Pharmacokinetics, Pharmacodynamics, Efficacy, and Safety of OPC-61815, a Prodrug of Tolvaptan for Intravenous Administration, in Patients With Congestive Heart Failure — A Phase II, Multicenter, Double-Blind, Randomized, Active-Controlled Trial —

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Background: Tolvaptan is an orally administered aquaretic drug indicated for patients with congestive heart failure (CHF) to remove excess fluid. OPC-61815, a prodrug of tolvaptan with improved water solubility, is considered suitable for intravenous (IV) administration. This Phase II study investigated the OPC-61815 dose that would result in an exposure equivalent to tolvaptan 15 mg.

Methods and Results: We conducted a multicenter, randomized study in Japanese patients aged 20–85 years with CHF and volume overload despite treatment with diuretics other than vasopressin antagonists. Patients received IV OPC-61815 2 mg (n=13), 4 mg (n=12), 8 mg (n=12), 16 mg (n=11), or oral tolvaptan 15 mg (n=12). The primary endpoint was tolvaptan exposure on treatment Day 1; efficacy and safety were also assessed. Tolvaptan exposure increased in a dose-dependent manner following a single IV administration of OPC-61815; the exposure following an IV dose of OPC-61815 16 mg was similar to that of a tolvaptan 15-mg tablet, with no marked differences in safety or tolerability. OPC-61815 increased urine volume from baseline, resulting in decreased body weight and improved lower limb edema. No notable safety concerns were observed.

Conclusions: In this first study of OPC-61815 in patients with CHF, exposure following a single IV administration of OPC-61815 16 mg was comparable with a single oral administration of tolvaptan 15 mg, with no safety concerns.

Key Words: Congestive heart failure; OPC-61815; Pharmacodynamics; Pharmacokinetics; Tolvaptan

Current data suggest that the main reason for hospitalization of patients with heart failure (HF) is related to the symptoms (dyspnea or breathlessness) and signs (jugular venous distension, rales, edema) of congestion. Because congestion is also related to water and sodium retention, the main goal of therapy is to remove excess intravascular and extravascular fluid without further activation of neurohormones, and without worsening renal function. Indeed, the acute decompensated heart failure syndromes (ATTEND) registry, the largest study of hospitalized HF patients conducted to date in Japan, found that approximately 70% of patients had fluid retention and 76.3% of patients had received in-hospital management with diuretics.

Treatment with loop diuretics reduces circulating blood volume and thereby reduces intravascular congestion. However, the osmolality of the circulating blood decreases with the use of loop diuretics, which may result in the less immediate translocation of fluid into the circulation system when the plasma refill rate is exceeded. By contrast, aquaretic drugs, such as vasopressin antagonists, predominantly cause water excretion, which increases the osmolality of the circulating blood, potentially improving translocation of fluid into the circulation system and thereby relieving tissue congestion.

The Japanese Circulation Society and the Japanese Heart Failure Society recommend the use of oral and intravenous (IV) loop diuretics to alleviate systemic fluid retention in patients with congestive HF (CHF). Should patients not have an adequate response to loop diuretics, the vasopres-
sin V2 receptor antagonist, tolvaptan, is recommended, except for patients with hypernatremia.

Tolvaptan is an orally active arginine vasopressin (AVP) V2 receptor antagonist that specifically inhibits the binding of AVP to the V2 receptor in the distal nephron to increase water excretion (aquaretic effect) without significant electrolyte excretion.1,2 The benefits of tolvaptan therapy on fluid loss and dyspnea in patients with acute decompensated HF have been confirmed in several studies.3–6 At present, tolvaptan is only available in oral formulations (tablet and granules)7–10 because it is not readily soluble in water11 and, therefore, cannot be used as a solution for injection. However, aquaretic drugs that can be administered intravenously are needed for HF patients when oral administration is not feasible/desirable; for example, due to impaired consciousness, impendence of oral intake due to ventilation, or an impaired swallowing reflex in elderly patients.

OPC-61815 is a prodrug of tolvaptan, in which a hydroxyl group on the benzazepine ring is phosphorylated, resulting in improved water solubility (Figure 1; Otsuka Pharmaceutical Co., Ltd. unpubl. data). After administration, the phosphate ester of OPC-61815 is hydrolyzed by phosphatases in the body and converted into tolvaptan. The administration of single and repeated doses of OPC-61815 to healthy male volunteers has been investigated in 3 Phase I trials, with no serious adverse events (AEs) or deaths reported (Otsuka Pharmaceutical Co., Ltd. unpubl. data).

The primary aim of this Phase II study was to investigate the dose of IV OPC-61815 that would result in an exposure equivalent to 15 mg of oral tolvaptan when administered once daily for 5 days in patients with CHF who were being treated with diuretics other than vasopressin antagonists.

Methods

Patients

Japanese men and women aged 20–85 years with CHF and volume overload despite treatment with diuretics other than vasopressin antagonists were included in this study. To be eligible for inclusion, patients were also required to have lower limb edema, pulmonary congestion, or jugular venous distension due to volume overload. Patients had to be able to take oral tablets and could continue to receive a loop diuretic equivalent to furosemide tablets or powder at ≥40mg/day, concomitant loop diuretic plus thiazide diuretic (at any dose), or concomitant loop diuretic plus aldosterone antagonist or a potassium-sparing diuretic (at any dose). Patients were also required to be currently hospitalized or be able to be hospitalized from the day before the run-in period to the end of the treatment period, be able to take a diuretic agent with no changes in dose and regimen during the run-in period, and have a body weight change ≤±1.0 kg over the 2 days before treatment administration.

Exclusion criteria included acute HF, predominantly non-cardiogenic congestive symptoms, or need for a ventricular assist device. Patients were also excluded if they had hypovolemia, hypertrophic cardiomyopathy, valvular disease with significant valvular stenosis, hepatic encephalopathy with difficulty in achieving adequate fluid intake, myocardial infarction within 30 days prior to screening, myocarditis, amyloid cardiomyopathy, poorly controlled diabetes, anuria, or dysuria with urinary tract obstruction, calculus, or tumor. Additional exclusion criteria were history of sustained ventricular tachycardia or ventricular fibrillation (without an implantable cardioverter defibrillator) or cerebrovascular disease (excluding asymptomatic cerebral infarction) within 30 days or 6 months of screening, respectively; body mass index (BMI) >35kg/m2; supine systolic blood pressure <90mmHg; abnormal relevant laboratory test results; concurrent symptoms or history of hepatic impairment; difficulty with fluid intake; lactation, pregnancy, or unwillingness to practice birth control or remain abstinent during the trial (where relevant); or receipt of any other investigational medicinal products within 30 days prior to screening.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki, Good Clinical Practice, and the applicable laws of Japan. The study was approved by the institutional review boards at each participating site. All patients provided written informed consent.

Study Design, Treatments and Blinding

This was a multicenter, randomized, double-blind, active-controlled, double-dummy, parallel-group study (ClinicalTrials.gov identifier: NCT03254108). The study comprised screening (Day −7 to −4), run-in (Day −3 to −1), treatment (Days 1–6), and follow-up (Days 12–15) periods (Supplementary Figure 1). All patients were admitted to hospital from the day before the run-in period to the end of the treatment period. The use of diuretics, body weight change, and congestive symptoms were evaluated during the run-in period.

Patients were randomly assigned (ratio 1:1:1:1:1) to receive 1 of 4 doses of IV OPC-61815 injection (2, 4, 8, or...
16 mg), administered over 1 h, or tolvaptan 15-mg oral tablets. All study drugs were administered once per day for 5 days during the treatment period, the end-of-trial examination was conducted on Day 6, and follow-up examinations were conducted 7–10 days after the final administration.

An Interactive Web Response System was used for randomization; patient allocation was documented in a separate allocation record, and the date of randomization and the assigned number was documented in the case report form. Blinding was maintained using the double-dummy design. Patients received a combination of either IV OPC-61815 and a placebo tablet, or IV placebo and a tolvaptan 15-mg tablet. Designated non-blinded staff at the trial site prepared the double-blinded treatments to control for differences in appearance between the OPC-61815 and placebo IV solutions.

Study Outcomes
The primary endpoint was the dose of OPC-61815 that was equivalent to 15 mg tolvaptan, which was assessed using maximum (peak) plasma drug concentration (C_{max}) and area under the concentration-time curve from time 0 to 24 h (AUC_{0-24h}).

Secondary endpoints included pharmacokinetic (PK), pharmacodynamic (PD), and efficacy outcomes. PK endpoints were plasma concentrations and parameters including AUC_{0-24h}, C_{max}, time to C_{max} (t_{max}), and the elimination half-life (t_{1/2}) of OPC-61815 on treatment Day 1. The t_{max} of tolvaptan was also measured on Day 1. PD endpoints included changes in urine volume per day and changes in urine osmolality. Plasma concentrations of OPC-61815 and tolvaptan were analyzed by Toray Research Center (Tokyo, Japan) using a validated high-performance liquid chromatography-tandem mass spectrometry method (measurable ranges of OPC-61815 and tolvaptan: 2–1,000 ng/mL). Efficacy outcomes included change in body weight, congestive symptoms (lower limb edema, jugular venous distension, pulmonary congestion confirmed by chest X-ray), and New York Heart Association (NYHA) classification.

In addition to the primary and secondary endpoints, safety outcomes were evaluated in this study using the data of AEs, clinical laboratory test results, physical examination findings, vital signs (blood pressure, pulse rate, and body temperature), and 12-lead ECG.

Statistical Analysis
The sample size was not based on any statistical considerations. The number of patients required to investigate the primary endpoint (tolvaptan exposure) was determined to be at least 10 patients/treatment group (50 in total) who completed blood sampling for measurement of plasma drug concentrations up until 24 h post-dose on Day 1. Thus, a target sample size of 11 patients/treatment group (55 in total) was prespecified, to account for potential withdrawals.

All analyses were conducted using patients who had received at least 1 dose of the study drug; these patients also comprised the safety analysis set. The PK analysis set included patients who had at least 1 evaluable plasma drug concentration measurement after treatment administration. The PD analysis set included patients who had evaluable PD data after treatment administration. The efficacy analysis set included patients who had body weight data after treatment administration.

For the primary endpoint, analyses were conducted using patients in the PK analysis set who had at least 1 primary endpoint measurement. Data were summarized by treatment group using descriptive statistics for each parameter. PK parameters were calculated by noncompartmental analysis. Logarithm-converted values were used to calculate the difference and 95% confidence intervals between the mean of each OPC-61815 group and the mean of the tolvaptan group.

Secondary PK and PD analyses were conducted using the PK and PD analysis sets, respectively. For PD endpoints,
Table 1. Patients’ Baseline Characteristics (Safety Analysis Set)

<table>
<thead>
<tr>
<th>OPC-61815</th>
<th>Tolvaptan</th>
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</thead>
<tbody>
<tr>
<td>2 mg (n=13)</td>
<td>15 mg (n=12)</td>
</tr>
<tr>
<td>4 mg (n=12)</td>
<td>Total (N=48)</td>
</tr>
<tr>
<td>8 mg (n=12)</td>
<td>16 mg (n=11)</td>
</tr>
<tr>
<td>Total (n=48)</td>
<td>15 mg (n=12)</td>
</tr>
<tr>
<td>16 mg (n=11)</td>
<td>Total (N=60)</td>
</tr>
</tbody>
</table>

### Age (years), mean (SD)
- OPC-61815: 73.7 (9.5) to 74.5 (11.9) to 72.2 (9.9) to 77.9 (3.8) to 74.5 (9.3)
- Tolvaptan: 74.8 (8.9) to 74.6 (9.1)

### Sex (male)
- OPC-61815: 8 (61.5) to 8 (66.7) to 7 (58.3) to 8 (72.7) to 31 (64.6)
- Tolvaptan: 10 (83.3) to 41 (68.3)

### Height (cm), mean (SD)
- OPC-61815: 157.6 (9.2) to 154.8 (8.6) to 162.2 (10.9) to 160.3 (7.0) to 158.7 (3.8)
- Tolvaptan: 159.4 (9.4) to 158.8 (9.2)

### Weight (kg), mean (SD)
- OPC-61815: 57.6 (12.7) to 53.2 (10.4) to 66.9 (11.0) to 61.2 (14.5) to 59.6 (12.8)
- Tolvaptan: 61.0 (16.0) to 59.9 (13.4)

### Etiology of heart failure
- Ischemic heart disease: 7 (53.8) to 8 (66.7) to 9 (75.0) to 4 (36.4) to 28 (58.3)
- Non-ischemic cardiomyopathy: 0 to 1 (8.3) to 0 to 4 (36.4) to 10 (20.8)
- Valvular disease: 4 (30.8) to 2 (16.7) to 5 (41.7) to 4 (36.4) to 20 (41.7)
- Hypertensive heart disease: 2 (15.4) to 1 (8.3) to 3 (25.0) to 4 (36.4) to 6 (12.5)

### NYHA functional class
- I: 0 to 9 (69.2) to 2 (16.7) to 1 (8.3) to 4 (8.3) to 0
- II: 9 (69.2) to 9 (75.0) to 6 (50.0) to 8 (72.7) to 32 (66.7)
- III: 4 (30.8) to 2 (16.7) to 5 (41.7) to 1 (9.1) to 4 (33.3)

### Comorbidities
- Hypertension: 7 (53.8) to 7 (58.3) to 9 (75.0) to 9 (81.8) to 32 (66.7)
- Angina pectoris: 3 (23.1) to 4 (33.3) to 2 (16.7) to 3 (27.3) to 12 (25.0)
- Diabetes mellitus: 5 (38.5) to 5 (41.7) to 8 (66.7) to 4 (36.4) to 22 (45.8)
- Renal impairment: 6 (46.2) to 10 (83.3) to 9 (75.0) to 6 (54.5) to 31 (64.6)

### Diuretic category
- Loop diuretic: 7 (53.8) to 4 (33.3) to 7 (58.3) to 3 (27.3) to 21 (43.8)
- Loop diuretic + thiazide: 0 (0.0) to 1 (8.3) to 0 (0.0) to 0 (0.0) to 1 (2.1)
- Loop diuretic + aldosterone antagonist: 5 (38.5) to 7 (58.3) to 5 (41.7) to 8 (72.7) to 25 (52.1)
- Loop diuretic + thiazide + aldosterone antagonist: 1 (7.7) to 0 (0.0) to 0 (0.0) to 0 (0.0) to 1 (2.1)

### Dose of loop diuretic (equivalent dose of furosemide) (mg/day)
- <40: 3 (23.1) to 2 (16.7) to 1 (8.3) to 2 (18.2) to 9 (18.8)
- 40 to 80: 7 (53.8) to 7 (58.3) to 7 (58.3) to 5 (45.5) to 26 (54.2)
- ≥80: 3 (23.1) to 2 (16.7) to 3 (25.0) to 1 (9.1) to 9 (18.8)

### Concomitant heart failure drugs
- ACEI: 4 (30.8) to 4 (33.3) to 3 (25.0) to 4 (36.4) to 15 (31.3)
- ARB: 2 (15.4) to 1 (8.3) to 7 (58.3) to 5 (45.5) to 15 (31.3)
- β-blocker: 9 (69.2) to 10 (83.3) to 10 (83.3) to 9 (81.8) to 38 (79.2)
- Digoxin: 1 (7.7) to 1 (8.3) to 4 (33.3) to 0 (0.0) to 6 (12.5)

### Lower limb edema
- None: 3 (23.1) to 4 (33.3) to 0 to 2 (18.2) to 9 (18.8)
- Mild: 8 (61.5) to 7 (58.3) to 8 (66.7) to 6 (54.5) to 29 (60.4)
- Moderate: 1 (7.7) to 0 to 2 (16.7) to 3 (27.3) to 6 (12.5)
- Severe: 1 (7.7) to 1 (8.3) to 2 (16.7) to 0 to 4 (8.3)

### Pulmonary congestion
- None: 4 (30.8) to 0 to 4 (33.3) to 5 (45.5) to 13 (27.1)
- Mild: 8 (61.5) to 10 (83.3) to 6 (50.0) to 6 (54.5) to 30 (62.5)
- Moderate: 1 (7.7) to 2 (16.7) to 2 (16.7) to 0 to 5 (10.4)
- Severe: 0 to 0 to 0 to 0 to 0

### Jugular venous distention
- Yes: 7 (53.8) to 8 (66.7) to 6 (50.0) to 5 (45.5) to 26 (54.2)
- Height (cm), mean (SD): 6.2 (3.0) to 5.2 (5.8) to 5.5 (4.2) to 4.7 (2.9) to 5.4 (4.1)
- Hepatomegaly, yes: 1 (7.7) to 1 (8.3) to 2 (16.7) to 1 (9.1) to 10 (10.4)
- Pulmonary rales, yes: 4 (30.8) to 3 (25.0) to 3 (25.0) to 1 (9.1) to 11 (22.9)
- Third cardiac sound, yes: 4 (30.8) to 2 (16.7) to 6 (50.0) to 1 (9.1) to 13 (27.1)

Data are shown as n (%) unless otherwise stated. ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; NYHA, New York Heart Association; SD, standard deviation.
OPC-61815 vs. Tolvaptan for HF

Results

Patients

Patient disposition is shown in Figure 2. In summary, between 6 November 2017 and 24 April 2018, 74 consenting patients were screened, and 61 met the eligibility criteria and were randomly assigned to receive treatment. The reasons for non-eligibility included failure to meet inclusion criteria or meeting exclusion criteria (n=7), diuretic

Figure 3. Mean (SD) tolvaptan concentrations on treatment period Day 1 with OPC-61815 injection and 15-mg tolvaptan oral tablet (pharmacokinetic analysis set). SD, standard deviation.
therapy was deemed unsuitable by a physician (n=4), and patient decided to not participate (n=2). One patient withdrew after randomization due to dehydration, and thus 60 patients received either OPC-61815 or tolvaptan. Treatment compliance was between 84.6% and 100% across all OPC-61815 groups and 91.7% in the tolvaptan group. The most common reason for discontinuation was the occurrence of AEs.

Patient characteristics were well balanced among the 5 treatment groups (Table 1). Most patients were male (68.3%) and aged 65 years or older (88.3%). The mean age was 74.6 years (range 44–85 years), the mean height was 158.8 cm (range 139.4–180.6 cm), and the mean body weight was 59.9 kg (range 33.3–88.5 kg).

PK Outcomes
The tolvaptan plasma concentration-time profiles following a single IV administration of OPC-61815 and a single oral administration of tolvaptan 15 mg are shown in Figure 3. The mean C_{max} and AUC_{0–24h} of tolvaptan increased dose-dependently following a single IV administration of OPC-61815 2, 4, 8, or 16 mg. The mean tolvaptan exposure (C_{max} and AUC_{0–24h}) on treatment Day 1 following a single IV administration of OPC-61815 16 mg was similar to that observed following a single oral administration of tolvaptan 15 mg (Table 2, Supplementary Table).

The median t_{max} of tolvaptan was 1.48, 1.73, 1.76, 1.52, and 4.07 following a single IV administration of OPC-61815 2, 4, 8, and 16 mg and a single oral administration of tolvaptan 15 mg, respectively (Table 2). Mean (standard deviation [SD]) plasma concentration-time profiles of OPC-61815 free form on treatment Day 1 following a single IV administration of OPC-61815 are shown in Supplementary Figure 2 and PK parameters are shown in Table 2.
OPC-61815 vs. Tolvaptan for HF

Mean (SD) changes from baseline in body weight was −1.0 kg (0.9) in the OPC-61815 16-mg group and −0.7 kg (0.5) in the tolvaptan 15-mg group. On Day 6, the respective changes were −2.1 kg (1.8) and −1.7 kg (0.9).

In patients with lower limb edema, the improvement rate on Day 6 was greater for all OPC-61815 groups (2 mg, 80.0%; 4 mg, 62.5%; 8 mg, 83.3%; 16 mg, 88.9%) compared with tolvaptan 15 mg (44.4%). Mean (SD) changes from baseline in jugular venous distension on Day 6 were −0.80 cm (1.15), −1.66 cm (3.05), −2.10 cm (3.05), −1.10 cm (1.19), and −2.50 cm (2.24) for OPC-61815 2 mg, 4 mg, 8 mg, and 16 mg, and tolvaptan 15 mg, respectively. The NYHA classification did not deteriorate for any patient.

For patients who received OPC-61815 2 mg, 4 mg, 8 mg, and 16 mg, and tolvaptan 15 mg, the NYHA classification improved in 4/13 patients, 2/12 patients, 4/12 patients, 7/11 patients, and 5/12 patients, respectively. Pulmonary con-

**PD Outcomes**
At baseline, respective mean (SD) daily urine volumes in the OPC-61815 2-mg, 4-mg, 8-mg, and 16-mg, and tolvaptan 15-mg groups were 1,522.7 mL (329.2), 1,391.3 mL (301.5), 1,536.9 mL (403.5), 1,725.5 mL (531.6), and 1,259.2 mL (421.6). Daily urine volumes increased and urine osmolality decreased from baseline in the OPC-61815 and tolvaptan groups throughout the treatment period. Mean (SD) changes in urine volume, water intake, fluid balance, and osmolality on treatment period Day 2 are shown in Figure 4. Mean increases were larger for daily urine volumes than for fluid intakes.

**Efficacy Outcomes**
Body weight decreased in all treatment groups after completion of study treatment (Figure 5). By the first day after study drug administration (Day 2), the mean (SD) change from baseline in body weight was −1.0 kg (0.9) in the OPC-61815 16-mg group and −0.7 kg (0.5) in the tolvaptan 15-mg group. On Day 6, the respective changes were −2.1 kg (1.8) and −1.7 kg (0.9).

In patients with lower limb edema, the improvement rate on Day 6 was greater for all OPC-61815 groups (2 mg, 80.0%; 4 mg, 62.5%; 8 mg, 83.3%; 16 mg, 88.9%) compared with tolvaptan 15 mg (44.4%). Mean (SD) changes from baseline in jugular venous distension on Day 6 were −0.80 cm (1.15), −1.66 cm (3.05), −2.10 cm (3.05), −1.10 cm (1.19), and −2.50 cm (2.24) for OPC-61815 2 mg, 4 mg, 8 mg, and 16 mg, and tolvaptan 15 mg, respectively. The NYHA classification did not deteriorate for any patient. For patients who received OPC-61815 2 mg, 4 mg, 8 mg, and 16 mg, and tolvaptan 15 mg, the NYHA classification improved in 4/13 patients, 2/12 patients, 4/12 patients, 7/11 patients, and 5/12 patients, respectively. Pulmonary con-
gestion was improved in 5/9 patients, 6/12 patients, 2/8 patients, 1/6 patients and 5/11 patients, respectively.

Safety Outcomes
The incidence of AEs and a list of TEAEs occurring in ≥2 patients are summarized in Table 3. The incidence of TEAEs ranged from 33.3% (4/12) to 72.7% (8/11) of patients in the OPC-61815 groups, compared with 83.3% (10/12) of patients in the tolvaptan 15-mg group. All TEAEs were mild to moderate in severity. TEAEs experienced by patients in the tolvaptan 15-mg group. All TEAEs were in the OPC-61815 groups, compared with 83.3% (10/12) of patients. TEAEs ranged from 33.3% (4/12) to 72.7% (8/11) of patients.

For example, this increase in serum sodium level was determined to be tolerable, and did not result in discontinuation.

Discussion
In patients with CHF, inhibition of AVP binding to the V$_2$-receptor in the distal nephron increases aquaresis without causing electrolyte imbalances or worsening renal function. Tolvaptan is an oral aquaretic drug that selectively blocks V$_2$-receptors, and its pharmacokinetics and pharmacodynamics have been extensively investigated. Currently, there is a need for aquaretic drugs that can be administered by IV injection, especially in CHF patients when administration of an oral drug is difficult or in those with reduced absorption. As tolvaptan has low solubility in water, it is expected that the higher solubility of the tolvaptan prodrug OPC-61815 will make it a clinically useful treatment option in these patients. Therefore, although interval urine volumes were not assessed, an earlier onset of drug effect is expected with OPC-61815 compared with tolvaptan. A dose-dependent trend was observed when administration of OPC-61815 2, 4, 8, and 16 mg. Furthermore, exposure on Day 1 following a single IV administration of OPC-61815 at 16 mg was the most similar to that following administration of a single 15-mg tolvaptan tablet. In this study, the mean dose-adjusted C$_{\text{max}}$ and AUC$_{0-24h}$ of tolvaptan in patients with CHF following a single IV administration of OPC-61815 were 1.5-fold (20.4 vs. 13.7 ng·h/mL) and 2.8-fold higher (185 vs. 65 ng·h/mL), respectively, compared with healthy subjects simulated using PK models based on the data from previous Phase I studies (Otsuka Pharmaceutical Co., Ltd. unpbl. data). Similarly, the mean dose-adjusted C$_{\text{max}}$ and AUC$_{0-24h}$ of tolvaptan in patients with CHF following administration of a single 15-mg tablet in this study were 2.4-fold (22.0 vs. 9.0 ng·h/mL) and 4.4-fold higher (190 vs. 43 ng·h/mL), respectively, compared with healthy volunteers in a Phase I study (Otsuka Pharmaceutical Co., Ltd. unpbl. data). Therefore, plasma concentrations of tolvaptan, following IV administration of OPC-61815 and oral administration of tolvaptan, are expected to be higher in patients with CHF compared with healthy individuals. This is a consequence of lower hepatic blood flow due to decreased cardiac output and a smaller distribution volume in patients with CHF.
observed in the effects of OPC-61815 on urine osmotic pressure and body weight. However, there was no dose-dependency in the effect on urine volume, with a particularly notable lack of difference between the OPC-61815 8-mg and 16-mg doses. Possible reasons for this include the limited number of evaluable patients, and the large variability in urine volume among groups prior to OPC-61815 or tolvaptan administration. In addition, there were differences in water intake, edema severity (NYHA classification and edema symptoms), body weight, and combined loop diuretic dose between the groups.

Although serum sodium concentrations did fluctuate, there was no rapid increase (defined as an increase exceeding 12 mEq from baseline within 24 h of treatment administration). Although 1 patient did show a gradual increase in serum sodium concentration, it was in the absence of any clinically significant events and this change was determined to be tolerable. Overall, there were no marked differences in safety and tolerability between OPC-61815 16 mg and tolvaptan 15 mg and there were no notable safety concerns.

Study Limitations
The results of this study are limited in their generalizability due to the enrollment of only Japanese patients. Furthermore, the small sample size is also a limitation, although the study was adequately powered to calculate the primary endpoint. The sample size was small because this study was a precursor step to a Phase III study (NCT03772041) that will evaluate the efficacy and safety of OPC-61815 in patients with CHF, using the dose of OPC-61815 that achieved an exposure equivalent to the 15-mg oral tolvaptan tablet that was identified herein (i.e., 16 mg).

Conclusions
In this first investigation of the dose of IV OPC-61815 equivalent to oral tolvaptan 15 mg in patients with CHF, we showed that tolvaptan exposure following a single IV administration of OPC-61815 16 mg was comparable to a single administration of oral tolvaptan 15 mg, with no marked differences in safety. Non-inferiority of 16 mg OPC-61815 compared with 15 mg tolvaptan, and tolerability in patients with CHF who have difficulty with, or are incapable of, oral intake are being investigated in Phase III studies.

Acknowledgments
The authors thank all the investigators from the contributing study sites for their participation. The authors also thank Matt Glasgow, PhD, and Sally-Anne Mitchell, PhD, of Edanz Pharma for providing medical writing services.

Data Availability
The deidentified participant data, data dictionaries, study protocol, and statistical analysis plan will be shared on a request basis, upon provision of a methodologically sound meta-analysis proposal. Data will be available after marketing approval in global markets, or starting 1-3 years following publication. There is no end date to the availability of the data. Please contact the corresponding author directly to request data sharing.

Contributor Statements
(1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work: N.S., S.U., Y.Y., T.H., S.K.
(2) Drafting the work or revising it critically for important intellectual content: N.S., S.U., Y.Y., T.H., S.K.
(3) Final approval of the version to be published: N.S., S.U., Y.Y., T.H., S.K.
(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: N.S., S.U., Y.Y., T.H., S.K.

Disclosures
N.S. has received lecture fees from Otsuka Pharmaceutical Co., Ltd.; S.U., Y.Y., T.H., and S.K. are employees of Otsuka Pharmaceutical Co., Ltd.

Funding
This study was financially supported by Otsuka Pharmaceutical Co., Ltd.

IRB Information
Review and approval of the study protocol and associated documentation was provided by the Institutional Review Board or Independent Ethics Committee at each of the 42 participating study sites. The representative Institutional Review Board was at the Nippon Medical School Musashi-Kosugi Hospital (#2017006).

References


Supplementary Files

Please find supplementary file(s);