STATISTICAL ANALYSIS PLAN

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
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Otsuka Pharmaceutical Co., Ltd.

Investigational New Drug OPC-131461

Protocol No. 351-102-00004

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

Statistical Analysis Plan

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List of Abbreviations and Definition of Terms

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{∞}	area under the concentration-time curve from time zero to infinity
AUC_{∞}/D	AUC∞ normalized by dose
AUC_{24h}	area under the concentration-time curve from time zero to 24 hours
AUC_{24h}/D	AUC_{24h} normalized by dose
AUC_{tau}	area under the concentration-time curve during a dosage interval (tau) at steady-state
AUC_t	area under the concentration-time curve calculated to the last observable concentration at time t
AUC_%Extrap	percentage of AUC due to extrapolation from t_{last} to infinity $[(AUC_{\infty}-AUC_t) / AUC_{\infty}\times 100]$
AVP	arginine vasopressin
BMI	body mass index
BNP	brain natriuretic peptide
[redacted]	[redacted]
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL/F	apparent clearance of drug after extravascular administration
CL/F/BW	CL/F normalized in body weight
C_{max}	maximum (peak) concentration of the drug
C_{max}/D	C_{max} normalized by dose
CRF	Case report form
$eGFR_{cre}$	estimated glomerular filtration rate using the creatinine
$eGFR_{cys}$	estimated glomerular filtration rate using the cystatin C
λ_z	apparent terminal-phase disposition rate constant (first-order)
λ_z(point)	number of points used in computing λ_z
λ_z(lower)	lower limit on time for values to be included in the calculation of λ_z
λ_z(upper)	upper limit on time for values to be included in the calculation of λ_z
λ_z(Rsq)	goodness of fit statistic for the terminal elimination phase, adjusted for the number of points used in the estimation of λ_z
[redacted]	[redacted]
NT-pro BNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
MedDRA	Medical Dictionary for Regulatory Activities
QTc	corrected QT interval
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}
$t_{1/2,z}$	terminal-phase elimination half-life
Treatment-emergent AEs (TEAEs)	treatment-emergent adverse event
t_{last}	time of last measurable (positive) concentration
t_{max}	time to maximum (peak) concentration

1 Introduction

This statistical analysis plan documents the details of the statistical analysis methodology to be applied in the protocol of Trial 351-102-00004.

2 Trial Objectives

Table 2-1 Trial Objectives and Endpoints

Objectives	Endpoints
Primary Objective: To investigate the dose response in respect of weight decrease following repeated oral administration of OPC-131461 at 1, 2, 5, 10 mg or placebo in patients with CHF with volume overload despite having diuretics other than vasopressin antagonists.	Primary Efficacy Endpoint: Change in body weight from baseline to the 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 the last assessment time point (the day after IMP administration) by Day 15 Percent change in body weight from baseline to the last assessment time point (the day after IMP administration) by Day 8 Percent change in body weight from baseline to the 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 distention, hepatomegaly, cardiothoracic ratio, pulmonary rales, and cardiac third sound) from the baseline to the 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 distention, hepatomegaly, cardiothoracic ratio, pulmonary rales, and cardiac third sound) from baseline to the last assessment (the day after IMP administration) by Day 15 Congestive findings (lower limb edema, pulmonary congestion, jugular venous distention, hepatomegaly, cardiothoracic ratio, pulmonary rales, and cardiac third sound), time to resolution of congestive findings, and the New York Heat Association (NYHA) Functional Classification

Table 2-1 Trial Objectives and Endpoints	
Objectives	**Endpoints**
Secondary Objectives: To confirm the safety, tolerability, pharmacokinetics (PK) and pharmacodynamic 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 findings, vital signs, 12-lead electrocardiogram (ECG) Pharmacodynamic Endpoints: Serum osmolality, serum electrolyte (sodium, potassium) concentration, serum troponin I concentration, serum NT-proBNP concentration, serum creatinine concentration, serum cystatin C concentration, estimated glomerular filtration rate (estimated glomerular filtration rate using creatinine [eGFRcre], estimated glomerular filtration rate using 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]

3 Trial Design

3.1 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 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.

3.2 Trial Treatments

- 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.)

3.3 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.

3.4 Handling of Time Points

Efficacy, safety, and exploratory endpoints will be described (see Section 11.2 for baseline pharmacodynamic endpoints).

The analysis visit used for tabulating each visit will be the CRF visit and time point values. Follow-up examinations for pharmacokinetic endpoints and pharmacodynamic endpoints will not be tabulated. However, the completion/discontinuation test visits will be classified into the following analysis visits.

- End-of-treatment examination in subjects who completed 14-day IMP administration: Day 15
- End-of-treatment examination in early completers: Visit on the applicable day (excluding congestive findings, chest X-ray [cardiothoracic ratio, pulmonary congestion], NYHA classification, and 12-lead ECG [Because these items, which are specified to be measured at a feasible time after IMP administration, are measured after IMP administration during treatment, while for early completers, IMP will not be administered the next day.])
- Withdrawal Examination: Visit at discontinuation (not tabulated as visit of discontinuation)

Post-treatment observation will be classified as Day 16 for patients who have completed 14 days of IMP administration (however, post-treatment observation analysis visits will also be prepared for items other than PK and PD endpoints).

Echocardiography will be classified as “Day 15-16” if it is assessed at the completion/discontinuation test visit or post-treatment observation.

For pulmonary congestion, cardiothoracic ratio, and NYHA classification, if IMP is administered for less than 7 days, the day after IMP administration will be included in the analysis visit "Last assessment by Day 7 (day of IMP administration)."

The baseline of each item is defined as follows.

Table 3.4-1 Handling of Time Points

Item	Baseline*
Body weight	Day 1 before IMP administration
Congestive findings (lower limb edema, jugular venous distension, hepatomegaly, pulmonary rales, and cardiac third sound)	Run-in period (last measurement)
Pulmonary congestion, cardiothoracic ratio	Run-in Period
NYHA Functional Classification	Run-in Period
Laboratory test values	Day 1 before IMP administration
Vital signs	Day 1 before IMP administration
12-lead ECG	Day 1 before IMP administration
[redacted]	[redacted]
[redacted]	[redacted]

*If there are multiple data in the run-in period, the data closest to Day 1 will be adopted as the baseline.

4 Sample Size

The sample size is set as 31 subjects per group.

Assuming that a dose of OPC-131461 at 5 mg or higher is equivalent to 15 mg of tolvaptan 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.

5 Statistical Analysis Datasets

5.1 Full Analysis Set

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.

5.2 Safety Analysis Set

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

5.3 PK Analysis Set

Includes all subjects who have been administered at least one OPC-131461 and have at least one measurement of plasma drug concentration.

5.4 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.

5.5 Handling of Missing Data

For missing values, no imputation will be applied.

6 Primary and Secondary Endpoints Analysis

6.1 Primary Endpoint

See Table 2-1.

6.2 Secondary Endpoints

See Table 2-1.

7 Disposition and Demographic Analysis

The following data will be aggregated by treatment group (OPC-131461 by dose and overall) and overall (excluding tabulation of subjects who gave informed consent).

7.1 Subject Disposition

For subjects from whom informed consent is obtained, the number of subjects who provided informed consent and were randomized, and the numbers and percentages of

subjects who did not receive IMP after randomization, subjects who received IMP, subjects who completed the trial after IMP administration (subjects who completed 14-day treatment and subjects who completed the trial early), and subjects who discontinued the trial after IMP administration will be presented (denominator is the number of subjects randomized). The number and percentage of subjects who discontinue IMP administration will be summarized by reason for discontinuation.

For the subjects who were randomized, the number and percentage of subjects included in each analysis set will be summarized.

7.2 Demographic and Baseline Characteristics

For the full analysis set and the safety analysis set Table 7.2-1, descriptive statistics (number of subjects, mean, standard deviation, minimum, median, maximum; the same applies hereinafter up to Section 9) or frequency distribution (number of subjects, %; the same applies hereinafter) will be tabulated.

Table 7.2-1 Demographic and Baseline Characteristics

Item	Timing	Method	Level
Age (years)	Time of informed consent	Descriptive statistics	–
		Frequency distribution	18-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-85, 86-89
			<65, ≥65
Sex	–	Frequency distribution	Female, Male
Height (cm)	Screening	Descriptive statistics	–
Weight (kg)	Screening	Descriptive statistics	–
BMI (kg/m^2)	Screening	Descriptive statistics	–
Country where the trial is conducted	–	Frequency distribution	JAPAN
Race	–	Frequency distribution	Asian, American Indian or Alaska Native, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other

Table 7.2-1	**Demographic and Baseline Characteristics**		
Item	**Timing**	**Method**	**Level**
Ethnicity	–	Frequency distribution	Not Hispanic or Latino, Hispanic or Latino, Unknown
Underlying disease (multiple choice) • Ischemic heart disease • Cardiomyopathy • Valvular disease • Hypertensive heart disease • Arrhythmia	Screening	Frequency distribution	Yes, No
Heart failure type	Screening	Frequency distribution	Right Heart Failure, Left Heart Failure, Bi-ventricular Failure, Unspecified
Presence or absence of arrhythmia	Screening	Frequency distribution	Yes, No
Presence or absence of pacemaker	Screening	Frequency distribution	Yes, No
Presence or absence of implantable cardioverter defibrillator	Screening	Frequency distribution	Yes, No
Complication (multiple choice) • Hypertension • Angina pectoris • Diabetes mellitus • Renal impairment	Screening	Frequency distribution	Yes, No
Presence or absence of complications	Screening	Frequency distribution	Yes, No
Presence or absence of medical history	Screening	Frequency distribution	Yes, No

7.3 Baseline Disease Evaluation

Each item at baseline will be tabulated in the full analysis set and the safety analysis set.

Table 7.3-1 Baseline Disease Evaluation

Item	Method	Level
Cardiothoracic ratio (%)	Descriptive statistics	–
NYHA Functional Classification	Frequency distribution	Class I, Class II, Class III, Class IV
Degree of lower limb edema	Frequency distribution	Absent, Mild, Moderate, Severe
Pulmonary congestion	Frequency distribution	Absent, Mild, Moderate, Severe
Presence or absence of jugular venous distention	Frequency distribution	Yes, No
Jugular venous distension (cm)	Descriptive statistics	–
Presence or absence of hepatomegaly	Frequency distribution	Yes, No
Hepatomegaly (cm)	Descriptive statistics	–
Pulmonary rales	Frequency distribution	Yes, No
III Sound	Frequency distribution	Yes, No
Daily urine volume	Frequency distribution	<1500 mL, ≥1500 mL
Creatinine	Frequency distribution	<2 mg/dL, ≥2 mg/dL
Plasma AVP concentration	Frequency distribution	≤3.1 ng/L, >3.1 ng/L
Albumin	Frequency distribution	<3 g/dL, ≥3 g/dL
[redacted]	[redacted]	[redacted]

7.4 Treatment Compliance

The full analysis set will be used. Frequency distribution will be determined for presence or absence of the days of IMP not administered.

7.5 Prior and Concomitant Medications

Frequency distributions of the use of concomitant medications and therapies on the starting day of IMP administration will be calculated for the full analysis set and the safety analysis set.

Table 7.5-1 Use of Concomitant Medications and Therapies on the Starting Day of IMP Administration

Item	Level
Loop diuretics	Loop diuretic alone, Loop diuretic + other diuretic, No loop diuretic
Loop diuretic dose (Furosemide equivalent*)	< 40 mg/day, ≥ 40 to < 80 mg/day, ≥ 80 mg/day, No loop diuretic
Diuretic category *Concomitant use of diuretics other than loop diuretics, thiazide diuretics, or mineralocorticoid receptor antagonists will not be considered	Loop diuretic alone, Loop diuretic + thiazide diuretic, Loop diuretic + mineralocorticoid receptor antagonist, Loop diuretic + thiazide diuretic + mineralocorticoid receptor antagonist, No loop diuretic
Thiazide diuretic	No, Yes
Mineralocorticoid receptor antagonist	No, Yes
Therapeutic drugs for heart failure other than diuretics	No, Yes
Digitalis preparation	No, Yes
ACE inhibitor	No, Yes
βblocker	No, Yes
Angiotensin receptor antagonist	No, Yes
SGLT2 inhibitor	No, Yes
HCN channel blocker	No, Yes
Angiotensin receptor neprilysin inhibitor (ARNI)	No, Yes
Soluble guanylate cyclase (sGC) stimulator	No, Yes
Salt restriction	No, Yes

*The amount equivalent to 40 mg of furosemide is 1 mg of bumetanide, 60 mg of azosemide, and 8 mg of torasemide.

7.6 Protocol Deviations

The frequency distribution of the presence or absence of significant deviations will be calculated for each CRF classification (Dosing, Inclusion/Exclusion Criteria, Met Withdrawal Criteria But Not Withdrawn, Prohibited Concomitant Medications) of the randomized subjects. The frequency distribution of subjects with any significant deviation will also be determined.

8 Efficacy Analyses

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

8.1 Primary Efficacy Endpoint

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.

8.1.1 Primary Efficacy Endpoint Analysis

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. The least squares mean and two-sided 95% confidence interval (t-distribution) of each dose group will be determined. In addition, the least squares mean difference between OPC-131461 dose groups and the placebo group and two-sided 95% CI (t-distribution) and p-value will be calculated by comparing those groups at a two-sided significance level of 5%. Control of experimental-wise type 1 error per test will not be performed.

Similar analysis will be performed using the primary analysis model excluding baseline body weight.

For the change from baseline in body weight at the last assessment, a bar graph of the least squares mean (two-sided 95% CI [t-distribution]) with the treatment group as the horizontal axis will be prepared for each model.

8.1.2 Sensitivity Analysis

Not performed.

8.1.3 Technical Details of Primary Efficacy Endpoint Analysis

The SAS code for the primary analysis is shown below.

```
proc glm data=DATA;
  class TRTP;
  model CHG= TRTP BASE;
  lsmeans TRTP / cl pdiff=control('CONTROL') adjust=t;
run;
```

8.2 Key Secondary Efficacy Endpoint

8.2.1 Key Secondary Efficacy Endpoint Analysis

For the key endpoint, in order to investigate the dose-response relationships for placebo, 1, 2, 5, and 10 mg, a model similar to that used in the primary analysis will be used to contrast the response saturated at 1 mg, response saturated at 2 mg, response saturated at 5 mg, and linear response.

Similar analysis will be performed using the primary analysis model excluding baseline body weight.

8.2.2 Sensitivity Analysis

Not performed.

8.2.3 Technical Details of Key Secondary Efficacy Endpoint Analysis

The SAS code for examination of dose-response relationship is shown below.

```
proc glm data = DATA;
  class TRTP;
  model CHG = TRTP BASE;
  contrast '1 mg saturated' TRTP 4 -1 -1 -1 -1;
  contrast '2 mg saturated' TRTP 7 2 -3 -3 -3;
  contrast '5 mg saturated' TRTP 9 4 -1 -6 -6;
  contrast 'linear' TRTP 2 1 0 -1 -2;
run;
```

8.3 Secondary Efficacy Endpoint Analyses

8.3.1 Body Weight

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, and a bar graph will be prepared. The same analysis as described in Section 8.2.1 will be performed.

For body weight at the last assessment by Day 8 (the day after IMP administration), the last assessment by Day 15 (the day after IMP administration), and each time point, descriptive statistics of the actual values, amount of change and percent change from the baseline will be calculated for each treatment group.

8.3.2 Lower Limb Edema, Pulmonary Congestion

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 8.3-1]) 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 (Clopper-Pearson) 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 time to improvement and time to resolution ("time to improvement/resolution or censoring" minus "starting point", the same applies hereinafter), Kaplan-Meier plots will be prepared by treatment group for subjects with symptoms at baseline to estimate the median and the two-sided 95% CI (log-log transformation). Day −1 will be used as the starting point, and if no events have occurred as of the day after the final IMP administration of the study drug, the study will be censored at that point.

For changes in the severity of symptoms, shift tables from baseline to the last assessment on Day 7 (day of IMP administration), the last assessment on Day 15 (the day after IMP administration) and each time point after IMP administration will be prepared for each treatment group.

The improvement rate at each time point after administration of the IMP will be calculated for each treatment group.

Table 8.3-1 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

8.3.3 Pulmonary Rales, Cardiac Third Sound

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 (Clopper-Pearson) 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 the time to resolution, 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 (log-log transformation). Day −1 will be used as the starting point, and if no events have occurred as of the day after the final IMP administration of the study drug, the study will be censored at that point.

For changes in the presence or absence of symptoms, shift tables from baseline to the last assessment on Day 7 (day of IMP administration), the last assessment on Day 15 (the day after IMP administration) and each time point after IMP administration will be prepared for each treatment group.

8.3.4 Jugular Venous Distention, Hepatomegaly, Cardiothoracic Ratio

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 (t-distribution) will be determined. Similar analysis will be performed using a model excluding baseline values.

For the last assessment by Day 7 (the day of IMP administration), the last assessment by Day 15 (the day after IMP administration), and each time point, descriptive statistics of the actual values and amount of change from the baseline will be calculated for each treatment group. For changes in the presence or absence of jugular venous distention and hepatomegaly, shift tables from baseline to the last assessment on Day 7 (day of IMP administration), the last assessment on Day 15 (the day after IMP administration) and each time point after IMP administration will be prepared for each treatment group.

For the time to resolution of jugular venous distention and hepatomegaly, 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 (log-log transformation). Day −1 will be used as the starting point, and if no events have occurred as of the day after the final IMP administration of the study drug, the study will be censored at that point.

8.3.5 NYHA Functional Classification

For the NYHA Functional Classification, 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 (Clopper-Pearson) 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 classification, shift tables from baseline to the last assessment on Day 7 (day of IMP administration), the last assessment on Day 15 (the day after IMP administration) and each time point after IMP administration will be prepared for each treatment group.

8.4 Subgroup Analyses

Subgroup analyses will be performed for the following stratification items in the main analysis of the primary endpoint. Similar analysis will be performed using the main analysis model excluding baseline body weight.

Table 8.4-1 Stratification Item	
Item	**Level**
Sex	Female, Male
Age	<65, >=65
NYHA Functional Classification	Class I, Class II, Class III and Class IV
Ischemic heart disease	Yes, No
Heart failure type	Right Heart Failure, Left Heart Failure, Bi-ventricular Failure
Loop diuretics	Loop diuretic alone, Loop diuretic + other diuretic
Loop diuretic dose (Furosemide equivalent)	< 40 mg/day, ≥ 40 to < 80 mg/day, ≥ 80 mg/day
Diuretic category *Concomitant use of diuretics other than loop diuretics, thiazide diuretics, or mineralocorticoid receptor antagonists will not be considered	Loop diuretic alone, Loop diuretic + thiazide diuretic, Loop diuretic + mineralocorticoid receptor antagonist, Loop diuretic + thiazide diuretic + mineralocorticoid receptor antagonist
Thiazide diuretic	No, Yes
Mineralocorticoid receptor antagonist	No, Yes
Daily urine volume (baseline)	<1500 mL, >=1500 mL
Creatinine (baseline)	<2 mg/dL, >=2 mg/dL
Plasma AVP concentration (baseline)	<=3.1 ng/L, >3.1 ng/L
Albumin (baseline)	<3 g/dL, >=3 g/dL
[redacted]	[redacted]

9 Safety Analyses

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

9.1 Extent of Exposure

The frequency distribution of the number of subjects will be calculated for each number of days of administration. Descriptive statistics will be calculated for the number of days of IMP administration.

9.2 Adverse Events

All AEs will be coded by system organ class and MedDRA preferred term. The incidence of the following events will be summarized by treatment group:

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

If the same event occurs more than once in the same subject, the higher severity will be used. TEAEs related to the IMP will be tabulated similarly.

TEAEs by time of first onset will be tabulated into the following categories.

- Category 1
  - From the start of IMP administration to Day 3 of the treatment period
  - From Day 4 to Day 7 of the treatment period
  - From Day 8 to Day 14 of the treatment period
  - From 1 day after to 2 days after the final IMP administration (including 1 day after and 2 days after the final IMP administration for discontinuation and early completion)
  - More than 2 days after the final IMP administration
- Category 2
  - 1 to 3 days after the start of IMP administration
  - 4 to 7 days after the start of IMP administration
  - 8 to 16 days after the start of IMP administration
  - 17 or more days after the start of IMP administration

9.3 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 of each parameter at baseline, each time point after IMP administration, and the last assessment time point will be prepared.

For each item other than the qualitative urinalysis, scatter diagrams of the values at the last assessment against the baseline will be prepared.

Serum electrolyte (K) will also be tabulated, excluding samples with hemolysis of 3+ or higher.

The number and percentage of subjects in which AST or ALT increased to 3 times the upper limit of normal or more and total bilirubin increased to 2 times the upper limit of normal or more at any point after IMP administration will be calculated.

9.4 Vital Sign 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 each visit 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 each time point after IMP administration.

9.5 Physical Examination Data

No tabulation will be performed.

9.6 Electrocardiogram Data

For 12-lead ECG parameters, descriptive statistics of the actual values and changes from baseline at each time point and at the last 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 visits from each 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 visits from the time after IMP administration to the last assessment time point will be calculated. Similarly, the above mentioned numbers and percentages of subjects will be calculated at baseline and each time point after IMP administration.

A shift table showing normal/abnormal judgment at baseline, each time point after IMP administration, and the last assessment time point will be prepared.

9.7 Other Safety Data

Not applicable.

10 Pharmacokinetic Analyses

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

10.1 Endpoints

1) Plasma concentrations of OPC-131461, M35101, and M35103 (Day 1 to Day 16)
2) Plasma pharmacokinetic parameters for OPC-131461, M35101, and M35103
   - Day 1
     C_{max}, AUC_{24h}, t_{max}, t_{last}, C_{max}/D, AUC_{24h}/D
   - Day 7
     C_{max}, AUC_{24h}, t_{max}, t_{last}, C_{max}/D, 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, AUC_{24h}/D
     #1: Not calculated for metabolites
3) Ratio of the AUC_{24h} of M35101 or M35103 to that of OPC-131461 (Day 1, Day 7, and Day 14)
4) Cumulative for OPC-131461, M35101, and M35103 (Day 7 and Day 14)
   - $R(C_{max})$, $R(AUC_{24h})$, and $R(C_{trough})$
5) Dose proportionality of the C_{max} and AUC_{24h} of OPC-131461 (Day 1, Day 7, and Day 14)

10.2 Statistical Methods

1) Data on each of the endpoints presented in Section 10.1 1) will be summarized by compound, treatment group, and day of IMP administration. In addition, data on the endpoints shown in Section 10.1 1) will be summarized by time point of blood sampling, while data on the endpoints shown in Section 10.1 2), 3), and 4) 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.

2) For the endpoints shown in Section 10.1 5), 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.

   $\ln Y = a + b \cdot \ln X$ ... (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.

3) For each compound in Section 10.1 1), a graph comparing changes in blood concentration between treatment groups by day of IMP administration and a graph comparing changes in blood concentration between day of IMP administration by treatment group will be prepared on a linear scale (mean ± SD and median) and a logarithmic scale (mean and median). In addition, a graph of the blood concentration versus time profile (spaghetti plot) for all subjects by day of IMP administration and treatment group will be prepared for each compound, and a comparative graph of the blood concentration versus time between administration days by treatment group will be prepared for each compound and subject, both on an actual value scale and a logarithmic scale. For trough concentrations, a comparison graph of blood concentrations between treatment groups will be prepared for each compound on an actual value scale (mean ± SD and median) and a logarithmic scale (mean and median). In addition, a graph of trough concentrations versus time profile (spaghetti plot) will be prepared for each compound and all subjects by treatment group. The C_{max}/D and AUC_{24h}/D of the unchanged drug in Section 10.1 2) will be plotted against dose for each day of IMP administration. The relationship graph will plot the individual values and mean ± standard deviation with the C_{max}/D or AUC_{24h}/D of the same treatment group as the vertical axis (Y-axis) and the treatment group as the horizontal axis (X-axis).

10.3 Technical Details of Pharmacokinetic Analysis

[redacted]

[redacted]

10.4 Pharmacokinetic/Pharmacodynamic Analysis

[redacted]

11 Pharmacodynamic Analyses

The pharmacodynamic analysis set will be used for the analyses in Section 11.3.

11.1 Method of Calculating Endpoints

For pharmacodynamic endpoints that require calculation, the calculation method is shown below. If the Allowable Time Windows for Postdose Examinations/Assessments specified in the protocol (Table 1.3-2) is exceeded, pharmacodynamic endpoints using values for that time cannot be calculated. However, 24-hour urine volume, water intake, fluid balance and urinary excretion of electrolytes (sodium, potassium), and urinary excretion of aquaporin 2 cannot be calculated only if the end point of the last interval exceeds the allowable time windows for postdose examinations/assessments specified in the protocol.

1) Urinary excretion rate (mL/h): /1-hour fluid intake/fluid balance: urine volume/fluid intake/fluid balance in each interval will be converted to excretion per unit time (1 hour).
2) Fluid balance: Fluid intake during urine collection interval − interval urine volume
3) Urinary electrolytes (sodium, potassium) and aquaporin 2 excretion: Calculated as the product of the concentration in the interval urine and the urine volume.
4) 24-hour urine volume/fluid intake/fluid balance and urinary electrolyte (sodium, potassium) excretion/urinary aquaporin-2 excretion: Calculate the sum of the values of urine volume/fluid intake/fluid balance/excretion in each interval from Day 1 to 0-24 hours after administration on Day 13, 0-24 and 24-48 hours after administration on Day 14, and 0-24 and 24-48 hours after the final administration in early completion subjects and discontinued subjects. If any interval is missing, the cumulative value will also be considered missing unless that interval volume is separately measured.
5) Free water clearance (mL/min): Calculated for each urine collection interval of 0-24 hours after administration on Day 1 and Day 7, 0-48 hours after administration on Day 14, and 0-48 hours after the final IMP administration in subjects who completed the study early and those who discontinued the study by the following formula. The values of serum osmolality used to calculate the free water clearance at each assessment time are shown in the table below. The mean values of serum osmolality (before) and serum osmolality (after) are used (if only one value is available, that value is used).
    - Free water clearance = Urine excretion rate (mL/min) × (serum osmolality − urine osmolality) / serum osmolality

Table 11.1-1 Serum Osmolality Values Used to Calculate Free Water Clearance

Timing (Day)	Timing (Urine Collection Interval)	Serum Osmolality (Before)	Serum Osmolality (After)
−1	0-4 hours after breakfast	Day 1 predose	–
−1	4-8 hours after breakfast	Day 1 predose	–
−1	8-12 hours after breakfast	Day 1 predose	–
−1	12-24 hours after breakfast	Day 1 predose	–
1	0-4 hours postdose	Day 1 predose	Day 1 4-6 hours postdose
1	4-8 hours postdose	4-6 hours postdose	–
1	8-12 hours postdose	Day 1 8-12 hours postdose	–
1	12-24 hours postdose	Day 1 8-12 hours postdose	Day 2 predose
7	0-4 hours postdose	Day 7 predose	Day 7 4-6 hours postdose
7	4-8 hours postdose	Day 7 4-6 hours postdose	–
7	8-12 hours postdose	Day 7 8-12 hours postdose	–
7	12-24 hours postdose	Day 7 8-12 hours postdose	Day 8 predose
14	0-4 hours postdose	Day 14 predose	EOT examination before breakfast
14	4-8 hours postdose	Day 14 predose	EOT examination before breakfast
14	8-12 hours postdose	Day 14 predose	EOT examination before breakfast
14	12-24 hours postdose	Day 14 predose	EOT examination before breakfast
14	24-28 hours postdose	EOT examination before breakfast	Post-treatment observation examination before breakfast
14	28-32 hours postdose	EOT examination before breakfast	Post-treatment observation examination before breakfast
14	32-36 hours postdose	EOT examination before breakfast	Post-treatment observation examination before breakfast
14	36-48 hours postdose	EOT examination before breakfast	Post-treatment observation examination before breakfast
Early completers/ EOT examination	Daily urine volume (EOT examination)	EOT examination before breakfast	–
Withdrawal Examination	Daily urine volume (withdrawal examination)	Withdrawal examination before breakfast	–

6) eGFRcre (mL/min/1.73m^2): Calculated from serum creatinine concentration, sex, and age on Day 1, Day 8, Day 15, and the day after the last dose for early completers and withdrawals, using the CKD-EPI formula[1] and the GFR estimation formula for Japanese[2].

- CKD-EPI formula (males):
  When serum creatine concentration ≤ 0.9 mg/dL:
  $eGFR = 141 \times (\text{serum creatinine concentration} / 0.9)^{-0.411} \times 0.993^{age}$
  When serum creatine concentration > 0.9 mg/dL:
  $eGFR = 141 \times (\text{serum creatinine concentration} / 0.9)^{-1.209} \times 0.993^{age}$
  CKD-EPI formula (females):
  $eGFR = 144 \times (\text{serum creatinine concentration} / 0.9)^{-0.329} \times 0.993^{age}$
  When serum creatine concentration > 0.9 mg/dL:
  $eGFR = 144 \times (\text{serum creatinine concentration} / 0.9)^{-1.209} \times 0.993^{age}$
- Estimated GFR in Japanese (males):
  $eGFR = 194 \times \text{serum creatinine concentration}^{-1.094} \times age^{-0.287}$
  Estimated GFR in Japanese (females):
  $eGFR = 194 \times \text{serum creatinine concentration}^{-1.094} \times age^{-0.287} \times 0.739$

7) eGFRcys: Calculated from serum cystatin C concentration, sex, and age on Day 1, Day 8, Day 15, and the day after the last dose for early completer and withdrawals, using the GFR estimation formula[3] for Japanese.
   - For males:
     $(104 \times \text{serum cystatin C concentration [mg/L]}^{-1.019} \times 0.996^{age}) - 8$
   - For females:
     $(104 \times \text{serum cystatin C concentration (mg/L)}^{-1.019} \times 0.996^{age} \times 0.929) - 8$

11.2 Definition of Baseline

For urine volume, urine excretion rate, urine osmolarity, urine Na excretion, urine K excretion, urine aquaporin-2 excretion, fluid intake, fluid balance, and free water clearance, the values on Day −1 corresponding to each measurement interval in the treatment period will be used.

eGFR is defined as the predose value on Day 1.

Blood endpoints (serum osmolality, serum Na concentration, serum K concentration, serum cystatin C concentration, serum creatinine concentration, plasma AVP concentration, plasma renin activity, plasma aldosterone concentration, plasma BNP concentration, serum NT-pro BNP concentration, and serum troponin I concentration) are used for pharmacodynamic evaluation before IMP administration on Day 1.

The significant figures of each baseline value shall be consistent with those of each endpoint.

11.3 Statistical Methods

Descriptive statistics of the actual values for each pharmacodynamic endpoint at each time point and descriptive statistics of the changes from baseline at each time point will be calculated by treatment group (by dose of OPC-131461). If the allowable time windows for postdose examinations/assessments specified in the protocol is exceeded, the values for that time will not be included in the tabulation.

The descriptive statistics to be calculated will be the number of subjects tabulated, mean, standard deviation, minimum, median, and maximum.

For urinary excretion rate, 1-hour fluid intake, 1-hour fluid balance, urine osmolarity, free water clearance, serum osmolality, serum Na concentration, serum K concentration, plasma AVP concentration, plasma BNP concentration, serum NT-proBNP concentration, and serum troponin I concentration, graphs of actual values or calculated values and changes from baseline (mean ± SD) will be prepared as line graphs representing the time course. For 24-hour urine volume, 24-hour urinary Na excretion, 24-hour urinary K excretion, 24-hour fluid intake, and 24-hour fluid balance, the actual values or calculated values and changes from baseline (mean ± SD) will be prepared as line graphs representing the time course. For 24-hour urinary aquaporin-2, a bar graph comparing calculated values and changes from baseline (mean ± SD) will be prepared.

12 Pharmacogenomic Analyses

Not performed.

13 Exploratory Endpoint Analyses

13.1 [redacted]

[redacted]

13.2 [redacted]

[redacted]

[redacted]

14 Interim Analysis

[redacted]

15 Changes in the Planned Analyses

Table 15-1 Changes in the Planned Analyses

Description in the Protocol	Description in the Statistical Analysis Plan	Reason for Change
9.4.3.3 Pharmacodynamic Analysis 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.	11.1 Method of Calculating Endpoints (No description)	Calculation of these pharmacodynamic endpoints was considered unnecessary.
9.4.3.2 Pharmacokinetic Analysis 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.	10.2 Statistical Methods (No description)	Application of such statistical analysis methods to this analysis was considered unnecessary.

16 References

Not applicable.

Appendix 1 List of Summary Tables

CT-1.1	Subject Disposition (Screened Subjects)
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CT-2.1	Reasons for Discontinuation (Randomized Subjects)
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CT-3.1.2	Demographic and Baseline Characteristics (Safety Analysis Set)
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CT-3.2.2	Underlying Disease Leading to Heart Failure (Safety Analysis Set)
CT-3.2.3	Medical History (Full Analysis Set)
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CT-3.3.1	Baseline Disease Evaluation (Full Analysis Set)
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CT-5.4	Analysis of Dose Response for Change from Baseline in Body Weight to Last Assessment Time Point (the Day After Investigational Medicinal Product Administration) by Day 15 (Full Analysis Set)

CT-5.5	Descriptive Statistics for Change from Baseline in Body Weight by Visit (Full Analysis Set)
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CT-6.1.2	Improvement Rate for Lower Limb Edema and Pulmonary Congestion by Visit (Full Analysis Set)
CT-6.1.3	Resolution Rate for Lower Limb Edema and Pulmonary Congestion (Full Analysis Set)
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CT-6.1.5	Shift Table for Lower Limb Edema and Pulmonary Congestion by Visit (Full Analysis Set)
CT-6.1.6	Time to Improvement for Lower Limb Edema and Pulmonary Congestion (Full Analysis Set)
CT-6.2.1	Resolution Rate for Pulmonary rales and Third Cardiac Sound (Full Analysis Set)
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CT-13.1 [redacted]

CT-13.2.1 [redacted]

CT-13.2.2 [redacted]

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PKT-7.2 Individual and Summary of M35101 Plasma Pharmacokinetic Parameters Following Multiple Oral Administration of OPC-131461 (Day 14) (Pharmacokinetics Analysis Set)

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PKF-4.3 Mean M35103 Plasma Concentrations Following Multiple Oral Administration of OPC-131461 on Day 7 (Pharmacokinetics Analysis Set)

PKF-5.1 Median OPC-131461 Plasma Concentrations Following Multiple Oral Administration of OPC-131461 on Day 7 (Pharmacokinetics Analysis Set)

PKF-5.2 Median M35101 Plasma Concentrations Following Multiple Oral Administration of OPC-131461 on Day 7 (Pharmacokinetics Analysis Set)

PKF-5.3 Median M35103 Plasma Concentrations Following Multiple Oral Administration of OPC-131461 on Day 7 (Pharmacokinetics Analysis Set)

PKF-6.1 Mean OPC-131461 Plasma Concentrations Following Multiple Oral Administration of OPC-131461 on Day 14 (Pharmacokinetics Analysis Set)

PKF-6.2 Mean M35101 Plasma Concentrations Following Multiple Oral Administration of OPC-131461 on Day 14 (Pharmacokinetics Analysis Set)

PKF-6.3 Mean M35103 Plasma Concentrations Following Multiple Oral Administration of OPC-131461 on Day 14 (Pharmacokinetics Analysis Set)

PKF-7.1 Median OPC-131461 Plasma Concentrations Following Multiple Oral Administration of OPC-131461 on Day 14 (Pharmacokinetics Analysis Set)

PKF-7.2 Median M35101 Plasma Concentrations Following Multiple Oral Administration of OPC-131461 on Day 14 (Pharmacokinetics Analysis Set)

PKF-7.3 Median M35103 Plasma Concentrations Following Multiple Oral Administration of OPC-131461 on Day 14 (Pharmacokinetics Analysis Set)

PKF-8.1 Mean OPC-131461 Plasma Trough Concentrations Following Oral Administration of OPC-131461 (Pharmacokinetics Analysis Set)

PKF-8.2 Mean M35101 Plasma Trough Concentrations Following Oral Administration of OPC-131461 (Pharmacokinetics Analysis Set)

PKF-8.3 Mean M35103 Plasma Trough Concentrations Following Oral Administration of OPC-131461 (Pharmacokinetics Analysis Set)

PKF-9.1 Median OPC-131461 Plasma Trough Concentrations Following Oral Administration of OPC-131461 (Pharmacokinetics Analysis Set)

PKF-9.2 Median M35101 Plasma Trough Concentrations Following Oral Administration of OPC-131461 (Pharmacokinetics Analysis Set)

PKF-9.3 Median M35103 Plasma Trough Concentrations Following Oral Administration of OPC-131461 (Pharmacokinetics Analysis Set)

PKF-10.1 Mean OPC-131461 Plasma Concentrations Following Single and Multiple Oral Administration of OPC-131461 (Pharmacokinetics Analysis Set)

PKF-10.2 Mean M35101 Plasma Concentrations Following Single and Multiple Oral Administration of OPC-131461 (Pharmacokinetics Analysis Set)

PKF-10.3 Mean M35103 Plasma Concentrations Following Single and Multiple Oral Administration of OPC-131461 (Pharmacokinetics Analysis Set)

PKF-11.1 Median OPC-131461 Plasma Concentrations Following Single and Multiple Oral Administration of OPC-131461 (Pharmacokinetics Analysis Set)

PKF-11.2 Median M35101 Plasma Concentrations Following Single and Multiple Oral Administration of OPC-131461 (Pharmacokinetics Analysis Set)

PKF-11.3 Median M35103 Plasma Concentrations Following Single and Multiple Oral Administration of OPC-131461 (Pharmacokinetics Analysis Set)

PKF-12.1 Individual OPC-131461 Plasma Concentrations Following Multiple Oral Administration of OPC-131461 on Day 7 (Pharmacokinetics Analysis Set)

PKF-12.2 Individual M35101 Plasma Concentrations Following Multiple Oral Administration of OPC-131461 on Day 7 (Pharmacokinetics Analysis Set)

PKF-12.3 Individual M35103 Plasma Concentrations Following Multiple Oral Administration of OPC-131461 on Day 7 (Pharmacokinetics Analysis Set)

PKF-13.1 Individual OPC-131461 Plasma Concentrations Following Multiple Oral Administration of OPC-131461 on Day 14 (Pharmacokinetics Analysis Set)

PKF-13.2 Individual M35101 Plasma Concentrations Following Multiple Oral Administration of OPC-131461 on Day 14 (Pharmacokinetics Analysis Set)

PKF-13.3 Individual M35103 Plasma Concentrations Following Multiple Oral Administration of OPC-131461 on Day 14 (Pharmacokinetics Analysis Set)

PKF-14.1 Individual OPC-131461 Plasma Trough Concentrations Following Oral Administration of OPC-131461 (Pharmacokinetics Analysis Set)

PKF-14.2 Individual M35101 Plasma Trough Concentrations Following Oral Administration of OPC-131461 (Pharmacokinetics Analysis Set)

PKF-14.3 Individual M35103 Plasma Trough Concentrations Following Oral Administration of OPC-131461 (Pharmacokinetics Analysis Set)

PKF-15.1 Individual OPC-131461 Plasma Concentrations Following Single and Multiple Oral Administration of OPC-131461 (Pharmacokinetics Analysis Set)

PKF-15.2	Individual M35101 Plasma Concentrations Following Single and Multiple Oral Administration of OPC-131461 (Pharmacokinetics Analysis Set)
PKF-15.3	Individual M35103 Plasma Concentrations Following Single and Multiple Oral Administration of OPC-131461 (Pharmacokinetics Analysis Set)
PKF-16	Dose-normalized Cmax of OPC-131461 Following Oral Administration of OPC-131461 (Pharmacokinetics Analysis Set)
PKF-1	7Dose-normalized AUC24h of OPC-131461 Following Oral Administration of OPC-131461 (Pharmacokinetics Analysis Set)
PKPDF-1	Correlation Between 24-Hour Urine Volume and AUC24h of OPC-131461 (Pharmacokinetics Analysis Set and Pharmacodynamic Analysis Set)
PKPDF-2	Correlation Between Change from Baseline of 24-Hour Urine Volume and AUC24h of OPC-131461 (Pharmacokinetics Analysis Set and Pharmacodynamic Analysis Set)
PDT-1	Descriptive Statistics for Urine Volume for Each Urine Collection Period (Pharmacodynamic Analysis Set)
PDT-2	Descriptive Statistics for 24-Hour Urine Volume (Pharmacodynamic Analysis Set)
PDT-3	Descriptive Statistics for Urine Excretion Rate (Pharmacodynamic Analysis Set)
PDT-4	Descriptive Statistics for Urine Osmolality (Pharmacodynamic Analysis Set)
PDT-5	Descriptive Statistics for Urine Excretion of Sodium for Each Urine Collection Period (Pharmacodynamic Analysis Set)
PDT-6	Descriptive Statistics for 24-Hour Urine Excretion of Sodium (Pharmacodynamic Analysis Set)
PDT-7	Descriptive Statistics for Urine Excretion of Potassium for Each Urine Collection Period (Pharmacodynamic Analysis Set)
PDT-8	Descriptive Statistics for 24-Hour Urine Excretion of Potassium (Pharmacodynamic Analysis Set)

PDT-9	Descriptive Statistics for Urine Excretion of Aquaporin2 for Each Urine Collection Period (Pharmacodynamic Analysis Set)
PDT-10	Descriptive Statistics for 24-Hour Urine Excretion of Aquaporin2 (Pharmacodynamic Analysis Set)
PDT-11	Descriptive Statistics for Fluid Intake Volume for Each Fluid Collection Period (Pharmacodynamic Analysis Set)
PDT-12	Descriptive Statistics for 24-Hour Fluid Intake Volume (Pharmacodynamic Analysis Set)
PDT-13	Descriptive Statistics for Hourly Fluid Intake Volume (Pharmacodynamic Analysis Set)
PDT-14	Descriptive Statistics for Fluid Balance for Each Urine Collection Period (Pharmacodynamic Analysis Set)
PDT-15	Descriptive Statistics for 24-Hour Fluid Balance (Pharmacodynamic Analysis Set)
PDT-16	Descriptive Statistics for Hourly Fluid Balance (Pharmacodynamic Analysis Set)
PDT-17	Descriptive Statistics for Free Water Clearance (Pharmacodynamic Analysis Set)
PDT-18	Descriptive Statistics for Serum Osmolality (Pharmacodynamic Analysis Set)
PDT-19	Descriptive Statistics for Serum Sodium Concentration (Pharmacodynamic Analysis Set)
PDT-20	Descriptive Statistics for Serum Potassium Concentration (Pharmacodynamic Analysis Set)
PDT-21	Descriptive Statistics for Serum Cystatin C Concentration (Pharmacodynamic Analysis Set)
PDT-22	Descriptive Statistics for Serum Creatinine Concentration (Pharmacodynamic Analysis Set)
PDT-23	Descriptive Statistics for Plasma AVP Concentration (Pharmacodynamic Analysis Set)
PDT-24	Descriptive Statistics for Plasma Renin Activity (Pharmacodynamic Analysis Set)

PDT-25	Descriptive Statistics for Plasma Aldosterone Concentration (Pharmacodynamic Analysis Set)
PDT-26	Descriptive Statistics for Plasma BNP Concentration (Pharmacodynamic Analysis Set)
PDT-27	Descriptive Statistics for Serum NT-pro BNP Concentration (Pharmacodynamic Analysis Set)
PDT-28	Descriptive Statistics for Serum Troponin I Concentration (Pharmacodynamic Analysis Set)
PDT-29	Descriptive Statistics for eGFRcre calculated by CKD-EPI Equation (Pharmacodynamic Analysis Set)
PDT-30	Descriptive Statistics for eGFRcre calculated by Japanese Equation (Pharmacodynamic Analysis Set)
PDT-31	Descriptive Statistics for eGFRcys calculated by Japanese Equation (Pharmacodynamic Analysis Set)

PDF-1	Mean (SD) 24-Hour Urine Volume
PDF-2	Mean (SD) Change from Baseline of 24-Hour Urine Volume
PDF-3	Mean (SD) Urine Excretion Rate on Day 1, 7, and 14
PDF-4	Mean (SD) Change from Baseline of Urine Excretion Rate on Day 1, 7, and 14
PDF-5	Mean (SD) Urine Osmolality on Day 1, 7, and 14
PDF-6	Mean (SD) Change from Baseline of Urine Osmolality on Day 1, 7, and 14
PDF-7	Mean (SD) 24-Hour Urine Excretion of Sodium
PDF-8	Mean (SD) Change from Baseline of 24-Hour Urine Excretion of Sodium
PDF-9	Mean (SD) 24-Hour Urine Excretion of Potassium
PDF-10	Mean (SD) Change from Baseline of 24-Hour Urine Excretion of Potassium
PDF-11	Mean (SD) 24-Hour Urine Excretion of Aquaporin2

PDF-12	Mean (SD) Change from Baseline of 24-Hour Urine Excretion of Aquaporin2
PDF-13	Mean (SD) 24-Hour Fluid Intake Volume
PDF-14	Mean (SD) Change from Baseline of 24-Hour Fluid Intake Volume
PDF-15	Mean (SD) Hourly Fluid Intake Volume on Day 1, 7, and 14
PDF-16	Mean (SD) Change from Baseline of Hourly Fluid Intake Volume on Day 1, 7, and 14
PDF-17	Mean (SD) 24-Hour Fluid Balance
PDF-18	Mean (SD) Change from Baseline of 24-Hour Fluid Balance
PDF-19	Mean (SD) Hourly Fluid Balance on Day 1, 7, and 14
PDF-20	Mean (SD) Change from Baseline of Hourly Fluid Balance on Day 1, 7, and 14
PDF-21	Mean (SD) Free Water Clearance on Day 1, 7, and 14
PDF-22	Mean (SD) Change from Baseline of Free Water Clearance on Day 1, 7, and 14
PDF-23	Mean (SD) Serum Osmolality on Day 1, 7, and 14
PDF-24	Mean (SD) Change from Baseline of Serum Osmolality on Day 1, 7, and 14
PDF-25	Mean (SD) Serum Sodium Concentration on Day 1, 7, and 14
PDF-26	Mean (SD) Change from Baseline of Serum Sodium Concentration on Day 1, 7, and 14
PDF-27	Mean (SD) Serum Potassium Concentration on Day 1, 7, and 14
PDF-28	Mean (SD) Change from Baseline of Serum Potassium Concentration on Day 1, 7, and 14
PDF-29	Mean (SD) Plasma AVP Concentration
PDF-30	Mean (SD) Change from Baseline of Plasma AVP Concentration
PDF-31	Mean (SD) Plasma BNP Concentration
PDF-32	Mean (SD) Change from Baseline of Plasma BNP Concentration
PDF-33	Mean (SD) Serum NT-pro BNP Concentration

Appendix 2 List of Subject Data Listings

AE-1	Adverse Events (Randomized Subjects)
AE-2	Adverse Events Observed Before Start of Investigational Medicinal Product Administration (Randomized Subjects)
DEMOG-1	Demographic and Baseline Characteristics (Randomized Subjects)
DREAS-1	Discontinued Subjects and Reason for Discontinuation (Randomized Subjects)
LAB-1	Laboratory Test Results - Biochemistry (Randomized Subjects)
LAB-2	Laboratory Test Results - Hematology and Coagulation (Randomized Subjects)
LAB-3	Laboratory Test Results - Urinalysis (Randomized Subjects)
LAB-4	Laboratory Test Results - Serum Sodium and Potassium Trial Site (Randomized Subjects)
	PDEV-1Protocol Deviations (Randomized Subjects)
SMED-1	Investigational Medicinal Product Compliance (Randomized Subjects)
SUBEX-1	Subjects Excluded From Analysis Set (Randomized Subjects)
PDATA-1	Study Completion Status (Randomized Subjects)
PDATA-2	Inclusion Criteria and Exclusion Criteria Not Met
PDATA-3.1	Medical History and Complications (Randomized Subjects)
PDATA-3.2	History of Congestive Heart Failure (Randomized Subjects)
PDATA-4.1	Concomitant Medications (Randomized Subjects)
PDATA-4.2	Concomitant Therapy Other Than Medication (Randomized Subjects)
PDATA-5.1	Vital Signs (Randomized Subjects)
PDATA-5.2	Height (Randomized Subjects)
PDATA-6.1	Electrocardiogram Results Central ECG Analysis Laboratory (Randomized Subjects)
PDATA-6.2	Electrocardiogram Results Trial Site (Randomized Subjects)
PDATA-7	Pharmacokinetic Blood Draw Time (Randomized Subjects)

PDATA-8	Screen Failures
PDATA-9	Physical Examination (Randomized Subjects)
PDATA-10	Urine Volume for Each Urine Collection Period, 24-Hour Urine Volume, Urine Excretion Rate, Urine Osmolality (Randomized Subjects)
PDATA-11	Urine Concentration (Sodium, Potassium, Aquaporin2) (Randomized Subjects)
PDATA-12	Urine Excretion for Each Urine Collection Period, 24-Hour Urine Excretion (Sodium, Potassium, Aquaporin2) (Randomized Subjects)
PDATA-13	Fluid Intake and Fluid Balance (Each Fluid Collection Period, 24-Hour, 1-Hour), Free Water Clearance (Randomized Subjects)
PDATA-14	Serum Osmolality, Serum Concentration (Sodium, Potassium, Cystatin C, Creatinine) (Randomized Subjects)
PDATA-15	Plasma AVP Concentration, Plasma Renin Activity, Plasma Aldosterone Concentration (Randomized Subjects)
PDATA-16	Plasma BNP Concentration, Serum NT-pro BNP, Serum Troponin I Concentration (Randomized Subjects)
PDATA-17	eGFRcre (CKD-EPI Equation and Japanese Equation), eGFRcys (Japanese Equation) (Randomized Subjects)
PDATA-18	[redacted]
PDATA-19	Echocardiography (Randomized Subjects)
PDATA-20	Previous Screened ID (Randomized Subjects)
PDATA-21	Post-treatment Follow-up (Randomized Subjects)
PDATA-22	Information of pregnancy
PDATA-23	SARS-CoV-2 Test
PDATA-24	Storage of human DNA samples
PDATA-25	Storage of Biomarker Samples
PDATA-26	Pregnancy Test
PDATA-27	Hospitalization
PDATA-28	Subject Randomization List (Randomized Subjects)
EFF-1	Body Weight (Randomized Subjects)

EFF-2	Congestive Symptoms (Lower Limb Edema, Jugular Venous Distension, Hepatomegaly, Pulmonary rales, Third Cardiac Sound) (Randomized Subjects)
EFF-3	Chest X-ray (Pulmonary Congestion, Cardiothoracic Ratio) (Randomized Subjects)
EFF-4	NYHA Classification (Randomized Subjects)
EFF-5	Time to Improvement for Lower Limb Edema and Pulmonary Congestion (Randomized Subjects)
EFF-6	Time to Resolution for Lower Limb Edema, Pulmonary Congestion, Jugular Venous Distension, Hepatomegaly, Pulmonary rales and Third Cardiac Sound (Randomized Subjects)

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