Efficacy and safety of intravenous OPC-61815 compared with oral tolvaptan in patients with congestive heart failure

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Abstract

Aims  This multicentre, randomized, controlled, double-blind, parallel-group Phase III study was conducted to confirm the non-inferiority of OPC-61815 (tolvaptan sodium phosphate) intravenous injections to oral tolvaptan tablets in patients with congestive heart failure and volume overload despite receiving diuretics other than vasopressin antagonists.

Methods and results  Congestive heart failure patients with volume overload despite receiving diuretics other than vasopressin antagonists were randomly assigned (1:1) to receive OPC-61815 (16-mg injection; n = 149) or oral tolvaptan (15-mg tablet; n = 145) once daily for 5 days. Most patients were male; the mean age and weight were 74.7 years and 62.1 kg, respectively; other demographic and clinical characteristics were similar between groups. In this study, the primary endpoint was the change in body weight from baseline to the day after the last dose. Secondary endpoints included improvement from baseline in congestive findings and New York Heart Association classification. The change in body weight was −1.67 kg [95% confidence interval (CI): −1.93, −1.41] and −1.36 kg (95% CI: −1.62, −1.10) in the OPC-61815 group and tolvaptan group, respectively; the difference in the least squares mean between the groups was −0.31 kg (95% CI: −0.68, 0.06). Given the upper CI did not exceed the pre-specified limit of 0.48, this confirmed the non-inferiority of injectable OPC-61815 to oral tolvaptan. Daily urine volume and daily fluid intake increased, and daily fluid balance was negative throughout the treatment period; changes were similar for both groups. All evaluated congestive symptoms and New York Heart Association classifications showed improvement and safety findings were similar between the groups. The incidence of hyperkalaemia was higher in the OPC-61815 group, and the incidence of thirst and dry mouth was higher in the tolvaptan group. Most treatment-emergent adverse events were mild to moderate; one serious treatment-emergent adverse event of hyperkalaemia in the OPC-61815 group was considered treatment related.

Conclusions  OPC-61815 (16-mg injection) was confirmed as non-inferior to oral tolvaptan (15-mg tablet) in patients with congestive heart failure and inadequate response to diuretics; no new safety concerns were observed.

Keywords  Arginine vasopressin V₂ receptor antagonist; Congestive heart failure; Intravenous; Non-inferiority study; OPC-61815; Tolvaptan

Introduction

Intravenous (i.v.) loop diuretics are a cornerstone of acute heart failure (HF) treatment,¹−³ with Japanese registry studies reporting that approximately 70–80% of patients who were hospitalized for HF in Japan had fluid retention and 76–84% of hospitalized patients were treated with a diuretic.⁴,⁵ Accurate assessment of early treatment interventions is critical for the management of disease; after starting therapy for acute HF, continued follow-up assessments should be appropriately timed.⁶,⁷ Furthermore, it is recommended that the diagnosis and treatment of
congestive symptoms are managed at the same time.\textsuperscript{8} A previous study demonstrated that early treatment with a loop diuretic was associated with better in-hospital clinical outcomes and lower mortality.\textsuperscript{9}

Loop diuretics block sodium re-absorption, which increases sodium excretion and urine output and induces natriuresis; however, in some patients, loop diuretics alone are not enough to improve congestion. Furthermore, treatment with loop diuretics promotes neurohormonal activation and worsening renal function.\textsuperscript{10} In contrast, aquaretic drugs antagonize the V2 receptor to directly promote free water excretion; treatment has little effect on neurohormonal activation and renal function.\textsuperscript{10–12}

Tolvaptan, an oral aquaretic, acts as an arginine vasopressin V\textsubscript{2} receptor antagonist,\textsuperscript{13} and in clinical trials and real-world studies, tolvaptan treatment reduces body weight and improves congestive symptoms in patients.\textsuperscript{14,15} In the EVEREST study, tolvaptan did not contribute to an improvement in the long-term prognosis of patients who were hospitalized for HF, although it did improve several signs and symptoms of HF.\textsuperscript{16} The observed improvement in congestive symptoms in patients with acute cardiac insufficiency is clinically significant. Tolvaptan was first approved in Japan in 2010 for the treatment of volume overload in patients with HF who did not achieve an adequate response on diuretics; approvals in other Asian countries for the same indication then followed.\textsuperscript{14,17} The ESC and AHA guidelines, meanwhile, suggest that tolvaptan be considered in patients with HF and hyponatraemia and symptoms and signs of congestion.\textsuperscript{8,18} Oral tolvaptan is increasingly used in combination with i.v. loop diuretics for the treatment of congestion in the acute phase of HF in Japan,\textsuperscript{19–21} and Japanese guidelines recommend tolvaptan as second-line therapy following an inadequate response to loop diuretics; approvals in other Asian countries for the same indication then followed.\textsuperscript{14,17} The ESC and AHA guidelines, meanwhile, suggest that tolvaptan be considered in patients with HF and hyponatraemia and symptoms and signs of congestion.\textsuperscript{8,18} Oral tolvaptan is increasingly used in combination with i.v. loop diuretics for the treatment of congestion in the acute phase of HF in Japan,\textsuperscript{19–21} and Japanese guidelines recommend tolvaptan as second-line therapy following an inadequate response to loop diuretics in acute HF.\textsuperscript{7} However, it was considered necessary to develop i.v. diuretics because the treatment of congestion in acute HF requires a rapid onset of effect and the ability to administer treatment to patients with difficulty in oral intake. Furthermore, as tolvaptan has low water solubility, it is not suitable for development as an injectable drug.\textsuperscript{22}

OPC-61815 (tolvaptan sodium phosphate), a prodrug of tolvaptan with improved water solubility, has been developed for i.v. use.\textsuperscript{22} As with oral tolvaptan, i.v. OPC-61815 is expected to be effective for the treatment of volume overload in HF and was evaluated over 5 days in a dose-determining Phase II trial in patients with congestive HF.\textsuperscript{22} The Phase II study determined that drug exposures for a single i.v. administration of 16-mg OPC-61815 and a single 15-mg oral tablet of tolvaptan were similar. Patients had increased urine volume, decreased body weight, and improved lower limb oedema on Day 6 of the treatment period.

Because OPC-61815 is a water diuretic that can be administered i.v., the primary expected use is for the treatment of congestion in acute HF, where there is a greater need for i.v. diuretics. However, it was first necessary to verify the efficacy of OPC-61815 in patients who are able to take tolvaptan orally. We conducted a multicentre, randomized, controlled, double-blind, parallel-group Phase III trial in Japan to confirm the non-inferiority of the OPC-61815 injection formulation (16 mg once daily) to oral tolvaptan tablets (15 mg once daily) in patients with congestive HF who had volume overload despite treatment with diuretics (other than vasopressin antagonists) [OPC-61815 tolvaptan sodium phosphate intravenous administration for heart failure (OPTION-HF)]. The non-inferiority study design was chosen so as to develop an indication that is similar to the active comparator, tolvaptan, which has shown superiority over placebo in cardiac oedema in Japan.

\section*{Methods}

\subsection*{Patients}

Male or female patients were potentially eligible for study inclusion if they were aged 20–85 years, had congestive HF, were taking oral diuretics [loop diuretics (equivalent to \(\geq 40\) mg oral furosemide if using loop diuretics alone), combination of loop diuretic and thiazide diuretic, or combination of loop diuretic and aldosterone antagonist or potassium-sparing diuretic agent], and were inpatients. Additional inclusion criteria were presence of lower limb oedema, jugular distention, or pulmonary congestion due to volume overload; received diuretics with no dose or regimen change during the run-in period; and had no more than a 1.0 kg change in body weight over the 2 days (of the run-in period) immediately prior to receiving the study drug. Major exclusion criteria were acute HF that required emergency treatment, mainly non-cardiogenic congestive symptoms, acute myocardial infarction within the 30 days prior to the screening visit, definitive diagnosis of active myocarditis or amyloid cardiomyopathy, difficulty with fluid intake, current symptoms or a history of hepatic impairment, systolic blood pressure \(< 90\) mmHg, serum creatinine \(> 3\) mg/dL, or serum sodium \(< 125\) or \(> 147\) mEq/L. A serum sodium level \(< 125\) mEq/L was a criterion for exclusion because in Japan it is recommended that tolvaptan is reduced to 7.5 mg/day in HF patients due to the possibility of inducing a serum electrolyte imbalance and causing hypernatraemia. All patients provided written informed consent prior to participation.

\subsection*{Study design and treatments}

This was a multicentre, randomized, controlled, double-blind, parallel-group Phase III study to assess the non-inferiority of OPC-61815 (16-mg injection once daily) vs. tolvaptan (15-mg tablet once daily) in patients with congestive HF who had
volume overload despite prior treatment with diuretics (other than vasopressin antagonists). The dosage and regimen of diuretics used before the start of the run-in period were maintained throughout the treatment period. Patients were randomly assigned (1:1) to receive either OPC-61815 16-mg injection or tolvaptan 15-mg tablet using an interactive web response system provided by an external vendor (BELLSYSTEM24, Inc., Tokyo, Japan).

Figure 1A shows the detailed trial design. Patients were hospitalized from the day before the start of the run-in period (Day −4) to the end of the treatment period (Day 6). The 3 days before the start of study drug administration comprised the run-in period, during which the use of diuretics, change in body weight, and congestive symptoms were assessed. Only patients who met the inclusion criteria for the run-in period entered the treatment period. During the treatment period, the study drug was administered once daily for 5 days; patients received either OPC-61815 injection plus placebo tablet or placebo injection plus tolvaptan tablet. Patients were instructed to ingest the oral tablet with water, after which the injection was administered by the investigator (infusion time: 1 h ± 5 min). The placebo and investigational agents were indistinguishable from each other. Blinding was maintained using a double-dummy method. There was a completion assessment on Day 6 and a follow-up assessment between Days 12 and 15.

The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization guidelines for Good Clinical Practice, and applicable local laws and regulations. The protocol was approved by the institutional review board at each study site. The study was registered at www.clinicaltrials.gov (NCT03772041) and www.clinicaltrials.jp (JapicCTI-173676).

Study endpoints

The primary endpoint was the change in body weight from baseline to the time of the final administration of study drug (considered to be the day after the final dosing), which was used as a measure to reflect the aquaretic effects of OPC-61815 and tolvaptan on the general state of volume overload. Patients were permitted to drink water at any time and urinate upon waking and prior to weighing with a calibrated weighing scale before breakfast. Secondary endpoints included improvement rates from baseline to the time of the
final administration of study drug in congestive symptoms (lower limb oedema and jugular venous pressure) and New York Heart Association (NYHA) classification. Pharmacodynamic parameters, including daily urine volume, daily fluid intake, daily fluid balance (daily urine volume — daily fluid intake), change in serum sodium and potassium, and biomarkers [plasma concentrations of plasma arginine vasopressin (AVP) and brain natriuretic peptide (BNP), and plasma renin activity] were assessed at baseline and Day 6. Adverse events (AEs), clinical laboratory tests, physical examinations, vital signs, and 12-lead electrocardiograms were monitored for safety. AEs were coded using the Medical Dictionary for Regulatory Activities (Version 23.0) system organ class and preferred term classifications.

Statistical methods

Based on the upper limit of the 95% confidence intervals (CI) for the least squares (LS) mean of the difference in body weight for tolvaptan (15 mg) and placebo [−0.99 (95% CI: −1.57, −0.42) and −0.96 (95% CI: −1.37, −0.55), respectively] in a Phase III clinical trial (unpublished data; Otsuka Pharmaceutical), the expected (95% probability) minimum difference in body weight decrease (maximum difference in body weight) between the tolvaptan 15-mg tablet group and the placebo group was considered to be in the range of 0.42–0.55. The non-inferiority margin for the present trial was therefore set at 0.48, which corresponds to half of the treatment difference of 0.96 between the tolvaptan 15-mg tablet group and the OPC-618 15 16-mg injection group, based on the value obtained with the tolvaptan 15-mg tablet group and the OPC-61815 group and 145 to the tolvaptan group (Figure 1B). In the OPC-61815 group, 135/149 (90.6%) patients completed the trial, and 14 (9.4%) discontinued, most commonly due to AEs [8/149 (5.4%)]. In the tolvaptan group, 135/149 (93.1%) patients completed the trial and 10 (6.9%) discontinued, most commonly due to AEs and physician decision [3/145 (2.1%) each]. AEs leading to discontinuation included aspartate aminotransferase/alanine aminotransferase increased to >3× the upper limit of normal or higher, serum or plasma sodium increased by ≥12 mEq/L within 24 h after the start of study drug administration, and serum or plasma sodium increased to ≥155 mEq/L.

Patient characteristics at baseline are shown in Table 1. Patients were predominantly male (210/294, 71.4%), had a mean age of 74.7 years, and had a mean weight of 62.1 kg. Demographic and clinical characteristics were generally similar between the two treatment groups.

Efficacy

The primary endpoint, the difference in the LS mean (95% CI) body weight between the OPC-61815 and tolvaptan groups, was −0.31 kg (−0.68, 0.06) (Figure 2A). The upper limit of the 95% CI was below the pre-defined non-inferiority margin of 0.48, thus confirming the non-inferiority of OPC-61815 16-mg injection to the tolvaptan 15-mg tablet. Mean change in body weight over time is shown in Figure 2B.

Daily urine volume (Figure 3A) and fluid intake (Figure 3B) increased from baseline throughout the treatment period in both groups, with the greatest increases observed on Day 2 (first day after study drug administration was initiated). Changes from baseline in daily urine volume and daily fluid
intake were similar for both treatment groups throughout the treatment period. Changes from baseline for daily fluid balance showed negative values for both groups throughout the treatment period and were similar between groups (Figure 3C). All congestive symptoms evaluated showed improvement from baseline at the time of final study drug administration in both treatment groups. Lower limb oedema improvement rates were 68.9 and 75.7%, respectively, in the OPC-61815 and tolvaptan groups and 56.1 and 64.7%, respectively, for pulmonary congestion.

The improvement rates in NYHA classification (patients who improved by ≥1 grade from baseline to the time of final study drug administration) were 44.9 and 42.5% in the OPC-61815 and tolvaptan groups, respectively. The difference in improvement (95% CI) between the two groups was 2.4% (−10.2, 14.6). The LS mean change (95% CI) from baseline in jugular venous distention were 52 (34.9) and 59 (40.7) in the OPC-61815 and tolvaptan groups and 111 (37.8) for pulmonary congestion.

Table 1 Baseline demographic and clinical characteristics (all randomly assigned patients)

|                          | OPC-61815 | Tolvaptan | Total |
|--------------------------|-----------|-----------|-------|
| n = 149                  | n = 145   | n = 294   |
| Male                     | 112 (75.2)| 98 (67.6) | 210 (71.4) |
| Age, years, mean (min–max)| 74.0 (40–85)| 75.4 (47–85)| 74.7 (40–85) |
| Age, >80 years           | 58 (38.9)| 50 (34.5) | 108 (36.7) |
| Weight, kg, mean (SD)    | 63.3 (14.6)| 61.0 (13.3)| 62.1 (14.0) |
| Primary disease           |           |           |       |
| Ischaemia                | 36 (24.2)| 51 (35.2)| 87 (29.6) |
| Cardiomyopathy           | 23 (15.5)| 15 (10.3)| 38 (12.9) |
| Valvular disease         | 40 (26.8)| 39 (26.9)| 79 (26.9) |
| Hypertensive heart disease| 51 (24.3)| 47 (32.4)| 98 (33.3) |
| Arrhythmia               | 58 (38.9)| 51 (35.2)| 109 (37.1) |
| NYHA class               |           |           |       |
| I                        | 13 (8.7)| 23 (15.9)| 36 (12.2) |
| II                       | 101 (67.8)| 95 (65.5)| 196 (66.7) |
| III                      | 34 (22.8)| 26 (17.9)| 60 (20.4) |
| IV                       | 1 (0.7)| 1 (0.7)| 2 (0.7) |
| Co-morbidities           |           |           |       |
| Hypertension             | 109 (73.2)| 112 (77.2)| 221 (75.2) |
| Angina pectoris          | 26 (17.4)| 29 (20.0)| 55 (18.7) |
| Diabetes mellitus        | 61 (40.9)| 63 (43.4)| 124 (42.2) |
| Renal impairment         | 79 (53.0)| 72 (49.7)| 151 (51.4) |
| Arrhythmia               | 124 (83.2)| 119 (82.1)| 243 (82.7) |
| Renal function<sup>a</sup>, mean (SD) | 1.30 (0.50)| 1.33 (0.53)| - |
| Blood urea nitrogen      | 27.53 (13.10)| 27.82 (12.37)| - |
| Brain natriuretic peptide<sup>b</sup> (pg/mL) | 290.42 (412.70)| 327.38 (369.47)| - |
| Use of loop diuretic     |           |           |       |
| Monotherapy              | 48 (32.2)| 59 (40.7)| 107 (36.4) |
| Combined with other diuretic | 1001 (67.8)| 86 (59.3)| 187 (63.6) |
| Dose of loop diuretic    |           |           |       |
| <40 mg/day               | 68 (45.6)| 46 (31.7)| 114 (38.8) |
| 40–<80 mg/day            | 67 (45.0)| 89 (61.4)| 156 (53.1) |
| ≥80 mg/day               | 14 (9.4)| 10 (6.9)| 24 (8.2) |
| Lower limb oedema        |           |           |       |
| None                     | 27 (18.1)| 34 (23.4)| 61 (20.7) |
| Mild                     | 97 (65.1)| 84 (57.9)| 181 (61.6) |
| Moderate                 | 19 (12.8)| 19 (13.1)| 38 (12.9) |
| Severe                   | 6 (4.0)| 8 (5.5)| 14 (4.8) |
| Pulmonary congestion     |           |           |       |
| None                     | 26 (17.4)| 24 (16.6)| 50 (17.0) |
| Mild                     | 97 (65.1)| 98 (67.6)| 195 (66.3) |
| Moderate                 | 25 (16.8)| 23 (15.9)| 48 (16.3) |
| Severe                   | 1 (0.7)| 0 (0.0)| 1 (0.3) |
| Jugular venous distention|           |           |       |
| Yes                      | 52 (34.9)| 59 (40.7)| 111 (37.8) |
| No                       | 96 (64.4)| 86 (59.3)| 182 (61.9) |
| Not done                 | 1 (0.7)| 0 (0.0)| 1 (0.3) |
| Hepatomegaly             |           |           |       |
| Yes                      | 12 (8.1)| 10 (6.9)| 22 (7.5) |
| No                       | 137 (91.9)| 135 (93.1)| 272 (92.5) |

NYHA, New York Heart Association; SD, standard deviation.
Data are n (%) unless stated otherwise.
<sup>a</sup>Safety analysis set (n = 149, n = 145).
<sup>b</sup>Pharmacodynamic analysis set (n = 148, n = 145).
venous pressure in patients with baseline values was 
\(-2.89\, \text{cmH}_2\text{O} (-3.45, -2.33)\) for the OPC-61815 group and
\(-3.15\, \text{cmH}_2\text{O} (-3.68, -2.62)\) for the tolvaptan group; for he-
patomegaly, the respective values were 
\(-0.93\, \text{cm} (-1.44, -0.43)\) and 
\(-0.88\, \text{cm} (-1.43, -0.33)\) (Table S1).

The pre-specified sub-group analysis revealed no differ-
ences in the LS mean changes from baseline in body weight
at the time of final study drug administration between the
treatment groups for sex, age, NYHA classification, ischaemic
heart disease, concomitant diuretics, daily urine volume
\(\geq 1500\, \text{mL}\), and creatinine, plasma AVP concentration, and al-
bumin at baseline (Table S2). Sub-groups with a weight loss
of \(>1\, \text{kg}\) compared with the tolvaptan group included age
\(<65\, \text{years}\), NYHA Classes III–IV, and albumin \(<3\, \text{g/dL}\). Serum
sodium concentrations increased on Day 2 vs. baseline in both
groups and remained generally constant throughout the treat-
ment period, with a similar degree of change in both groups
(Figure 4A). Serum potassium concentrations were relatively
unchanged throughout the treatment period (Figure 4B).
There were no clinically meaningful changes in haemody-
amics or renal function from baseline through follow-up (Figures
S1A to S1D). Changes in each biomarker (plasma AVP, BNP,
and renin activity) on Day 6 compared with baseline were sim-
ilar in both groups. For both the OPC-61815 and tolvaptan
groups, plasma AVP concentrations increased (Figure S1E)
and plasma BNP concentrations decreased slightly (Figure
S1F) from baseline. No notable changes from baseline were
seen in plasma renin activity on Day 6 in either group (Figure
S1G). Urine osmolality decreased from baseline throughout
the treatment period for both groups; the degree of change
was similar (Table S3). Levels of daily sodium excretion (urine)
demonstrated minimal change throughout the treatment pe-
riod, with a slight increase from Day 2 through Day 4 and a
slight decrease on Day 6 in both groups (Table S3).

Safety

Safety data are shown in Table 2. The overall incidences of
AEs (OPC-61815 vs. tolvaptan: 63.1\% vs. 66.9\%),
treatment-emergent AEs (TEAEs; 55.7\% vs. 58.6\%), and
treatment-related TEAEs (30.2\% vs. 30.3\%) were similar be-
tween the two treatment groups. Constipation, thirst, dry
mouth, dehydration, and hyperkalaemia were reported as

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**Figure 2** Change in body weight as (A) LS mean (95% CI) change from baseline to the time of final study drug administration and (B) mean (standard deviation) change from baseline over time. CI, confidence interval; LS, least squares. The non-inferiority of OPC-61815 16-mg injection to tolvaptan 15-mg oral tablet was confirmed, as the upper limit of the CI did not exceed the pre-set non-inferiority margin of 0.48.
TEAEs in ≥5% of patients in either treatment group. The incidence of dehydration and hyperkalaemia was higher in the OPC-61815 group (vs. tolvaptan), and the incidence of thirst and dry mouth was higher in the tolvaptan group (vs. OPC-61815). Most TEAEs were mild to moderate in severity. The incidence of serious TEAEs was similar in both groups [OPC-61815, 6/149 (4.0%); tolvaptan, 5/145 (3.4%)]; only one serious TEAE (hyperkalaemia, OPC-61815 group) was considered related to the study treatment. Sodium-related AEs included blood sodium increased in 2/149 patients (1.3%) in the OPC-61815 group, hypernatraemia in 4/149 patients (2.7%) in the OPC-61815 group, and 3/145 patients (2.1%) in the tolvaptan group.
group and rapid correction of hyponatraemia in 1/149 patients (0.7%) in the OPC-61815 group. The incidence of TEAEs leading to treatment discontinuation was higher in the OPC-61815 vs. tolvaptan group [8/149 (5.4%) vs. 3/145 (2.1%), respectively] (Table S4). There were no deaths reported during the trial.

Discussion

This study demonstrated that when using body weight change over 5 days as a primary outcome measure, daily treatment with OPC-61815 16-mg injection was non-inferior to tolvaptan 15-mg oral tablet in patients with congestive HF and an inadequate response to diuretics other than vaso-pressin antagonists. The mean change (SD) in body weight from baseline to the time of final tolvaptan administration (5 days) was $-1.32 (1.36) \text{ kg}$, which is comparable with that reported in the Phase III QUEST trial of tolvaptan that confirmed its superiority over placebo [15-mg tablet, 7 days, $-1.54 (1.61) \text{ kg}$]. The QUEST trial is the only study that has verified diuretic superiority over placebo in a randomized controlled trial, which suggests that 15-mg tolvaptan is an appropriate active control for OPC-61815. Notably, patients in the present study had no restrictions regarding drinking; therefore, the effect of weight loss was confirmed in patients who were drinking normally.

In this study, a maximum increase in urine output was observed on Day 2 (first day after study drug administration was initiated), and urine output was increased throughout the treatment period for both study drugs. Fluid balance was negative throughout the treatment period although water intake increased; similar results were obtained regardless of treatment. Urine sodium concentration did not change in any meaningful way. Urine osmolality was reduced from baseline throughout the study for both treatment groups, thus confirming the aquaretic effect of both OPC-61815 and tolvaptan. The incidence of AEs and TEAEs was similar between the groups, and most TEAEs were mild or moderate; no safety concerns were observed.

Figure 4 Serum electrolyte changes over time for (A) sodium (B) potassium.
In general, decreased renal function and hypoalbuminaemia can affect a patient’s response to diuretics. In this study, sub-group analysis found that weight loss was not affected by creatinine levels in patients treated with OPC-61815, with similar outcomes between patients with <2 and ≥2 mg/mL creatinine. This was in line with the trend reported in the phase III QUEST study of tolvaptan vs. placebo in HF patients with volume overload despite treatment with diuretics. However, both studies are somewhat in contrast to a study by Kida et al., which reported a trend towards greater urine output and weight loss in HF patients with Stage 3b chronic kidney disease compared with Stage 4 or 5 chronic kidney disease. This discrepancy is expected to be resolved following the collection of real-world data in future analyses.

Although more pronounced in the OPC-61815 group, patients in both treatment groups with an albumin value of <3 g/dL tended to have greater weight loss. This outcome is consistent with that reported in two small studies of tolvaptan in patients with congestive HF with and without hypoalbuminaemia. The incidence of serious TEAEs was similar in both groups (OPC-61815, 4.0%; tolvaptan, 3.4%). Only one serious TEAE (hyperkalaemia; OPC-61815 group) was considered treatment related by study investigators. Of note, TEAEs with higher incidences in the OPC-61815 treatment group (vs. tolvaptan) included dehydration, sodium-related TEAEs (hypernatraemia and rapid correction of hyponatraemia), and hyperkalaemia. The higher incidence of sodium-related TEAEs, dehydration, and hyperkalaemia may be attributed to the direct injection of OPC-61815 into the bloodstream, which results in a shorter time to onset of effect. In addition, 4/9 patients with hyperkalaemia also had concomitant renal dysfunction. Notably, thirst (8.4%) and hypernatraemia (4.4%) were the most commonly reported adverse drug reactions in the real-world SMILE study. The present study reported comparable incidences, with 8.7% and 11.0% of patients who received OPC-61815 and tolvaptan, respectively, reporting thirst and a respective 2.7% and 2.1% experiencing hypernatraemia.

The results from a combined analysis of data from the double-blind Phase II comparative study of OPC-61815

| Table 2 Adverse events (safety analysis set) | OPC-61815 n = 149 | Tolvaptan n = 145 |
|----------------------------------------------|-------------------|------------------|
| Patients with AEs                            | 94 (63.1)         | 97 (66.9)        |
| AEs, number of events                        | 201               | 177              |
| Patients with TEAEs                          | 83 (55.7)         | 85 (58.6)        |
| TEAEs, number of events                      | 163               | 139              |
| Patients with treatment-related TEAEs        | 45 (30.2)         | 44 (30.3)        |
| Serious TEAEs                                | 6 (4.0)           | 5 (3.4)          |
| Patients with treatment-related serious TEAEs| 1 (0.7)           | 0 (0.0)          |
| Deaths                                       | 0 (0.0)           | 0 (0.0)          |
| Discontinuations due to an AE                | 8 (5.4)           | 3 (2.1)          |
| Discontinuations due to a treatment-related AE| 5 (3.4)           | 3 (2.1)          |
| TEAEs occurring in ≥5% of patients           |                   |                  |
| Constipation                                 | 9 (6.0)           | 9 (6.2)          |
| Dehydration                                  | 15 (10.1)         | 6 (4.1)          |
| Dry mouth                                    | 4 (2.7)           | 8 (5.5)          |
| Hyperkalaemia                                | 9 (6.0)           | 3 (2.1)          |
| Thirst                                       | 13 (8.7)          | 16 (11.0)        |
| Serious TEAEs                                |                   |                  |
| Atrial fibrillation                          | 1 (0.7)           | 0 (0.0)          |
| Cardiac failure                              | 1 (0.7)           | 0 (0.0)          |
| Cardiac failure acute                        | 1 (0.7)           | 0 (0.0)          |
| Coronary artery stenosis                     | 0 (0.0)           | 1 (0.7)          |
| Gastric antral vascular ectasia              | 1 (0.7)           | 0 (0.0)          |
| General infarction                           | 0 (0.0)           | 1 (0.7)          |
| Hyperkalaemia                                | 1 (0.7)           | 0 (0.0)          |
| Sepsis                                       | 1 (0.7)           | 0 (0.0)          |
| Sinus node dysfunction                       | 0 (0.0)           | 1 (0.7)          |
| Urinary tract infection                      | 0 (0.0)           | 1 (0.7)          |
| Ventricular tachycardia                      | 0 (0.0)           | 1 (0.7)          |
| Na-related adverse events                    |                   |                  |
| Blood sodium increase                        | 2 (1.3)           | 0 (0.0)          |
| Hyponatraemia                                | 4 (2.7)           | 3 (2.1)          |
| Rapid correction of hyponatraemia            | 1 (0.7)           | 0 (0.0)          |

AE, adverse event; TEAE, treatment-emergent adverse event. Data are n (%) unless stated otherwise. Serious hyperkalaemia was judged by an investigator and solely based on serum potassium levels.
and the current Phase III non-inferiority confirmatory trial, both of which used tolvaptan as a control, showed no significant difference in the incidence of hypernatremia-related AEs between the treatment groups (OPC-61815 16 mg vs. tolvaptan 15 mg). Given that OPC-61815 is a new i.v. diuretic and is not exactly the same as oral tolvaptan, it is necessary to adequately monitor serum electrolytes as well as monitor for the common side effect of dry mouth.

As OPC-61815 is being developed for the same target indication as tolvaptan, which is to treat ‘fluid retention in heart failure with inadequate response to other diuretics such as loop diuretics’, the inclusion/exclusion criteria, criteria for moving to the treatment period, prohibited concomitant medications, and restriction of medication use for the present study were set to be similar to those used in the pivotal Phase III study of tolvaptan in Japan (HF patients with volume overload despite treatment with diuretics) to ensure a similar background for data analysis. Congestion-related symptoms are often the first presentations of acute cardiac insufficiency, and early improvement in congestion is time sensitive and prognostically important. However, oral medications take longer to take effect relative to i.v. medications owing to the nature of their formulation. Additionally, oral medications can be difficult to administer when patients are under non-invasive positive pressure ventilation to relieve dyspnoea or have a reduced level of consciousness due to impaired oxygenation. As such, there is a clinical need for i.v. drugs to provide immediate decongestion. To further confirm the tolerability of OPC-61815, a separate Phase III trial has been conducted in patients with cardiac oedema (including acute HF) who are currently being administered i.v. diuretics. This study verified the non-inferiority of OPC-61815 to oral tolvaptan. Because oral tolvaptan has been shown to improve congestion in Western studies such as the EVEREST study, the non-inferiority of OPC-61815 indicates that it may be effective not only in Japan but also in the rest of the world. However, we still believe further data is required on i.v. diuretic use in patients with acute heart failure in the future.

Limitations

A key limitation was the lack of a placebo comparator group; however, because tolvaptan is considered the standard of care in this patient population, it was deemed inappropriate to compare OPC-61815 with placebo, and, thus, a non-inferiority trial was conducted. In general practice, OPC-61815 is expected to be used primarily for acute HF requiring i.v. diuretic treatment. However, in our study, patients with acute HF who required emergency treatment were excluded, and concomitant use of i.v. diuretics was prohibited. Therefore, the current results cannot be extrapolated to the use of OPC-61815 in patients with acute HF. Furthermore, patients with low serum sodium levels (<125 mEq/L) were excluded, which limits the generalizability of these results to real-world settings where HF patients are often complicated by hyponatraemia. In addition, a detailed (hourly) timing of urine volume increase was not conducted in this study, and this information remains to be clarified. Finally, this was a non-inferiority study and was designed with the primary endpoint of weight change after treatment with i.v. OPC-61815 or oral tolvaptan; it was not designed to detect significant differences in the occurrence of AEs between the two drugs. As such, careful monitoring during use in clinical practice is recommended.

Conclusions

The non-inferiority of OPC-61815 16-mg injection to tolvaptan 15-mg oral tablet was confirmed using change in body weight as the primary outcome measure, and no new safety concerns were observed. The i.v. route of administration of OPC-61815 makes this a viable alternative for decompensated HF patients with overload despite receiving diuretics. Overall, better strategies to improve congestion are required, and we believe that the novel diuretic OPC-61815 is a clinically meaningful addition to the treatment options available for symptoms of congestion.

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Conflict of interest

N.S. reports consultation fees from Otsuka Pharmaceutical Co., Ltd., Terumo Corporation, Novartis, Bristol Myers Squibb, and Bayer and lecture fees from Otsuka Pharmaceutical Co., Ltd., Ono Pharmaceutical, Terumo Corporation, Novartis, Bristol Myers Squibb, and Bayer. S.U., Y.K., and S.K. are employed by Otsuka Pharmaceutical Co., Ltd.
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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Improvements in congestive findings.
Table S2. Subgroup analysis for change from baseline in body weight at the time of final study drug administration.

Table S3. Urine osmolality and urinary sodium excretion.
Table S4. Adverse events leading to withdrawal.
Table S5. Participating sites and investigators.

Figure S1. Change in (A) blood pressure, (B) pulse rate, (C) creatinine, (D) blood urea nitrogen, (E) plasma AVP, (F) plasma BNP, (G) plasma renin activity. For panel A, filled symbols indicate systolic blood pressure and open symbols indicate diastolic blood pressure. AVP, arginine vasopressin; BNP, brain natriuretic peptide.

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