any clinically significant physical finding not observed at screening but observed later will be recorded as an AE in the eCRF.

The investigator or subinvestigator will bear primary responsibility for the assessment of physical examination findings. Whenever possible, the same person will assess the physical examination findings of an individual subject throughout the course of the trial.

8.7.3 Vital Signs

Vital signs (systolic and diastolic blood pressure, pulse rate, and body temperature) will be collected at the time points described in the schedule of assessments (Table 1.3-1). Subjects should be monitored for clinically significant vital sign values.

After a rest of at least 3 minutes, axillary temperature will be measured, after which systolic blood pressure, diastolic blood pressure, and pulse rate will be measured in a supine position, according to the methods specified by the trial site. Body temperature should be recorded to one decimal place. Values measured to more than one decimal place will be rounded to one decimal place. The presence/absence of measurement, the date and time of measurement, and the results of measurement will be recorded in the source documents and eCRF.

8.7.4 Electrocardiography

Electrocardiography will be performed at the time points described in the schedule of assessments (Table 1.3-1). Subjects should be monitored for clinically significant ECG findings.

A 12-lead electrocardiograph provided by the central ECG measurement facility will be used to measure resting 12-lead ECGs, according to the method specified by the central ECG measurement facility. The investigator or subinvestigator will assess the measurement result as either normal or abnormal and record the presence/absence of assessment, the date of ECG, and the result of the assessment (normal or abnormal; and if abnormal, the abnormal findings) in the source documents and eCRF. If a local measurement of serum potassium concentration is found to exceed 5.5 mEq/L on any day in the treatment period when a 12-lead ECG is not scheduled in the protocol, then an additional 12-lead ECG will be performed as an unscheduled examination.

The record of the ECGs measured using the 12-lead electrocardiograph provided by the central ECG measurement facility will be sent to the central ECG measurement facility for measurement of heart rate, PR interval, RR interval, QRS interval, QT interval, and QTc interval (QTcB and QTcF). The central ECG measurement facility will send a 12-lead ECG measurement report to the investigator or subinvestigator.

The investigator or subinvestigator will reconfirm the result of the 12-lead ECG assessment with reference to the 12-lead ECG measurement report, and sign and store the report.

The electronic file containing the 12-lead ECG measurement report submitted from the central ECG measurement facility to the sponsor will be used as a source document. Recording the heart rate, PR interval, RR interval, QRS interval, QT interval, and QTc interval (QTcB, and QTcF) in the eCRF is not necessary.

8.7.5 Suicidality Monitoring

Not applicable.

8.7.6 Other Safety Variables

Not applicable.

8.8 Adverse Events

8.8.1 Definitions

An AE is defined as any untoward medical occurrence in a clinical trial subject administered a drug used in the clinical trial and which does not necessarily have a causal relationship with this treatment. In this trial, any untoward medical occurrence in a subject not administered a drug used in the clinical trial is also deemed as an AE. 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 a drug used in the clinical trial, related to any dose administered.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug used in the clinical trial caused the AE.

There are 2 different definitions of an adverse reaction: One is an adverse reaction to a drug used in the clinical trial that should be reported by the investigator as specified in Article 48 of the GCP and the other is an adverse reaction to the IMP as an endpoint in the trial. This section refers to the former definition.

Treatment-emergent AEs (TEAEs) are defined as AEs with an onset date on or after the start of double-blind treatment. In more detail, TEAEs are all AEs that started after the start of double-blind IMP treatment, or are continuous from baseline and worsen.

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 inpatient hospitalization or prolongs hospitalization.
  - Hospitalization itself should not be reported as an SAE; whenever possible the reason for the hospitalization should be reported. Note that hospitalization is an outcome of some event, and, therefore, the reason for the hospitalization should be reported whenever possible. In the event the reason is not known, the event of hospitalization should still be reported as an SAE.
  - Hospitalizations or prolonged hospitalizations for social admissions (ie, those required for reasons of convenience or other nonmedical need) are not considered SAEs.
  - Prescheduled hospitalization to address a condition that has existed prior to the signing of the ICF should not be considered an SAE.
- 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 AEs are all AEs that do not meet the criteria for a "serious" AE.

Adverse Events of Special Interest (AESIs): A noteworthy event for the particular product/IMP or class of products that a sponsor may wish to monitor carefully. All AESIs are to be reported as IREs. No AESIs have been identified for the IMP to be administered during this trial.

Immediately Reportable Event (IRE):

- Any SAE.
- Any AE related to occupational exposure.
- Potential serious hepatotoxicity (see Section 8.8.6).
- 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 and the Pregnancy Surveillance Form(s) to the sponsor. This includes pregnancy of the

subject or the partner of the subject. Pregnancy will only be documented on the AE eCRF if the pregnancy occurs in a female subject and there is an abnormality or complication.

Clinical Laboratory Test Value Changes: It is the investigator's or subinvestigator's responsibility to review the results of laboratory tests for each individual subject as they become available. This review will be documented by the investigator/subinvestigator's dated signature on the laboratory report. The investigator or subinvestigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. If the laboratory value is considered medically relevant (ie, clinically significant) 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, it is considered an AE.

Severity: Adverse events will be graded on a 3-point scale and reported as indicated in the eCRF. The severity 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.

8.8.2 Eliciting and Reporting Adverse Events

The investigator or subinvestigator will regularly assess or examine subjects for the occurrence of AEs. To avoid bias in eliciting AEs, subjects should be asked the nonleading 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 eCRF provided by the sponsor. Adverse event collection will begin after a subject signs the ICF, and will continue until the end of follow-up. All AEs must be recorded in the eCRF after subject informed consent has been obtained, including screening failures due to AEs, irrespective of trial intervention administration.

Medical terminology should be used for 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. A reported AE that worsened in severity or seriousness should be reported as a new AE in the eCRF.

In addition, the sponsor must be notified immediately by e-mail, in principle, of any IREs according to the procedure outlined below, in Section 8.8.3. Special attention should be paid to recording hospitalization and concomitant medications.

The AE, start date, end date (or start date and time and end date and time if the subject is hospitalized), seriousness, severity, relationship to trial treatment (IMP causality), action taken with trial treatment, and outcome will be recorded on the source documents and in the eCRF. When an SAE is reported using an IRE form or other methods, any drugs other than the IMP used in the clinical trial will also be assessed in terms of relationship to and action taken with treatment with the drugs, as with the IMP, and will be recorded on the source documents.

Note: For AEs occurring during hospitalization, time will also be recorded if possible. If the exact time of onset/resolution is unknown (cannot be identified in minutes), time in terms of hours will be identified. Particular attention should be paid to determination of the time of onset and resolution of vomiting during hospitalization to provide a basis for considering the extent of IMP absorption.

8.8.3 Immediately Reportable Events

The investigator or subinvestigator must immediately report (within 24 hours), using an IRE form, after he/she or site personnel become aware of any IRE (SAE, AE related to occupational exposure, AESI, potential serious hepatotoxicity, or confirmed pregnancy), by e-mail in principle to the sponsor or designee using the contact information on the cover page of this protocol (please note that the IRE form is NOT the AE eCRF). Patient confidentiality must be protected and contact information such as name, address, phone number or any other protected health information as determined by applicable local regulation must be redacted when forwarding Safety Information and supporting documentation. Details regarding the follow-up of IREs are included in Section 8.8.8.2

8.8.4 Medical Device Incidents (Including Malfunctions)

Not applicable.

8.8.5 Adverse Events of Special Interest

Not applicable.

8.8.6 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 in the eCRF.

8.8.7 Procedure for Breaking the Blind

In the event that an SAE or other significant event occurs and the investigator or subinvestigator decides that the emergency code needs to be opened to ensure subject safety, the investigator or subinvestigator may obtain the emergency code through IWRS according to the separately specified procedure.

The investigator or subinvestigator is encouraged to contact the sponsor/Clinical Research Organization (CRO) medical advisor to discuss their rationale for unblinding. However, to prevent delays to the investigator/subinvestigator or medical personnel responding to a potentially emergent situation, unblinding of IMP will not be dependent upon the investigator or subinvestigator receiving approval from the sponsor/CRO medical advisor (ie, the investigator or subinvestigator will be able to obtain the code break information independent of the sponsor/CRO medical advisor). The investigator or subinvestigator must contact the sponsor/CRO medical advisor by telephone or e-mail with an explanation of the need for opening the treatment assignment code within 24 hours of opening the code. If the blind is broken, the Office of Pharmacovigilance Operations, Department of Pharmacovigilance must be notified immediately (see the cover page of this protocol for contact information). Documentation of breaking the blind should be recorded in the subject's medical record with the date and time the blind was broken and the names of the personnel involved. Once the blind is broken for a subject, that subject may not reinitiate treatment with the IMP.

8.8.8 Follow-up of Adverse Events

8.8.8.1 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 in 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).

8.8.8.2 Follow-up of Immediately Reportable Events

This trial requires that subjects be actively monitored for IREs up to 10 to 14 days after the last dose of IMP is administered.

Immediately reportable events that are **identified or ongoing at the last scheduled contact** must be recorded as such on the AE eCRF page and the IRE form. If updated information (eg, resolved status) on IRE status becomes available after a subject's last scheduled contact (up to last in-clinic visit for the entire trial), this must be reported to the sponsor and recorded on the AE eCRF page and the IRE form, according to the appropriate reporting procedures described in Section 8.8.3.

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. The investigator or subinvestigator will follow IREs until the events are:

- Resolved,
- Stabilized,
- 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. The investigator or subinvestigator will continue to report any significant follow-up information to the sponsor up to the point the event has resolved or stabilized, or the subject is lost to follow-up, or has died.

Refer to Section 10.3 for additional information regarding the follow-up period for subjects that become pregnant or for pregnant partners of male subjects.

8.8.8.3 Follow-up and Reporting of Immediately Reportable Events Occurring after Last Scheduled Contact

Any new IREs reported to the investigator or subinvestigator which occur after the last scheduled contact and are determined by the investigator or subinvestigator to be reasonably associated with the use of the drug used in the clinical trial, should be reported to the sponsor according to the procedures outlined in Section 8.8.3. This may include IREs that are captured on follow-up telephone contact or at any other time point after the defined trial period and continue to report any significant follow-up information to the

sponsor until the events are resolved or stabilized, or the subject is lost to follow-up or has died.

8.9 Treatment of Overdose

For treatment of overdoses, please refer to Section 6.4 in the IB for OPC-131461.

8.10 Subject Assessment Recording

Not applicable.

8.11 Other Assessments

Not applicable.

9 Statistical Considerations

9.1 Sample Size

The sample size is set as 31 subjects per group.

Assuming that a dose of OPC-131461 5 mg or higher is equivalent to that of tolvaptan 15 mg in patients with CHF, the sample size required to demonstrate the superiority of OPC-131461 over placebo in terms of the primary endpoint, ie, the change in body weight from baseline to the last assessment time point (the day after IMP administration) by Day 8, was determined (multiplicity relating to the use of more than one OPC-131461 dose group was not considered).

The results of the phase 3 confirmatory trial of tolvaptan (Protocol 156-06-002; placebo-controlled 7-day treatment) demonstrated that the change from baseline in body weight on the day after the final IMP administration (LOCF) was −0.45 ± 0.93 kg (mean ± standard deviation [hereinafter, the same applies]) for the placebo group and −1.54 ± 1.61 kg for the tolvaptan 15-mg group. Based on these results, assuming a treatment difference of −1.09, standard deviation (combined) of 1.30, statistical power of 90%, and two-sided significance level of 5%, the sample size required is set as 31 subjects per group for a total of 155 subjects.

9.2 Datasets for Analysis

The full analysis set includes all subjects who have been administered at least one treatment of the IMP, and for whom efficacy data after IMP administration are available.

The safety analysis set includes all subjects who have been administered at least one treatment of the IMP.

The PK analysis set includes all subjects who have been administered at least one treatment of OPC-131461 and have at least one measurement of plasma drug concentration.

The PD analysis set includes all subjects who have been administered at least one treatment of the IMP and have evaluable PD data after IMP administration.

9.3 Handling of Missing Data for Primary and Secondary Endpoint Analysis

For missing values, no imputation will be applied.

9.4 Statistical Analyses

9.4.1 Efficacy Analyses

The following analyses will be performed using the full analysis set.

9.4.1.1 Primary Efficacy Endpoint Analysis

The primary endpoint is the change in body weight from baseline (before IMP administration on Day 1) to the last assessment time point (the day after IMP administration) by Day 8.

For the primary analysis, an analysis of covariance model with treatment group as a fixed effect and baseline body weight as a covariate will be used. Comparisons between each OPC-131461 dose group and the placebo group will be performed at a two-sided significance level of 5%, and the difference in the least squares means between the treatment groups and the two-sided 95% CIs will be determined.

In addition, to investigate the dose-response relationships for placebo, 1, 2, 5, and 10 mg, the above-mentioned model will be used to contrast the response saturated at 1 mg, response saturated at 2 mg, response saturated at 5 mg, and linear response.

9.4.1.2 Key Secondary Efficacy Endpoint Analysis

Not applicable.

9.4.1.3 Secondary Efficacy Endpoint Analysis

For the change in body weight from baseline (before IMP administration on Day 1) to the last assessment time point (the day after IMP administration) by Day 15, an analysis will be performed in the same manner as the primary endpoint analysis.

For the percent changes in body weight from baseline to the last assessment time point (the day after IMP administration) by Day 8 and to the last assessment time point (the day after IMP administration) by Day 15, descriptive statistics will be calculated.

For lower limb edema and pulmonary congestion, improvement rates (percentages of subjects who have symptoms at baseline and show markedly improved or improved after IMP administration [improvement grading is as per Table 9.4-1]) and resolution rates (percentages of subjects who have symptoms at baseline and no symptoms after IMP administration) at the last assessment time point (the day of IMP administration) by Day 7 and the last assessment time point (the day after IMP administration) by Day 15, and their two-sided 95% CIs will be determined for each group. Fisher's exact test will be used to compare each OPC-131461 dose group and the placebo group.

Table 9.4-1 Improvement Grading for Lower Limb Edema and Pulmonary Congestion

	Improvement Grading	Criteria for Assessment
1	Markedly improved	Symptom resolution or improvement by at least 2 grades
2	Improved	Improvement by 1 grade (symptom resolution will be assessed as markedly improved)
3	Unchanged	No change in the severity of symptoms/no symptoms throughout the trial period
4	Worsened	Worsening by at least 1 grade

For pulmonary rales and cardiac third sound, resolution rates (percentages of subjects who have symptoms at baseline and no symptoms after IMP administration) at the last assessment time point (the day of IMP administration) by Day 7 and the last assessment time point (the day after IMP administration) by Day 15, and their two-sided 95% CIs will be determined for each group. Fisher's exact test will be used to compare each OPC-131461 dose group and the placebo group.

For changes in jugular venous distension, hepatomegaly, and cardiothoracic ratio from baseline, an analysis of covariance will be performed using treatment group as a fixed effect and baseline value as a covariate, and the differences in the least squares means between each OPC-131461 dose group and the placebo group at the last assessment time point (the day of IMP administration) by Day 7 and the last assessment time point (the day after IMP administration) by Day 15, and the two-sided 95% CIs will be determined.

For the time to resolution of each congestive finding, a Kaplan-Meier plot will be prepared for each treatment group in subjects with symptoms at baseline to estimate the median and two-sided 95% CI.

For the NYHA Functional Classification,[1] the percentages of subjects who show improvement by at least 1 class from baseline at the last assessment time point (the day of IMP administration) by Day 7 and the last assessment time point (the day after IMP

administration) by Day 15 among subjects classified as at least Class II, and their two-sided 95% CIs will be determined for each group. Fisher's exact test will be used to compare each OPC-131461 dose group and the placebo group.

9.4.1.4 Control of Experiment-wise Type 1 Error

Control of experiment-wise type 1 error will not be performed.

9.4.1.5 Other Efficacy Endpoint Analysis

Not applicable.

9.4.2 Safety Analysis

The following analyses will be performed by treatment group (and by dose and overall for the OPC-131461 groups) on the safety analysis set.

9.4.2.1 Adverse Events

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

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

Treatment-emergent AEs related to the IMP will be summarized similarly. Treatment-emergent AEs by time of first onset will also be summarized.

9.4.2.2 Clinical Laboratory Data

Clinical laboratory values measured at the central laboratory will be used. For clinical laboratory tests other than the qualitative urinalysis, the descriptive statistics of the actual values and changes from baseline at each time point and at the last assessment time point (the day after IMP administration; the same applies, hereinafter) will be calculated. A shift table of parameters for the qualitative urinalysis from baseline at each time point and the final time point of the assessment will be prepared. Parameters other than those for the qualitative urinalysis will be categorized based on the reference range into "within normal," "below the lower limit of normal," and "above the upper limit of normal," and a shift table from baseline at each time point and the final time point of the assessment will be prepared.

9.4.2.3 Physical Examination and Vital Signs Data

For vital signs, descriptive statistics of the actual values and changes from baseline at each time point and the last assessment time point will be calculated.

For subjects with a baseline systolic blood pressure of at least 90 mmHg, the number and percentage of subjects who have an actual value of "< 90 mmHg" at least once in the period from the time after IMP administration to the last assessment time point will be calculated. Similarly, the abovementioned numbers and percentages of subjects will be calculated at baseline and each time point after IMP administration.

9.4.2.4 Electrocardiogram Data

For 12-lead ECG parameters, descriptive statistics of the actual values and changes from baseline at each time point and at the final assessment time point will be calculated.

For QTc interval (QTcF), respective numbers and percentages of subjects who showed an actual value of "> 450 ms," "> 480 ms," and "> 500 ms" at least once in the period from the time after IMP administration to the last assessment time point will be calculated. In addition, respective numbers and percentages of subjects who showed a change from baseline of "> 30 ms" and "> 60 ms" at least once in the period from the time after IMP administration to the last assessment time point will be calculated. Similarly, the abovementioned numbers and percentages of subjects will be calculated at baseline and each time point after IMP administration.

A shift table showing normal/abnormal judgment from baseline at each time point and the final time point of the assessment will be prepared.

9.4.2.5 Other Safety Data

Not applicable.

9.4.3 Other Analyses

9.4.3.1 Analysis of Demographic and Baseline Characteristics

The frequency distribution or descriptive statistics of subject demographics will be calculated by treatment group (and by dose and overall for the OPC-131461 groups) in the full analysis set and safety analysis set.

9.4.3.2 Pharmacokinetic Analysis

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

1) Endpoints
   a) Plasma concentrations of OPC-131461, M35101, and M35103 (Day 1 to Day 16)

b) Plasma pharmacokinetic parameters for OPC-131461, M35101, and M35103

- Day 1
  C_{max}, AUC_{24h}, t_{max}, t_{last}, C_{max}/D, and AUC_{24h}/D
- Day 7
  C_{max}, AUC_{24h}, t_{max}, t_{last}, C_{max}/D, and AUC_{24h}/D
- Day 14
  C_{max}, AUC_{24h}, t_{max}, $t_{1/2,z}$, $CL/F^{\#1}$, $CL/F/BW^{\#1}$, t_{last}, λ_z, C_{max}/D, and AUC_{24h}/D

  #1: Not calculated for metabolites

c) Ratio of the AUC_{24h} of M35101 or M35103 to that of OPC-131461 (Day 1, Day 7, and Day 14)

d) Cumulative coefficients for OPC-131461, M35101, and M35103 (Day 7 and Day 14)

- $R(C_{max})$, $R(AUC_{24h})$, and $R(C_{trough})$

e) Dose proportionality of the C_{max} and AUC_{24h} of OPC-131461 (Day 1, Day 7, and Day 14)

2) Statistical Methods

a) Data on each of the endpoints presented in Section 9.4.3.2 1) will be summarized by compound, treatment group, and day of IMP administration. In addition, data on the endpoints shown in Section 9.4.3.2 1) a) will be summarized by time point of blood sampling, while data on the endpoints shown in Section 9.4.3.2 1) b), c), and d) will be summarized by parameter.

The descriptive statistics to be calculated will include the number of subjects in the analysis set, number of subjects tabulated, arithmetic mean, standard deviation, coefficient of variation, and minimum, median, and maximum values for plasma drug concentration, and the number of subjects in the analysis set, number of subjects tabulated, arithmetic mean, standard deviation, coefficient of variation, geometric mean, and minimum, median, and maximum values for PK parameters. For t_{max} and t_{last}, the arithmetic mean, standard deviation, coefficient of variation, and geometric mean will not be calculated. For λ_z, descriptive statistics will not be calculated.

For any parameter for which the number of tabulated subjects is half of the number of subjects in the analysis set or less, descriptive statistics will not be calculated.

b) For the endpoints shown in Section 9.4.3.2 1) e), data will be analyzed by day of IMP administration using regression equation (I) to obtain an estimate of b and its two-sided 95% CI.

$$\ln Y = a + b \cdot \ln X \quad \text{... (I)}$$

X: Dose

Y: Parameter (C_{max} and AUC_{24h})

The parameter will be determined to show dose proportionality when the two-sided 95% CI of the estimate of b includes 1.

9.4.3.3 Pharmacodynamic Analysis

Data will be summarized by treatment group in the PD analysis set. Baseline will be the time point before IMP administration in the treatment period (or Day −1).

For each endpoint, descriptive statistics of the actual values and changes from baseline at each time point will be calculated.

Calculation methods for the PD effect endpoints are shown below.

- Fluid balance: Subtract the urine volume in a time point set from the fluid intake in the same time point as the time point for urine accumulation.
- Urine volume (urine excretion rate)/fluid intake/fluid balance per hour: Convert the urine volume/fluid intake/fluid balance in a time point set to the value per hour.
- Cumulative urine volume/fluid intake/fluid balance and cumulative urine electrolyte (sodium, potassium) excretions: Sum up the values in time points for urine accumulation or fluid intake. If there are missing data in any of the intervals, the cumulative value will also be handled as missing data.
- Daily urine volume/fluid intake/fluid balance and cumulative urine electrolyte (sodium, potassium) excretions: Sum up the values in time points for urine accumulation or fluid intake. If there are missing data in any of the intervals, the cumulative value will also be handled as missing data.
- Free water clearance: Calculate using the formula below.

  Free water clearance = urine excretion rate × (serum osmolality − urine osmolality) / serum osmolality
- eGFRcre: Calculate using the formula for estimation of the glomerular filtration rate (GFR) for Japanese[8] using serum creatinine concentration, sex, and age.
- eGFRcys: Calculate using the formula for estimation of the GFR for Japanese[9] using serum cystatin C concentration, sex, and age.

9.4.3.4 Pharmacokinetic/Pharmacodynamic Analysis

No PK/PD analysis is planned.

9.4.3.5 Pharmacogenomic Analysis

No pharmacogenomics analysis is planned.

9.4.3.6 Exploratory Endpoint Analysis

[redacted]

[redacted]

9.5 Interim Analysis and Adaptive Design

[redacted]

No adaptive design is applicable.

9.5.1 Data Monitoring Committee

Not applicable.

10 Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Trial Oversight Considerations

10.1.1 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, applicable ICH-GCP guidance, international ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Science (CIOMS) guidelines, and applicable local laws and regulations. Each trial site will seek approval by an IRB according to regional requirements, and 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, IRE, and any safety information, the investigator, subinvestigator, and their staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject ID 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.

10.1.2 Informed Consent

Informed consent will be freely obtained from all subjects (or their guardian or legally acceptable representative, as applicable for local laws). The ICF will be approved by the same IRB that approves this protocol.

Each ICF will comply with the ICH-GCP Guidelines 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 before initiation of any procedures that are performed solely for the purpose of determining eligibility for this trial, including withdrawal from current medication(s).

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

Once appropriate essential information has been provided and fully explained in layman’s language to the subject by the investigator or subinvestigator (or a qualified designee), and it has been documented that the subject has had the opportunity to ask questions, the IRB-approved written ICF will be signed and dated by both the subject and the person obtaining consent (investigator/subinvestigator or designee), as well as by any other parties required by the IRB. The subject will receive a copy of the signed ICF; the

original shall be kept on file by the investigator or subinvestigator. Subjects may be asked to sign additional ICFs if the protocol is amended and the changes to the protocol result in additional information that needs to be provided to the subjects, so that they can make a knowledgeable and voluntary decision on continued trial participation. Female partners of male subjects who become pregnant during the course of the trial may be asked to sign additional ICFs in order to collect additional information regarding the nonsubject partner and fetus.

Separate and similar consent procedures will be followed for the optional sample collection for FBR. Consent must be obtained before the sample is collected. Participation in sample storage for FBR is optional. Refusal to participate in this aspect of the study will not affect participation in the main trial.

10.1.3 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 ID in the eCRF. 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.

10.1.4 Quality Control and Quality Assurance

The sponsor will perform quality management activities for this trial in compliance with the ICH-GCP guidance and standard operating procedures.

10.1.4.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, the applicable ICH-GCP guidance, and applicable regulatory requirements and local laws. As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the progress of the trial), the sponsor's monitors will visit the site during the trial, as well as communicate frequently via telephone, e-mail, and written communications. In addition, all investigators or

subinvestigators and trial site personnel will undergo initial and ongoing training for this particular trial, and this training will be clearly documented.

10.1.4.2 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, site operations, delegation of authority and training, and a review of the eCRF with source documents, as applicable. The investigator will agree to cooperate and participate with audits.

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

10.1.5 Protocol Deviations

In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent process, IMP dispensing or subject dosing error, treatment assignment error, subject enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator/subinvestigator or designee will contact the sponsor or designee at the earliest possible time by telephone or via e-mail. The investigator/subinvestigator and sponsor (or designee) 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/subinvestigator and the sponsor (or designee), and reviewed by the site monitor.

Any major protocol deviation will be recorded in the eCRF along with the start date and details of the deviation.

10.1.6 Records Management

10.1.6.1 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 medical records, electronic data, logs, and recorded data from automated instruments or applications. All source documents pertaining to this trial (excluding drug concentration measurements and materials pertaining to FBR) will be maintained by the trial site and made available for direct inspection by authorized persons.

Investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB review, and regulatory inspection(s), by providing direct access to source data/documents by authorized persons as defined in the ICF. Documents related to drug concentration

measurement and FBR (eg, original reports, measurement data, etc) will be retained respectively by the bioanalytical laboratory, biorepository, and organization related to biospecimen research. In all cases, subject confidentiality must be maintained in accordance with local regulatory requirements.

10.1.6.2 Data Collection

During each subject's visit to the site, an investigator/subinvestigator or their designee participating in the trial will record information 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/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/subinvestigator's assessment of relationship to IMP must also be recorded;
- Any changes in concomitant medications or dosages;
- A general reference to the procedures completed, including dosing and IMP compliance; and,
- The signature (or initials) and date of the investigator/subinvestigator (or designee) who made an entry in the medical record.

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 the entries in medical records and other source documents will be initialed and dated on the day the change is made by a trial site staff member who is 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). Unless the reason for the changes is clear, the investigator/subinvestigator will briefly describe the reason for the changes in the source documents. If an electronic data system is used, a complete audit trail of the changes must be maintained.

Information from medical records and other source documents will be entered by investigative site personnel onto eCRFs in the sponsor's electronic data capture (EDC)

system that is 21 CFR Part 11 compliant. Changes to the data will be captured by an automatic audit trail in the EDC system.

Electronic data not entered on eCRF, such as data received from central laboratories or central ECG measurement facility, will be reconciled using key data fields by the sponsor or the contract research organization with the eCRF data to ensure consistency.

10.1.6.3 File Management at the Trial Site

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

10.1.6.4 Records Retention at the Trial Site

The trial site will maintain all materials and records relevant to this trial for the longest of the following 3 periods. If the sponsor needs a longer retention, however, the trial site will discuss the period and method of retention with the sponsor.

- A period of at least 2 years after the date on which approval to market the drug is obtained; however, if the sponsor notifies the trial site that the drug development is terminated or the results of the trial are not included in the NDA application form, a period of at least 3 years after the notification.
- A period of at least 3 years after the trial is discontinued or completed.
- FBR samples storage period

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 to maintain adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial including any data clarification forms received from the sponsor. Such documentation is subject to inspection by the sponsor and relevant regulatory authorities.

10.1.6.5 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 subjects 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 subjects consent to such acknowledgement in any publications resulting from its conduct.

10.2 Appendix 2: Clinical Laboratory Tests

The tests described in Table 10.2-1 will be performed.

Table 10.2-1 Clinical Laboratory Assessments

Hematology: Hematocrit Hemoglobin Platelets MCHC MCV Red blood cell count White blood cell count White blood cell differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils) Coagulation (plasma): PT-INR APTT Urinalysis: Specific gravity pH Qualitative test Protein Glucose Occult blood Ketone bodies Bilirubin Urobilinogen	Biochemistry: Total protein Albumin Total bilirubin AST ALT ALP γ-GTP LDH Creatine kinase (creatine phosphokinase) (CK [CPK]) Glucose Total cholesterol Triglycerides Urea nitrogen Creatinine Uric acid Serum electrolytes (sodium, Mg, potassium, Ca, Cl) Additional Tests: Urine (or serum) pregnancy for FOCBP (A urine pregnancy test will be performed at screening and follow-up. It the result of the urine test is positive, a serum test will be performed.)

10.3 Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

Females of childbearing potential (FOCBP) are females whose menstruation has started and who are not documented as sterile (eg, have had a bilateral oophorectomy, or hysterectomy, or who have been postmenopausal for at least 12 months). Females of nonchildbearing potential do not meet definition of FOCBP.

For males or their partners and FOCBP or their partners, who are sexually active, there must be a documented agreement that the subject and their partner will take effective measures (ie, 2 different approved methods of birth control) to prevent pregnancy during the course of the trial and for 90 days after the last dose of IMP and during the course of the trial and for 180 days after the last dose of IMP, respectively. Unless the subject or their partner is sterile (ie, females who have had a bilateral oophorectomy, have had a hysterectomy, or have been postmenopausal for at least 12 consecutive months; or males who have had a bilateral orchiectomy), and during the trial and after the last dose of IMP (unless 90 and 180 days have passed after the last dose of IMP in sexually active males and FOCBP or their partners, respectively), 2 of the following approved methods of birth control must be used: vasectomy, tubal ligation, IUD, birth control pill, or condom (all of these methods are approved in Japan). Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy.

Before enrolling males and females in this clinical trial, investigators or subinvestigators must review the below information about trial participation as part of the ICF process. The topics should generally include:

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

Before trial enrollment, males and FOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. Subjects must sign the ICF confirming that the above-mentioned risk factors and the consequences were discussed.

All FOCBP will undergo a urine pregnancy test (hCG) at screening. If the result of the urine test is positive, the investigator or subinvestigator should perform a serum test for confirmation.

All FOCBP must be instructed to contact the investigator or subinvestigator immediately, during the trial, if they are suspected to be pregnant (eg, missed or late menstrual cycle). Male subjects must be instructed to contact the investigator or subinvestigator immediately, during the trial, if their partner is suspected to 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 serum 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. Exceptions to trial discontinuation may be considered for life-threatening conditions only after consultations with the IRE contact (see the title page of this protocol for contact information).

The investigator or subinvestigator must immediately notify the sponsor (within 24 hours) of any pregnancy associated with IMP exposure during the trial and for at least 90 and 180 days after the last dose of IMP in sexually active males or their partners and FOCBP or their partners, respectively, and record the event on the IRE form and forward it to the sponsor. The sponsor will forward the Pregnancy Surveillance Form(s) to the investigator or subinvestigator 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 the 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.

10.4 [redacted]

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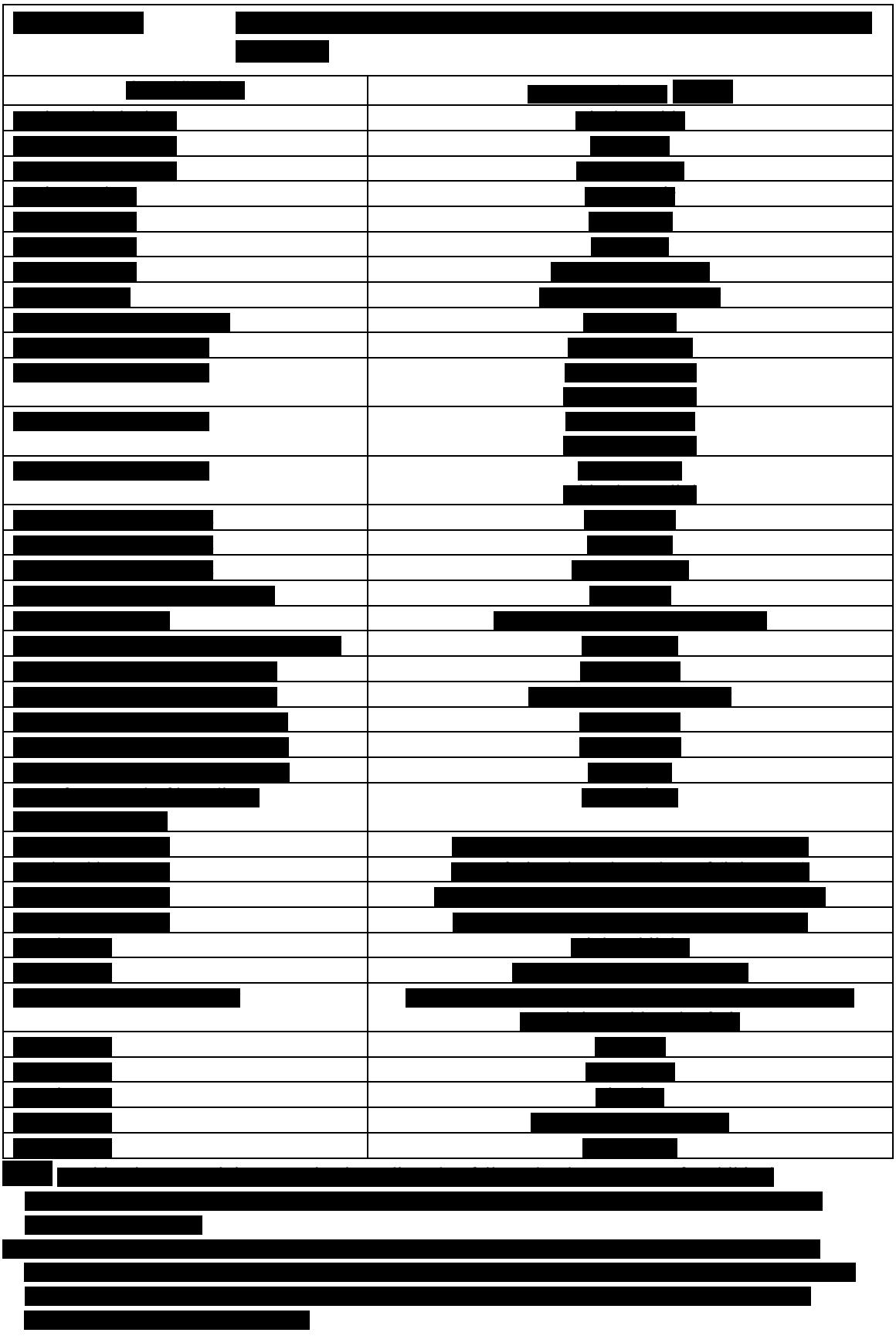

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10.7 Appendix 7: Protocol Amendments

The investigator or subinvestigator will not make any changes to this protocol without the sponsor's prior written consent and subsequent approval 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 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 the 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. If necessary, the sponsor will submit protocol amendments to the applicable regulatory agencies within local applicable timelines.

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

10.7.1 Protocol Amendment(s)/Administrative Change(s)

10.7.1.1 Protocol Amendment 1

Amendment 1 Approval Date: 31 Aug 2022

PURPOSE:

Changes to the time points of measurement of plasma drug concentration, serum electrolyte (sodium, potassium) concentrations, and urine aquaporin 2 concentration; correction of writing errors in the allowable time windows for examination of serum electrolyte (sodium, potassium) concentrations and serum osmolality; clarification of the contents of descriptions; correction of omissions; and, correction of other writing errors

BACKGROUND:

The time points of measurement of plasma drug concentration and serum electrolyte (sodium, potassium) concentrations were reviewed in consideration of feasibility. The time points of measurement of urine aquaporin 2 concentration were reviewed and changed to appropriate time points. Writing errors in the allowable time windows for examination of serum electrolyte (sodium, potassium) concentrations and serum osmolality were corrected to appropriate descriptions. With regard to handling of the results of blinded laboratory tests for PD evaluation, as well as use of measurements of serum potassium concentration obtained at the trial sites for use in considering the necessity of a 12-lead ECG (unscheduled examination), clear descriptions were added. Omissions and other writing errors were corrected.

MODIFICATIONS TO THE PROTOCOL:

Sectional Revisions:

Changed Part	Before Change	After Change
Section 1.3 Table 1.3-1 Schedule of Assessments Annotation	No description	[e]Urine aquaporin 2 concentration will be measured on Day −1 and Day 14 (or the final IMP administration day). (The subsequent annotation symbols were moved down by 1 character.)
Section 1.3 Table 1.3-1 Schedule of Assessments Annotation g	12-lead ECG will be performed before breakfast and 2 to 4 hours postdose on Day 1, at a feasible postdose time on Day 7, and at a feasible time on other days. If a local or central measurement of serum potassium concentration is found to exceed 5.5 mEq/L on any day in the treatment period when a 12-lead ECG is not scheduled in the protocol, then an additional 12-lead ECG will be performed as an unscheduled examination.	12-lead ECG will be performed before breakfast and 2 to 4 hours postdose on Day 1, at a feasible postdose time on Day 7, and at a feasible time on other days. If a local measurement of serum potassium concentration is found to exceed 5.5 mEq/L on any day in the treatment period when a 12-lead ECG is not scheduled in the protocol, then an additional 12-lead ECG will be performed as an unscheduled examination.

Changed Part	Before Change	After Change
Section 1.3 Table 1.3-2 Allowable Time Windows for Postdose Examinations/ Assessments	Plasma drug concentration Day 1 2, 4, and 6 h postdose: Specified time ± 20 min 12 h postdose: Specified time ± 1 h Day 7 and Day 14 2, 4, and 6 h postdose: Specified time ± 20 min 12 h postdose: Specified time ± 1 h Day 15 (EOT examination) 36 h after Day 14 dosing (or the final IMP administration*): Specified time ± 2 h	Plasma drug concentration Day 1 2, 4, 6, and 8 h postdose: Specified time ± 20 min Day 7 and Day 14 2, 4, 6, and 8 h postdose: Specified time ± 20 min Day 15 (EOT examination) 32 h after Day 14 dosing (or the final IMP administration*): Specified time ± 90 min
Section 1.3 Table 1.3-2 Allowable Time Windows for Postdose Examinations/ Assessments	Serum electrolyte (sodium, potassium) concentrations, and serum osmolality Day 1 and Day 7 4 h postdose: Specified time ± 10 min 8 and 12 h postdose: Specified time ± 40 min Day 2 8 h after Day 2 dosing: Specified time ± 90 min Day 2 and Day 8 24 h after Day 1 or Day 7 dosing (predose and before breakfast on Day 2 or Day 8): Within 2 h predose	Serum electrolyte (sodium, potassium) concentrations, and serum osmolality Day 1 and Day 7 4-6 h postdose: — 8-12 h postdose: — Day 2 8 h after Day 2 dosing: Specified time ± 1 h Day 2, Day 3, Day 4, Day 5, Day 6, Day 8, Day 10, Day 12, and Day 14 Predose and before breakfast: Within 2 h predose
Section 1.3.2 Screening	• Serum electrolyte (sodium, potassium) concentrations	• Serum electrolyte (sodium, potassium) concentrations and serum osmolality
Section 1.3.3 Run-in Period (Day −3, Day −2, and Day −1)	2) After breakfast • Daily urine osmolality, daily urine electrolyte (sodium, potassium) concentrations, and daily urine aquaporin 2 concentration (on Day −3 and Day −2)	2) After breakfast • Daily urine osmolality and daily urine electrolyte (sodium, potassium) concentrations (on Day −3 and Day −2)
Section 1.3.4 Randomization and Proceeding to the Treatment Period	2) Assignment of IMP treatment to subjects (Omitted) The investigator or subinvestigator will check the randomization number assigned in the IWRS. The date of randomization and randomization number will be recorded in the eCRF.	2) Assignment of IMP treatment to subjects (Omitted) The investigator or subinvestigator will check the randomization number assigned in the IWRS. The date of randomization, randomization number, and IMP number will be recorded in the eCRF.
Section 1.3.5 Treatment Period (Day 1)	3) After breakfast and 5) After IMP administration • Urine osmolality in a time point set, urine electrolyte (sodium, potassium)	3) After breakfast and 5) After IMP administration

Changed Part	Before Change	After Change
	concentrations in a time point set, and urine aquaporin 2 concentration in a time point set	• Urine osmolality in a time point set and urine electrolyte (sodium, potassium) concentrations in a time point set
Section 1.3.6 Treatment Period (Day 2) Section 1.3.7 Treatment Period (Day 3 and Day 4) Section 1.3.8 Treatment Period (Day 5) Section 1.3.9 Treatment Period (Day 6) Section 1.3.11 Treatment Period (Day 8) Section 1.3.12 Treatment Period (Day 9 and Day 11) Section 1.3.13 Treatment Period (Day 10) Section 1.3.14 Treatment Period (Day 12) Section 1.3.15 Treatment Period (Day 13)	2) After breakfast • Daily urine osmolality, daily urine electrolyte (sodium, potassium) concentrations, and daily urine aquaporin 2 concentration	2) After breakfast • Daily urine osmolality and daily urine electrolyte (sodium, potassium) concentrations
Section 1.3.10 Treatment Period (Day 7)	2) After breakfast and 4) After IMP administration • Urine osmolality in a time point set, urine electrolyte (sodium, potassium) concentrations in a time point set, and urine aquaporin 2 concentration in a time point set	2) After breakfast and 4) After IMP administration • Urine osmolality in a time point set and urine electrolyte (sodium, potassium) concentrations in a time point set
Section 1.3.17 Treatment Period (EOT Examination on Day 15 or the Withdrawal Examination: the Day after the Final IMP Administration)	2) After breakfast • Daily urine osmolality, daily urine electrolyte (sodium, potassium) concentrations, and daily urine aquaporin 2 concentration (only for early completers and withdrawals) • Urine osmolality in a time point set, urine electrolyte (sodium, potassium) concentrations in a time point set, and urine aquaporin 2 concentration in a time point set (only for completers)	2) After breakfast • Daily urine osmolality and daily urine electrolyte (sodium, potassium) concentrations (only for early completers and withdrawals) • Urine osmolality in a time point set and urine electrolyte (sodium, potassium) concentrations in a time point set (only for completers)
Section 1.3.18 Post-treatment Observation Period (Post-treatment	3) After breakfast • Daily urine osmolality, daily urine electrolyte (sodium, potassium) concentrations, and daily urine	3) After breakfast • Daily urine osmolality and daily urine electrolyte (sodium, potassium) concentrations (only for early completers and withdrawals)

Changed Part	Before Change	After Change
Examination on Day 16: 2 Days after the Final IMP Administration)	aquaporin 2 concentration (only for early completers and withdrawals) • Urine osmolality in a time point set, urine electrolyte (sodium, potassium) concentrations in a time point set, and urine aquaporin 2 concentration in a time point set (only for completers)	• Urine osmolality in a time point set and urine electrolyte (sodium, potassium) concentrations in a time point set (only for completers)
Section 2 Introduction	Refer to the current OPC-13461 Investigator's Brochure (IB) for more detailed information.	Refer to the current OPC-131461 Investigator's Brochure (IB) for more detailed information.
Section 6.3 Measures to Minimize/Avoid Bias	(Omitted) The measurements of serum osmolality, plasma AVP concentration, urine osmolality, urine sodium concentration, and urine potassium concentration may unblind trial treatments, and the measurement of urine aquaporin 2 concentration may lead to an evaluation bias. Therefore, measurement results from laboratories will not be disclosed until unblinding, and even when the measurement results are disclosed for blind review by the sponsor, treatment assessment codes will not be revealed to maintain blindness.	(Omitted) The measurements of serum osmolality, plasma AVP concentration, urine osmolality, urine sodium concentration, and urine potassium concentration may unblind trial treatments, and the measurement of urine aquaporin 2 concentration may lead to an evaluation bias. Therefore, measurement results from laboratories will not be disclosed until unblinding.
Section 8.2.1 Pharmacokinetic Blood/Plasma Samples	3) Rationale for blood sampling time points [redacted]	3) Rationale for blood sampling time points [redacted]
Section 8.3.4 Clinical Laboratory Tests for	(Omitted) To maintain blindness, the results of measurements of serum osmolality, plasma AVP concentration, urine osmolality, and urine electrolyte	(Omitted) To maintain blindness, the results of measurements of serum osmolality, plasma AVP concentration, urine osmolality, and urine electrolyte

Changed Part	Before Change	After Change
Pharmacodynamic Assessments	(sodium, potassium) concentrations will be kept undisclosed until unblinding at the end of the trial.	(sodium, potassium) concentrations will be kept undisclosed until unblinding at the end of the trial. The results of measurements of urine aquaporin 2 concentration will also be kept undisclosed until unblinding at the end of the trial, because an evaluation bias may occur. The measurement results will be securely stored by the laboratory, reported to the investigator or subinvestigator after unblinding, and provided to the sponsor in an electronic file.
Section 8.3.4 Clinical Laboratory Tests for Pharmacodynamic Assessments	(Omitted) If a local or central measurement of serum potassium concentration is found to exceed 5.5 mEq/L, a 12-lead ECG will be performed with reference to Section 8.7.4.	(Omitted) If a local measurement of serum potassium concentration is found to exceed 5.5 mEq/L, a 12-lead ECG will be performed with reference to Section 8.7.4.
Section 8.7.1 Clinical laboratory tests	(Omitted) If a local or central measurement of serum potassium concentration is found to exceed 5.5 mEq/L, a 12-lead ECG will be performed with reference to Section 8.7.4.	(Omitted) If a local measurement of serum potassium concentration is found to exceed 5.5 mEq/L, a 12-lead ECG will be performed with reference to Section 8.7.4.
Section 8.7.4 Electrocardiogram Data	(Omitted) If a local or central measurement of serum potassium concentration is found to exceed 5.5 mEq/L on any day in the treatment period when a 12-lead ECG is not scheduled in the protocol, then an additional 12-lead ECG will be performed as an unscheduled examination.	(Omitted) If a local measurement of serum potassium concentration is found to exceed 5.5 mEq/L on any day in the treatment period when a 12-lead ECG is not scheduled in the protocol, then an additional 12-lead ECG will be performed as an unscheduled examination.
Section 8.8.2 Eliciting and Reporting Adverse Events	(Omitted) 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.	(Omitted) 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. A reported AE that worsened in severity or seriousness should be reported as a new AE in the eCRF.

10.7.2 Protocol Amendment 2

Amendment 2 Approval Date: 07 Mar 2023

PURPOSE:

[redacted]

BACKGROUND:

[redacted] Collection of data on the start time and end time of AE "vomiting" was clearly described, because PK assessment will be performed in the trial. Terms, omissions, and other writing errors were corrected.

MODIFICATIONS TO THE PROTOCOL:

Sectional Revisions:

Changed Part	Before Change	After Change
Section 1.1 Synopsis Objectives and Endpoints	Pharmacodynamic endpoint: (Omitted) No description	Pharmacodynamic endpoint: (Omitted) , and free water clearance
Section 1.1 Synopsis Objectives and Endpoints	Exploratory Objective: To explore the indicator of systemic congestion by comparing OPC-131461 and placebo.	Exploratory Objective: To conduct an exploratory investigation of OPC-131461 compared to placebo.
Section 1.1 Synopsis Objectives and Endpoints	Exploratory endpoint: [redacted]	Exploratory endpoint: [redacted]
Section 1.1 Synopsis Exclusion Criterion 17)	Drugs, Foods, Beverages, and Supplements: [redacted]	Drugs, Foods, Beverages, and Supplements: [redacted]

Changed Part	Before Change	After Change
Section 1.1 Synopsis Exclusion Criterion 17)	No description	Drugs, Foods, Beverages, and Supplements: [redacted]
Section 1.1 Synopsis Exclusion Criterion 17)	[redacted]	[redacted]
Section 1.1 Synopsis Exclusion Criterion 17)	Drugs, Foods, Beverages, and Supplements: [redacted]	Drugs, Foods, Beverages, and Supplements: [redacted]
Section 1.1 Synopsis Investigational Medicinal Product(s), Dose, Dosage Regimen, Treatment Duration, Formulation, and Mode of Administration	• Treatment duration: 14 days (If all congestive findings have been resolved and the investigator or subinvestigator judges that further improvement of volume overload is not necessary, however, treatment will be terminated before completing 14 days of treatment.)	• Treatment duration: 14 days (If all congestive findings [lower limb edema, pulmonary congestion, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound] have been resolved and the investigator or subinvestigator judges that further improvement of volume overload is not necessary, however, treatment will be terminated before completing 14 days of treatment.)
Section 1.1 Synopsis Trial Assessments	Exploratory endpoint: [redacted]	Exploratory endpoint: [redacted]
Section 1.3 Table 1.3-1 Schedule of Assessments	No description	Echocardiography[1] Run-in Period ♦ Once in the run-in period Day 15 and Day 16 ♦ Once by 2 days after the final IMP administration
Section 1.3 Table 1.3-1 Schedule of Assessments Annotation a	Subject enrollment and randomization: The interactive web response system (IWRS) will be used to enroll subjects at screening and to randomize them on Day 1.	Subject enrollment and randomization: The interactive web response system (IWRS) will be used to enroll subjects at the time of informed consent and to randomize them on Day 1.

Changed Part	Before Change	After Change
Section 1.3 Table 1.3-1 Schedule of Assessments Annotation g	Annotation g 12-lead ECG will be performed before breakfast and 2 to 4 hours postdose on Day 1, at a feasible postdose time on Day 7, and at a feasible time on other days. If a local measurement of serum potassium concentration is found to exceed 5.5 mEq/L on any day in the treatment period when a 12-lead ECG is not scheduled in the protocol, then an additional 12-lead ECG will be performed as an unscheduled examination.	Annotation k 12-lead ECG will be performed at a predose time and 2 to 4 hours postdose on Day 1, at a feasible postdose time on Day 7, and at a feasible time on other days. If a local measurement of serum potassium concentration is found to exceed 5.5 mEq/L on any day in the treatment period when a 12-lead ECG is not scheduled in the protocol, then an additional 12-lead ECG will be performed as an unscheduled examination.
Section 1.3 Table 1.3-1 Schedule of Assessments Annotation	No description	Echocardiography [redacted]
Section 1.3 Table 1.3-2 Allowable Time Windows for Postdose Examinations/ Assessments	No description	Annotation a Any allowable window will not be applied to the starting time points of 0 hours after breakfast and 0 hours postdose.
Section 1.3.2 Screening	• Demographics (Omitted) complications, medical history [within the past 5 years prior to informed consent]), and classification of the disease underlying CHF	• Demographics (Omitted) complications, classification of the complications, medical history [within the past 5 years prior to informed consent]), and classification of the disease underlying CHF
Section 1.3.2 Screening	• BMI (Formula: BMI = body weight [kg] / height [m]^2. BMI will be calculated based on the height and body weight at screening. The first decimal place will be rounded down.)	• BMI (Formula: BMI = body weight [kg] / height [m]^2. BMI will be calculated based on the height and body weight at screening. The first decimal place will be rounded up.)
Section 1.3.3 Run-in Period (Day −3, Day −2, and Day −1)	No description	(Omitted) Hospitalization information will be recorded in the eCRF.
Section 1.3.3 Run-in Period (Day −3, Day −2, and Day −1)	3) At a feasible time on each evaluation day (Omitted) No description	3) At a feasible time on each evaluation day (Omitted) • [redacted]
Section 1.3.17	3) At a feasible time (Omitted)	3) At a feasible time (Omitted)

Changed Part	Before Change	After Change
Treatment Period (EOT Examination on Day 15 or the Withdrawal Examination: the Day after the Final IMP Administration)	No description	[redacted]
Section 1.3.18 Post-treatment Observation Period (Post-treatment Examination on Day 16: 2 Days after the Final IMP Administration)	3) At a feasible time (Omitted) No description	[redacted]
Section 1.3.19 Follow-up Examination (Day 24 to Day 28: 10 to 14 Days after the Final IMP Administration)	The investigator or subinvestigator will perform the following examinations and investigations between 10 and 14 days after the final IMP administration. Subjects who have been discharged will undergo the examinations and investigations on an outpatient basis.	The investigator or subinvestigator will perform the following examinations and investigations between 10 and 14 days after the final IMP administration. Subjects who have been discharged will undergo the examinations and investigations on an outpatient basis. Discharge information will be recorded in the eCRF.
Section 3 Objectives and Endpoints Table 3-1	Pharmacodynamic endpoint: (Omitted) No description	Pharmacodynamic endpoint: (Omitted) , and free water clearance
Section 3 Objectives and Endpoints Table 3-1	Exploratory Objective: To explore the indicator of systemic congestion by comparing OPC-131461 and placebo.	Exploratory Objective: To conduct an exploratory investigation of OPC-131461 compared to placebo.
Section 3 Objectives and Endpoints Table 3-1	Exploratory endpoint: [redacted]	Exploratory endpoint: [redacted]
Section 4.3 Dosing Rationale	• Treatment duration: 14 days (However, if all congestive findings have been resolved and the investigator or subinvestigator judges that further improvement of volume overload is not necessary, treatment will be terminated before completing 14 days of treatment.)	• Treatment duration: 14 days (However, if all congestive findings [lower limb edema, pulmonary congestion, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound] have been resolved and the investigator or subinvestigator judges that further improvement of volume overload is not necessary, treatment will be terminated before completing 14 days of treatment.)
Section 4.5	(Omitted) Subjects who terminate treatment before completing 14 days of treatment because	(Omitted) Subjects who terminate treatment before completing 14 days of treatment because

Changed Part	Before Change	After Change
Definition of Completed Subjects	all congestive findings have been resolved and the investigator or subinvestigator judges that further improvement of volume overload is not necessary,	all congestive findings (lower limb edema, pulmonary congestion, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound) have been resolved and the investigator or subinvestigator judges that further improvement of volume overload is not necessary,
Section 5.2.2 Exclusion Criterion 17)	Drugs, Foods, Beverages, and Supplements: [redacted]	Drugs, Foods, Beverages, and Supplements: [redacted]
Section 5.2.2 Exclusion Criterion 17)	No description	Drugs, Foods, Beverages, and Supplements: [redacted]
Section 5.2.2 Exclusion Criterion 17)	[redacted]	[redacted]
Section 5.2.2 Exclusion Criterion 17)	Drugs, Foods, Beverages, and Supplements: [redacted]	Drugs, Foods, Beverages, and Supplements: [redacted]
Section 6.3 Measures to Minimize/ Avoid Bias	The measurements of serum osmolality, plasma AVP concentration, urine osmolality, urine sodium concentration, and urine potassium concentration may unblind trial treatments, (Omitted) These measurements will be performed at specified laboratories, and will not be performed at local laboratories.	The measurements of serum osmolality, plasma AVP concentration, urine osmolality, urine sodium concentration, and urine potassium concentration may unblind trial treatments, (Omitted) These measurements during the trial will be performed at specified laboratories, and will not be performed at local laboratories.

Changed Part	Before Change	After Change
Section 6.5.1 Prohibited Medications and Therapies Table 6.5.1-1 List of Prohibited Medications No. 4	Drugs, Foods, Beverages, and Supplements: [redacted]	Drugs, Foods, Beverages, and Supplements: [redacted]
Section 6.5.1 Prohibited Medications and Therapies Table 6.5.1-1 List of Prohibited Medications No. 5	No description	Drugs, Foods, Beverages, and Supplements: [redacted]
Section 6.5.1 Prohibited Medications and Therapies Table 6.5.1-1 List of Prohibited Medications No. 6	[redacted]	[redacted]
Section 6.5.1 Prohibited Medications and Therapies Table 6.5.1-1 List of Prohibited Medications No. 7	Drugs, Foods, Beverages, and Supplements: [redacted]	Drugs, Foods, Beverages, and Supplements: [redacted]
Section 6.5.1 Prohibited Medications and Therapies Rationale for Prohibited Concomitant Medications	No. 4 [redacted] No. 6 [redacted]	No. 4 and No. 5 [redacted] No. 7 [redacted]

Changed Part	Before Change	After Change
Section 6.5.3 Restricted Medications and Therapies Table 6.5.3-1	5) Nonsteroidal antiinflammatory drugs (excluding those used, as needed for local action.)	5) Nonsteroidal antiinflammatory drugs (excluding those used, as needed for local action; For drugs used for local action, refer to those permitted for concomitant use in Table 10.5.3-1.)
Section 8.5.2 [redacted]	No description	[redacted]
Section 8.8.2 Eliciting and Reporting Adverse Events	Note: For AEs occurring during hospitalization, time will also be recorded if possible. If the exact time of onset is unknown (cannot be identified in minutes), time in terms of hours will be identified.	Note: For AEs occurring during hospitalization, time will also be recorded if possible. If the time of onset/resolution is unknown (cannot be identified in minutes), time in terms of hours will be identified. Particular attention should be paid to determination of the time of onset and resolution of vomiting during hospitalization to provide a basis for considering the extent of IMP absorption.
Section 9.4.2.3 Physical Examination and Vital Signs Data	(Omitted) For subjects with a baseline systolic blood pressure of less than 90 mmHg, the number and percentage of subjects who have an actual value of "< 90 mmHg" at least once in the period from the time after IMP administration to the last assessment time point will be calculated.	(Omitted) For subjects with a baseline systolic blood pressure of at least 90 mmHg, the number and percentage of subjects who have an actual value of "< 90 mmHg" at least once in the period from the time after IMP administration to the last assessment time point will be calculated.
Section 9.4.3.6 [redacted]	No description	[redacted]

Changed Part	Before Change	After Change
		time point after IMP administration will be prepared for each treatment group.
Section 10.3 Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information	(Omitted) For males and FOCBP or their partners, who are sexually active, there must be a documented agreement that the subject and their partner will take effective measures (ie, 2 different approved methods of birth control) to prevent pregnancy during the course of the trial and for 90 days after the last dose of IMP and during the course of the trial and for 180 days after the last dose of IMP, respectively.	(Omitted) For males or their partners and FOCBP or their partners, who are sexually active, there must be a documented agreement that the subject and their partner will take effective measures (ie, 2 different approved methods of birth control) to prevent pregnancy during the course of the trial and for 90 days after the last dose of IMP and during the course of the trial and for 180 days after the last dose of IMP, respectively.
Section 10.3 Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information	(Omitted) The investigator or subinvestigator must immediately notify the sponsor (within 24 hours) of any pregnancy associated with IMP exposure during the trial and for at least 90 and 180 days after the last dose of the IMP in sexually active males and FOCBP or their partners, respectively, and record the event on the IRE form and forward it to the sponsor.	(Omitted) The investigator or subinvestigator must immediately notify the sponsor (within 24 hours) of any pregnancy associated with IMP exposure during the trial and for at least 90 and 180 days after the last dose of the IMP in sexually active males or their partners and FOCBP or their partners, respectively, and record the event on the IRE form and forward it to the sponsor.
Section 10.4 Appendix 4: List of Prohibited Medications Table 10.4-1	No description	[redacted]
Section 10.4 Appendix 4: List of Prohibited Medications Table 10.4-1	[redacted]	[redacted]
Section 10.4 Appendix 4: List of Prohibited Medications Table 10.4-3 Table 10.4-4 Table 10.4-5	[redacted]	[redacted]
Section 10.5 Appendix 5: Allowability of	[redacted]	[redacted]

Changed Part	Before Change	After Change
Concomitant Use of Topical Agents among Prohibited Concomitant Medications	[redacted]	[redacted]

10.7.3 Protocol Amendment 3

Amendment 3 Approval Date: 15 Jun 2023

PURPOSE:

Change of inclusion criteria; deletion of exclusion criteria; review of conditions for early completion; change of the timing to prohibit concomitant use of specified medications; addition of prohibited concomitant medications; and correction of writing errors

BACKGROUND:

Adverse reactions that may occur in association with OPC-131461 are assumed to include increased serum sodium concentration, thirst, dehydration, and hypotension. However, appropriate use of vasopressin receptor antagonists in heart failure patients has become widespread among medical institutions after the launch of SAMSCA®, which has a mechanism of action similar to that of OPC-131461. In addition, subjects of this trial are to be hospitalized and undergo appropriate control of fluid and blood pressure through protocol-specified observations, examinations, and evaluations. It was therefore judged that there would be no problem in securing subject safety, even if the upper limit of subject age in the inclusion criteria was increased from 85 years to 89 years. Given the fact that aging of heart failure patients is seen in clinical settings, the upper limit of age was increased.
Because COVID-19 was reclassified as a Class V Infectious Disease in the Infectious Disease Act, the necessity of a PCR test specified in the exclusion criteria was reviewed.
Resolution of all congestive findings (lower limb edema, pulmonary congestion, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound) was required for early completion. However, this condition for early completion was reviewed considering the development of these findings for reasons other than volume overload in heart failure.
Regarding prohibited concomitant medications, [redacted]
Writing errors were corrected.

MODIFICATIONS TO THE PROTOCOL:

Sectional Revisions:

Changed Part	Before Change	After Change
Section 1.1 Synopsis Trial Population	A total of 155 Japanese male and female subjects (31 subjects each in 5 groups; the target number of subjects who will begin trial treatment), who are between the ages of 18 and 85 years, inclusive at the time of informed consent	A total of 155 Japanese male and female subjects (31 subjects each in 5 groups; the target number of subjects who will begin trial treatment), who are between the ages of 18 and 89 years, inclusive at the time of informed consent

Changed Part	Before Change	After Change
Section 1.1 Synopsis Inclusion Criterion 3)	Males or females between the ages of 18 and 85 years inclusive (at the time of informed consent)	Males or females between the ages of 18 and 89 years inclusive (at the time of informed consent)
Section 1.1 Synopsis Exclusion Criterion 13)	Subjects with a positive polymerase chain reaction (PCR) test for SARS-CoV-2	(Removed due to deletion in Protocol Amendment 3) (Deletion of the exclusion criterion)
Section 1.1 Synopsis Exclusion Criterion 17)	No description	Drugs, Foods, Beverages, and Supplements: [redacted]
Section 1.1 Synopsis Treatment duration	14 days (If all congestive findings [lower limb edema, pulmonary congestion, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound] have been resolved and the investigator or subinvestigator judges that further improvement of volume overload is not necessary, however, treatment will be terminated before completing 14 days of treatment.)	14 days (However the treatment will be terminated before completing 14 days of treatment, if the investigator or subinvestigator judges that no further improvement of volume overload is necessary in a case that all congestive findings [lower limb edema, pulmonary congestion, jugular venous distension, hepatomegaly, pulmonary rales, or cardiac third sound] were resolved or in other cases).
Table 1.3-1	PCR test	No description
Section 1.3.2 [Examination and Investigation Items]	• PCR test (SARS-CoV-2)	No description
Section 1.3.16	The investigator or subinvestigator will perform the following examinations and investigations. 1) After breakfast Subjects will be instructed to urinate completely after breakfast and by the time immediately before administration, and measurement of urine volume and fluid intake will be started after complete urination immediately before administration, which will be set as the starting time point to evaluate the items shown below. Urine volume in a time point set, fluid intake in a time point set, and fluid balance in a time point set (at the times specified in Table 1.3-2) will also be evaluated. • Urine volume in a time point set, fluid intake in a time point set, and fluid balance in a time point set (at the times specified in Table 1.3-2) • Urine osmolality in a time point set, urine electrolyte (sodium, potassium) concentrations in a time point set, and	The investigator or subinvestigator will perform the following examinations and investigations. 1) Before breakfast and IMP administration • Plasma drug concentration (at the time specified in Table 1.3-2) • Serum electrolyte (sodium, potassium) concentrations and serum osmolality (at the time specified in Table 1.3-2) • Body weight • Vital signs (systolic and diastolic blood pressures, pulse rate, and body temperature) 2) After breakfast Subjects will be instructed to urinate completely after breakfast and by the time immediately before administration, and measurement of urine volume and fluid intake will be started after complete urination immediately before administration, which will be set as the starting time point to evaluate the items shown below. Urine volume in a time

Changed Part	Before Change	After Change
	urine aquaporin 2 concentration in a time point set 2) IMP administration The investigator or subinvestigator will confirm that the subject has taken the IMP completely, and record the date and time of administration and the dose in the source documents and eCRF. • Status of IMP administration 3) Before breakfast and IMP administration • Plasma drug concentration (at the time specified in Table 1.3-2) • Serum electrolyte (sodium, potassium) concentrations and serum osmolality (at the time specified in Table 1.3-2) • Body weight • Vital signs (systolic and diastolic blood pressures, pulse rate, and body temperature)	point set, fluid intake in a time point set, and fluid balance in a time point set (at the times specified in Table 1.3-2) will also be evaluated. • Urine volume in a time point set, fluid intake in a time point set, and fluid balance in a time point set (at the times specified in Table 1.3-2) • Urine osmolality in a time point set, urine electrolyte (sodium, potassium) concentrations in a time point set, and urine aquaporin 2 concentration in a time point set <u>3) IMP administration</u> The investigator or subinvestigator will confirm that the subject has taken the IMP completely, and record the date and time of administration and the dose in the source documents and eCRF. • Status of IMP administration
Section 4.1 Type/Design of Trial	During the treatment period, subjects will orally receive the IMP once daily for 14 days. However, if all congestive findings have been resolved and the investigator or subinvestigator judges that further improvement of volume overload is not necessary, treatment will be terminated before completing 14 days of treatment.	During the treatment period, subjects will orally receive the IMP once daily for 14 days. However, the treatment will be terminated before completing 14 days of treatment, if the investigator or subinvestigator judges that no further improvement of volume overload is necessary in a case that all congestive findings present at baseline are resolved or in other cases.
Section 4.3 Treatment duration	14 days (however, if all congestive findings [lower limb edema, pulmonary congestion, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound] have been resolved and the investigator or subinvestigator judges that further improvement of volume overload is not necessary, treatment will be terminated before completing 14 days of treatment.)	14 days (However, the treatment will be terminated before completing 14 days of treatment, if the investigator or subinvestigator judges that no further improvement of volume overload is necessary in a case that any of congestive findings [lower limb edema, pulmonary congestion, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound] were resolved or in other cases.)
Section 4.3 [Rationale]	Treatment is to be terminated before completing the 14-day treatment if all congestive findings have been resolved and the investigator or subinvestigator judges that further improvement of volume overload is not necessary.	Treatment is to be terminated before completing the 14-day treatment if the investigator or subinvestigator judges that no further improvement of volume overload is necessary in a case that all congestive findings present at baseline are resolved or in other cases.
Section 4.5 Definition of Completed Subjects	Subjects who terminate treatment before completing 14 days of treatment because all congestive findings (lower limb edema, pulmonary congestion, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound)	Subjects who terminate treatment before completing 14 days of treatment, because the investigator or subinvestigator judges that no further improvement of volume overload is necessary in a case that all congestive findings (lower limb edema,

Changed Part	Before Change	After Change
	have been resolved and the investigator or subinvestigator judges that further improvement of volume overload is not necessary, and who undergo the evaluation at the last scheduled visit during the treatment period are defined as early completers.	pulmonary congestion, jugular venous distension, hepatomegaly, pulmonary rales, or cardiac third sound) present at baseline are resolved or in other cases, and who undergo the evaluation at the last scheduled visit during the treatment period are defined as early completers.
Section 5 Trial Population	A total of 155 Japanese male and female subjects (31 subjects each in 5 groups; the target number of subjects who will begin trial treatment), who are between the ages of 18 and 85 years, inclusive at the time of informed consent	A total of 155 Japanese male and female subjects (31 subjects each in 5 groups; the target number of subjects who will begin trial treatment), who are between the ages of 18 and 89 years, inclusive at the time of informed consent
Section 5.2.1.1 Inclusion Criterion 3)	Males or females between the ages of 18 and 85 years inclusive (at the time of informed consent)	Males or females between the ages of 18 and 89 years inclusive (at the time of informed consent)
Section 5.2.1.1 Rationale for Inclusion Criterion 3)	The lower age limit is specified to select subjects who are legally competent to provide consent and the upper age limit is set at 85 years based on the fact that cardiac edema commonly affects the elderly and in consideration of subject safety.	The lower age limit is specified to select subjects who are legally competent to provide consent and the upper age limit is set at 89 years based on the fact that cardiac edema commonly affects the elderly and in consideration of subject safety.
Section 5.2.2 Exclusion Criterion 13)	Subjects with a positive polymerase chain reaction (PCR) test for SARS-CoV-2	(Removed due to deletion in Protocol Amendment 3) (Deletion of the exclusion criterion)
Section 5.2.2 Exclusion Criterion 17)	No description	Drugs, Foods, Beverages, and Supplements: [redacted]
Table 6.5.1-1 No. 8	No description	Drugs, Foods, Beverages, and Supplements: [redacted]
Section 6.5.1 Rationale for Prohibited Concomitant Medications No. 8	No description	[redacted]
Section 7.3.2	As per the protocol, subjects who terminate treatment before completing the 14 days of the treatment period because their congestive findings have been resolved will undergo the EOT/withdrawal examination, post-treatment examination, and follow-up examination at the specified timing,	As per the protocol, subjects who terminate treatment before completing the 14 days of the treatment period because the investigator or subinvestigator judges that no further improvement of volume overload is necessary in a case that all congestive findings (lower limb edema, pulmonary congestion, jugular venous distension,

Changed Part	Before Change	After Change
	following the final IMP administration of each early completer.	hepatomegaly, pulmonary rales, or cardiac third sound) present at baseline are resolved or in other cases will undergo the EOT/withdrawal examination, post-treatment examination, and follow-up examination at the specified timing following the final IMP administration of each early completer.
Section 8.7.6	8.7.6.1 PCR Test A PCR test (SARS-CoV-2) at screening will be performed according to the procedure specified by the trial site. The presence/absence of test, the date of test, and results of the test will be recorded in the source documents and eCRF.	Not applicable.
Section 10.4 Appendix 4: List of Prohibited Medications Table 10.4-1	No description	[redacted]
Section 10.4 Appendix 4: List of Prohibited Medications Table 10.4-1	[redacted]	No description

10.7.4 Protocol Amendment 4

Amendment 4 Approval Date: 27 Dec 2023

PURPOSE:

Change of trial period; change of exclusion criteria; change of prohibited and restricted concomitant medications; correction of writing errors; clarifications of descriptions; and adjustments of descriptions

BACKGROUND:

[redacted]

Corrections of writing errors, clarifications of descriptions, and adjustments of descriptions were made.

MODIFICATIONS TO THE PROTOCOL:

Sectional Revisions:

Changed Part	Before Change	After Change
Section 1.1 Inclusion Criterion (Screening Period) 1)	Subjects with CHF with lower limb edema, pulmonary congestion, or jugular venous distension due to volume overload.	Subjects with CHF with <u>any of</u> lower limb edema, pulmonary congestion, or jugular venous distension due to volume overload.
Section 1.1 Exclusion Criterion 8)	[redacted]	[redacted]
Section 1.1 Exclusion Criterion 17)	[redacted]	[redacted]
Section 1.1 Exclusion Criterion 17)	[redacted]	[redacted]
Section 1.1 Synopsis Trial Duration	Overall, the trial duration is from signing of the first informed consent form to the final subject assessment is expected to be approximately 15 months.	Overall, the trial duration<u>,</u> from signing of the first informed consent form to the final subject assessment<u>,</u> is expected to be <u>approximately 21 months.</u>
Section 1.3 Schedule of Assessments	No description	<u>Items that are not permitted to measure at hospitals during the trial period (See Section 6.3): Serum osmolality, plasma AVP concentration, urine osmolality, urine sodium concentration, urine potassium concentration, and urine aquaporin 2 concentration</u>
Section 1.3 Schedule of Assessments	c During the treatment period, serum sodium and potassium concentrations will be measured not only at the central laboratory but also at the trial site.	g <u>Serum sodium and potassium concentrations will be measured at the central laboratory during the screening period, post-treatment observation period, and follow-up period, and</u> will be measured not only at the central laboratory but also at the trial sites <u>during the treatment period.</u>

Changed Part	Before Change	After Change
Section 5.2.1.1 Inclusion Criterion (Screening Period) 1)	Subjects with CHF with lower limb edema, pulmonary congestion, or jugular venous distension due to volume overload.	Subjects with CHF with any of lower limb edema, pulmonary congestion, or jugular venous distension due to volume overload.
Section 5.2.2 Exclusion Criterion 8)	[redacted]	[redacted]
Section 5.2.2 Exclusion Criterion 17)	[redacted]	[redacted]
Section 5.2.2 Exclusion Criterion 17)	[redacted]	[redacted]
Section 6.5 Concomitant Medications and Therapies	(Omitted) For concomitant therapies, the name of therapy, purpose, and start and end dates of treatment will be recorded in the eCRF.	(Omitted) For concomitant therapies (including salt restriction), the name of therapy, purpose, and start and end dates of treatment will be recorded in the eCRF.
Section 6.5.1 Prohibited Medications and Therapies Table 6.5.1-1	[redacted]	[redacted]
Section 6.5.1 Prohibited Medications and Therapies Table 6.5.1-1	[redacted]	[redacted]
Section 6.5.1 Prohibited Medications and Therapies	No. 7 [redacted]	No. 7 [redacted]
Section 6.5.2 Medications Requiring	[redacted]	[redacted]

Changed Part	Before Change	After Change
Caution for Concomitant Use	[redacted]	[redacted] such use may cause interactions.
Section 6.5.3 Restricted Medications and Therapies Table 6.5.3-1	[redacted]	[redacted] and finerenone) and SGLT2 inhibitors
Section 6.5.3 Restricted Medications and Therapies	[redacted]	[redacted]
Section 9.4.3.2 Pharmacokinetic Analysis 2) Statistical methods	The parameter will be determined to statistically show dose proportionality when the two-sided 95% CI of the estimate of b includes 1.	The parameter will be determined to show dose proportionality when the two-sided 95% CI of the estimate of b includes 1.
Section 10.3 Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information	(Omitted) If a subject is suspected to be pregnant before she receives the IMP, the IMP administration must be withheld until the result of a pregnancy test is available.	(Omitted) If a subject is suspected to be pregnant before she receives IMP, the IMP administration must be withheld until the result of a serum pregnancy test is available.
Section 10.4 Appendix 4: List of Prohibited Medications Table 10.4-2	No description	[redacted]
Section 10.4 Appendix 4: List of	The following changes were made (deleted parts are shown with a strikethrough, while corrected parts are shown in bold):	

Changed Part	Before Change	After Change
Prohibited Medications Table 10.4-5	[redacted]	

Changed Part	Before Change	After Change
	[redacted]	
Section 10.5 Appendix 5: Allowability of Concomitant Use of Topical Agents among Prohibited Concomitant Medications	[redacted]	[redacted]
Section 10.6 Appendix 6: List of Medications Requiring Caution for Concomitant Use Table 10.6-1	No description	[redacted]
Section 10.6	[redacted]	No description

Changed Part	Before Change	After Change
Appendix 6: List of Medications Requiring Caution for Concomitant Use Table 10.6-1	[redacted]	
Section 10.6 Appendix 6: List of Medications Requiring Caution for Concomitant Use Table 10.6-1	The following changes were made (deleted parts are shown with a strikethrough): [redacted]	

Changed Part	Before Change		After Change
	[redacted]	[redacted]	[redacted]

ADDITIONAL RISKS TO THE SUBJECT:

No additional risks will be imposed on the subjects.

11 References

1 Japanese Circulation Society, et al. JCS 2017/JHFS 2017 Guideline on Diagnosis and Treatment of Acute and Chronic Heart Failure. 2018.

2 Matsuzaki M, Hori M, Tohru Izumi, Fukunami M. Efficacy and Safety of Tolvaptan in Heart Failure Patients with Volume Overload Despite the Standard Treatment with Conventional Diuretics: A Phase III, Randomized, Double-blind, Placebo-controlled Study (QUEST Study). 2011;25(Suppl 1):S33-S45.

3 Goldsmith SR, Gheorghiade M. Vasopressin Antagonism in Heart Failure. J Am Coll Cardiol. 2005;46(10):1785-91.

4 Kato R (supervising ed.), Ieiri I, Kusuhara H (eds.). Clinical Pharmacokinetics. Amendment 5. Nankodo. 2017.

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

6 Ministry of Health, Labour and Welfare. Regarding clinical studies utilizing pharmacogenomics: PFSB/ELD Notification No. 0930007. 2008.

7 Ministry of Health, Labour and Welfare. Guidelines on genomic sampling and management of genomic data: PSEHB/PED Notification No. 0118-1. 2018.

8 Matsuo S. New development of measures against CKD (chronic kidney disease). J. Jpn. Soc. Dial. Ther. 2009;42(4):317-23.

9 Japanese Society of Nephrology (ed.). Evidence-based Clinical Practice Guide for CKD 2018. Tokyo Igakusha. 2018.

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 them to ensure that they are sufficiently informed regarding the investigational new drug (OPC-131461), 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-131461 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 authorities 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, I do not comply with the protocol to eliminate an immediate hazard to subjects, I will provide the information to the IRB within the required local applicable timelines. Administrative changes to the protocol will be transmitted to the IRB for informational purposes only, if required by local regulations.

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

_____	_____
Principal Investigator Print Name	Trial Site Name
_____	_____
Signature	Date

This agreement is electronically signed by the sponsor. The sponsor signature page is attached to this document.