Synopsis

Clinical Report Synopsis for Protocol 263-102-00001

Name of Sponsor: Otsuka Pharmaceutical Co., Ltd

Name of Investigational Medicinal Product: OPC-61815

Protocol Title: A Multicenter, Double-blind, Randomized, Active-controlled, Parallel-group Comparison Clinical Pharmacology Trial to Investigate the Dose of OPC-61815 Injection Equivalent to Tolvaptan 15-mg Tablet in Patients With Congestive Heart Failure

Trial Centers: Multicenter (41 sites received investigational medicinal product, 35 sites screened subjects, 32 sites randomized subjects), Japan

Publications: None to date

Trial Period:

Date of first signed informed consent: 06 Nov 2017
Date of last trial observation: 24 Apr 2018

Clinical Development Phase: 2/Clinical pharmacology

Trial Interruption: There was no unplanned trial interruption.

Scientific Background and Explanation of Rationale: OPC-61815 provides an aquaretic intravenous treatment option for "congestive heart failure patients with excessive fluid retention despite treatment with other diuretics" and should prove useful. We started clinical development of OPC-61815 in heart failure patients with persistent fluid retention despite treatment with conventional diuretics for the intended indication of "volume overload in heart failure when adequate response is not obtained with other diuretics (eg, loop diuretics)." The aquaretic effect of OPC-61815 was thought to be produced by the active metabolite tolvaptan. Because tolvaptan is widely used in heart failure patients who have fluid retention despite treatment with conventional diuretics, treating patients with placebo in a clinical trial of OPC-61815 was considered unethical. A phase 3 trial of OPC-61815 therefore is planned to investigate the noninferiority of OPC-61815 to tolvaptan 15-mg tablet instead of using placebo as control.
OPC-61815 has not previously been administered to heart failure patients, the dose-exposure relationships of intravenous administration of OPC-61815 and oral administration of tolvaptan in heart failure patients were not yet clear. This phase 2 clinical pharmacology trial was planned to determine the dose of OPC-61815 injection equivalent to tolvaptan 15-mg tablet, which is used in clinical setting in heart failure patients with fluid retention despite treatment with conventional diuretics.

Objectives:
Primary: To investigate the dose of OPC-61815 injection formulation achieving exposure equivalent to that for tolvaptan 15-mg tablet by 1-hour intravenous administration of OPC-61815 at 2, 4, 8, or 16 mg once daily or oral administration of tolvaptan tablet at 15 mg once daily for 5 days in congestive heart failure (CHF) patients with volume overload despite having received diuretics other than vasopressin antagonists.

Secondary: To investigate the efficacy, pharmacokinetics, pharmacodynamics, and safety of OPC-61815 in comparison with tolvaptan tablet by 1-hour intravenous administration of OPC-61815 at 2, 4, 8, or 16 mg once daily or oral administration of tolvaptan tablet at 15 mg once daily for 5 days in CHF patients with volume overload despite having received diuretics other than vasopressin antagonists.

Methodology: This was a multicenter, randomized, double-blind, active-controlled (with tolvaptan tablet), double-dummy, parallel-group comparison trial. Fifty CHF patients with volume overload despite having received diuretics other than vasopressin antagonists were randomly assigned to OPC-61815 injection 2 mg, 4 mg, 8 mg, or 16 mg or tolvaptan 15 mg tablet group (10 per group) to investigate the dose of OPC-61815 injection required to achieve exposure equivalent to tolvaptan 15-mg tablet. To account for withdrawals, 11 subjects per group (total 55 patients) were required to start investigational medicinal product (IMP) administration.

Number of Subjects: A total of 50 subjects comprising 10 subjects in each group were planned for enrollment into the trial. A total of 74 subjects were screened for the trial and 61 subjects were randomized.

Diagnosis and Main Criteria for Inclusion: The trial population included consenting Japanese male or female CHF patients with volume overload despite having received diuretics other than vasopressin antagonists, age 20 to 85 years, inclusive.

- Subjects who are currently on treatment with any of the following diuretics
  - Loop diuretics equivalent to furosemide tablet or fine granules at a dose of 40 mg/day or higher
  - Concomitant use of a loop diuretic and a thiazide diuretic (including thiazide analogs) at any dose
  - Concomitant use of a loop diuretic and an aldosterone antagonist or potassium-sparing diuretic agent at any dose
- Subjects with CHF in whom lower limb edema, pulmonary congestion, or jugular venous distension due to volume overload is present
- Male or female subjects aged 20 to 85 years, inclusive, at time of informed consent
- Subjects who are currently hospitalized or who are able to be hospitalized from day before the run-in period (Day −4) to the end of the treatment period.
- Subjects who are capable of taking oral tablets

- Subjects who are given diuretic agents with no changes in dose and regimen during the run-in period
- Subjects with no more than 1.0 kg changes in body weight over the 2 days (Day −2 to Day −1 of the run-in period) prior to IMP administration

Investigational Medicinal Product, Dose, Dosage Regimen, Formulation, Mode of Administration, and Lot No(s):

- OPC-61815 Lyophilized Vials for Injectable Solution

Dosage	2 mg/vial	4 mg/vial	8 mg/vial	16 mg/vial	0 mg/vial
Lot No. (Product)	17C97A002	17D72A004	17D73A008	17D79A016	17C96P000
Lot No. (Kit)	KN263102A-01				

Reference Product, Dose, Dosage Regimen, Formulation, Mode of Administration, and Lot No(s):

- OPC-41061 Tablets

Dosage	15 mg	0 mg
Lot No. (Product)	15L77A015A	15K99P000A
Lot No. (Kit)	KN263102B-01	

Manufacturer: Otsuka Pharmaceutical Co., Ltd. (Japan)

Duration of Treatment: The total duration of treatment was 5 days.

Trial Assessments:

Pharmacokinetics: Blood sampling for measurement of plasma concentrations of a parent drug and metabolites

Pharmacodynamics: Blood sampling for serum concentrations of sodium and potassium, serum osmolality, and biomarker measurements; and urine sampling or cumulative urine volume collection for daily urine volume, daily fluid balance, daily urine sodium excretion, daily urine potassium excretion, urine osmolality, and daily fluid intake

Efficacy: Body weight, congestive symptoms (lower limb edema, other edema, jugular venous distension, pulmonary congestion confirmed by chest X-ray, pulmonary rales, third cardiac sound, and hepatomegaly), cardiothoracic ratio, and New York Heart Association (NYHA) classification

Safety: Adverse event (AE) reporting, clinical laboratory tests, physical examination, vital signs (blood pressure, pulse rate, and body temperature), and 12-lead electrocardiogram (ECG)

Criteria for Evaluation:

Primary Endpoint: Tolvaptan exposure (maximum [peak] plasma drug concentration [C_{max}] and area under the concentration-time curve from time zero to 24 hours [AUC_{24h}] on Day 1 of the treatment period)

Secondary Endpoint:
Pharmacokinetics: Plasma concentrations and pharmacokinetic (PK) parameters of OPC-61815, tolvaptan, DM-4103, and DM-4107

Pharmacodynamics: Serum concentrations of sodium and potassium, serum osmolality, biomarkers (plasma concentrations of arginine vasopressin and brain natriuretic peptide [BNP], plasma renin activity, and serum concentrations of NT-pro BNP and troponin), daily urine volume, daily fluid intake, daily fluid balance, daily urine sodium excretion, daily urine potassium excretion, and urine osmolality

Efficacy: Body weight, congestive symptoms (lower limb edema, other edema, jugular venous distension, pulmonary congestion confirmed by chest X-ray, pulmonary rales, third cardiac sound, and hepatomegaly), cardiothoracic ratio, and NYHA classification

Safety: AE reporting, clinical laboratory tests (including pregnancy test), physical examination, vital signs (blood pressure, pulse rate, and body temperature), and 12-lead ECG

Pharmacokinetic/Pharmacodynamic Methods:
Bioanalytical: Plasma concentrations of OPC-61815 free form, tolvaptan, DM-4103, and DM-4107 were analyzed using a validated HPLC-MS/MS method by Toray Research Center.
Pharmacokinetics: PK parameters of OPC-61815 free form, tolvaptan, DM-4103, and DM-4107 were calculated by noncompartmental methods.

Statistical Methods:
Determination of Sample Size: The primary objective of this clinical trial was to compare tolvaptan exposure in order to investigate the dose of OPC-61815 injection required to achieve exposure equivalent to tolvaptan 15-mg tablet for use in conducting phase 3 confirmatory clinical trials of OPC-61815. The number of subjects required for this purpose was determined to be at least 10 subjects per group (50 subjects in total) who completed blood sampling for measurement of plasma drug concentrations up until 24 hours postdose on Day 1. In consideration of the possibility of some subjects withdrawing from the trial prior to 24 hours postdose on Day 1, the approximate target number of subjects for the start of IMP administration was set at 11 subjects per group (55 subjects in total).

Subject Samples: Subject samples identified for this trial included the pharmacokinetic analysis set (ie, all subjects treated with the IMP at least once and had at least 1 evaluable plasma drug concentration measurement after IMP administration), the safety analysis set (ie, all subjects treated with the IMP at least once), the efficacy analysis set (ie, all subjects treated with the IMP at least once and had body weight data after IMP administration), and the pharmacodynamics analysis set (ie, all subjects treated with the IMP at least once and had pharmacodynamic data after IMP administration).

Efficacy: Analysis of covariance using baseline weight (before IMP administration on Day 1) as covariate were performed on the change from baseline in body weight after final administration (the day after final IMP administration) to calculate the least-square mean of the difference between each OPC-61815 injection group and tolvaptan 15-mg tablet group and its 95% confidence interval.

The proportion of responders (subjects with a "markedly improved" or "improved" response) and the proportion of subjects who achieved resolution of lower limb edema and pulmonary congestion after final administration were calculated for each OPC-61815 injection group, together with the difference in the proportions between each OPC-61815 injection group and tolvaptan 15-mg tablet group with the 95% confidence interval of each difference.

Descriptive statistics were used to summarize baseline values, change from baseline at each time point, and change from baseline to the last visit for body weight, jugular venous distension, hepatomegaly, cardiothoracic ratio, pulmonary rales, and third cardiac sound. Changes in NYHA classification at each time point were summarized for each treatment group in a shift table.

Pharmacokinetics/pharmacodynamics: The PK data were summarized by descriptive statistics, respectively. For tolvaptan exposure, the difference (each OPC-61815 injection group − tolvaptan 15-mg tablet group) in mean value and its 95% confidence interval were calculated using logarithm converted value (natural logarith).
Daily urine volume, daily fluid intake, and daily fluid balance after IMP administration on Days 1 and 5, the difference (each OPC-61815 injection group − tolvaptan 15-mg tablet group) in mean change from baseline and its 95% confidence interval were calculated.

Safety: The AE data were summarized by safety analysis set. A treatment-emergent adverse event (TEAE) was defined as any AE with an onset date on or after the start of double-blind IMP, or if the event was continuous from baseline and worsened, became serious, trial-IMP related, or resulted in death, discontinuation, interruption, or reduction of trial therapy. The incidences of TEAEs were summarized for all TEAEs, TEAEs by severity, IMP-related TEAEs, serious TEAEs, and discontinuations of the IMP due to TEAEs.

Descriptive statistics were used to summarize baseline values, change from baseline at each time point, and change from baseline to the last visit for clinical laboratory tests, vital signs, and ECGs.

Summary of Results:
Disposition, Demographics, and Baseline Characteristics: A total of 74 subjects were screened for this trial, and 61 were randomized to double-blind treatment. One of the randomized subjects was withdrawn due to dehydration before initiation of the trial drug administration; therefore, 60 subjects received IMP and thus were included in the efficacy analysis set and safety analysis set: 13 subjects who received OPC-61815

2 mg/day, 12 subjects who received OPC-61815 4 mg/day, 12 subjects who received OPC-61815 8 mg/day, 11 subjects who received OPC-61815 16 mg/day, and 12 subjects who received tolvaptan 15 mg/day.

Demographic and other baseline characteristics were generally similar between the 5 treatment groups. Most subjects were males (68.3%) and aged ≥ 65 years (88.3%). The mean age of subjects was 74.6 years (range 44 to 85 years), and mean body mass index (BMI) was 23.6 kg/m^2 (13.9 to 32.7 kg/m^2).

Efficacy Results:

- The changes in body weight at the final IMP administration from baseline were −0.6 ± 0.6 kg (mean ± SD) in the OPC-61815 2-mg, −1.1 ± 0.8 kg in the OPC-61815 4-mg, −1.5 ± 1.1 kg in the OPC-61815 8-mg, −2.1 ± 1.8 kg in the OPC-61815 16-mg, and −1.7 ± 1.2 kg in the tolvaptan 15-mg groups, and body weight decreased in all treatment groups after completion of trial treatment. The decrease at Day 2 (the day after first IMP administration) was −1.0 kg in the OPC-61815 16-mg and −0.7 kg in the tolvaptan 15-mg groups.
- The improvement rate for lower limb edema in subjects who had lower limb edema at baseline at the final IMP administration was 80.0% in the OPC-61815 2-mg, 62.5% in the OPC-61815 4-mg, 83.3% in the OPC-61815 8-mg, 88.9% in the OPC-61815 16-mg groups, which were higher than that in the tolvaptan 15-mg group (44.4%). The changes in jugular venous distension at the final IMP administration from baseline in subjects who had jugular venous distension at baseline were −0.80 ± 1.15 cm (mean ± SD) in the OPC-61815 2-mg, −1.66 ± 3.05 cm in the OPC-61815 4-mg, −2.10 ± 3.05 cm in the OPC-61815 8-mg, −1.10 ± 1.19 cm in the OPC-61815 16-mg, and −2.50 ± 2.24 cm in the tolvaptan 15-mg groups.
- The NYHA classification was improved in 4 of 13 subjects in the OPC-61815 2-mg, 2 of 12 subjects in the OPC-61815 4-mg, 4 of 12 subjects in the OPC-61815 8-mg, 7 of 11 subjects in the OPC-61815 16-mg, and 5 of 12 subjects in the tolvaptan 15-mg groups. No subjects experienced worsening NYHA classification in any treatment groups.

Pharmacokinetic Results:

- The mean C_{max} and AUC of OPC-61815 free form and its metabolites OPC-41061 increased dose-dependently following single intravenous administration of OPC-61815 at 2, 4, 8, and 16 mg.
- The median t_{max} of OPC-61815 free form and OPC-41061 respectively ranged from 1.03 to 1.04 hours and from 1.48 to 1.76 hours following single intravenous administration of OPC-61815 at 2, 4, 8, and 16 mg.
- The mean $t_{1/2,z}$ of OPC-61815 free form and OPC-41061 respectively ranged from 1.8 to 3.8 hours and from 7.4 to 8.6 hours following single intravenous administration of OPC-61815 at 2, 4, 8, and 16 mg.

- The mean CL and V_z of OPC-61815 free form respectively ranged from 4.29 to 5.50 L/h and from 10.5 to 24.7 L following single intravenous administration of OPC-61815 at 2, 4, 8, and 16 mg.
- The mean AUC_{24h} ratio, AUC_t ratio, and AUC_∞ ratios of OPC-41061 to OPC-61815 respectively ranged from 0.846 to 1.42, from 0.847 to 1.45, and from 0.989 to 1.77 following single intravenous administration of OPC-61815 at 2, 4, 8, and 16 mg.
- OPC-61815 free form did not accumulate and OPC-41061 accumulated approximately 1.2- to 1.4-fold by repeated intravenous administration of OPC-61815 at 2, 4, 8, and 16 mg once daily for 5 consecutive days.
- OPC-41061 exposure (C_{max} and AUC_{24h}) on Day 1, which was the primary variable, following single intravenous administration of OPC-61815 at 16 mg was the closest, and similar, to that following single administration of tolvaptan 15-mg tablet.
- OPC-41061 accumulated approximately 1.3-fold by repeated administration of tolvaptan 15-mg tablet once daily for 5 consecutive days, which was similar to the accumulation following repeated intravenous administration of OPC-61815 at 16 mg once daily for 5 consecutive days.
- PK parameters of DM-4103 and DM-4107 following single and repeated intravenous administration of OPC-61815 at 16 mg were similar to those following single and repeated administration of tolvaptan 15-mg tablet.

Pharmacodynamic Results:

- Both daily urine volumes increased from baseline in the both OPC-61815 and tolvaptan groups throughout the treatment period. The mean increases in daily urine volumes were larger than those in fluid intakes, and the fluid balances (difference between fluid intake and urine volume) showed mostly negative values in all treatment groups thought the treatment period.
- The mean increases from baseline in serum osmolality, plasma AVP concentrations, and plasma renin activity were seen in all treatment groups throughout the treatment period. Small mean increases in serum sodium concentration were seen in the OPC-61815 8-mg, 16-mg, and tolvaptan 15-mg groups throughout the treatment period.
- The mean decreases from baseline in urine osmolality were seen in the both OPC-61815 and tolvaptan groups throughout the treatment period.
- No notable changes were seen in serum potassium concentrations, plasma BNP and serum pro BNP concentrations, serum troponin concentrations, and daily urine sodium and potassium excretions in both OPC-61815 and tolvaptan groups during the treatment period.

Safety Results:

- The incidence of TEAEs was 53.8% (7/13 subjects) in the OPC-61815 2-mg, 58.3% (7/12 subjects) in the OPC-61815 4-mg, 33.3% (4/12 subjects) in the OPC-61815 8-mg, 72.7% (8/11 subjects) in the OPC-61815 16-mg, and 83.3% (10/12 subjects) in the tolvaptan 15-mg groups. All TEAEs were mild to moderate in severity.

- The TEAEs occurred in 2 or more subjects treated with OPC-61815 at 2 to 16 mg were pyrexia, thirst, vessel puncture site reaction, blood creatinine increased, blood urea increased, and headache in 2 subjects each.
- The incidence of IMP-related TEAEs was 12.5% (6/48 subjects) in the subjects treated with OPC-61815 at 2 to 16 mg, which were lower than that in the subjects treated with tolvaptan at 15 mg (41.7% [5/12 subjects]).
- No deaths occurred during the trial. One subject had 2 serious TEAEs, of those serious TEAEs atrial fibrillation was considered potentially related to the IMP.
- The TEAEs leading to discontinuation of IMP were atrial fibrillation and renal impairment (1 subject each in OPC-61815 4-mg) and hepatic congestion, liver disorder, and renal impairment (1 subject each in tolvaptan 15-mg).
- No notable TEAEs that were frequently reported in the repeated intravenous dose trial (263-09-001) were reported during this trial.
- No clinically relevant changes from baseline were found in laboratory parameters, vital signs, or ECG findings.

Conclusions:

OPC-41061 exposure (C_{max} and AUC_{24h}) on Day 1 following single intravenous administration of OPC-61815 at 16 mg was the most similar to that following single administration of tolvaptan 15-mg tablet. There was no marked difference in tolerability between OPC-61815 at 16 mg and tolvaptan 15-mg tablet, and no clinically significant problems were observed.