Synopsis

Clinical Report Synopsis for Protocol 263-102-00004

Name of Sponsor: Otsuka Pharmaceutical Co., Ltd.

Name of Investigational Medicinal Product: OPC-61815

Protocol Title: A Multicenter, Open-label, Uncontrolled Clinical Trial to Confirm the Tolerability of OPC-61815 in Patients With Congestive Heart Failure Who Have Difficulty With or Are Incapable of Oral Intake

Trial Centers: Multicenter (30 sites received investigational medicinal product, and screened and enrolled subjects), Japan

Publications: None to date

Trial Period:

Date of first signed informed consent: 17 Jun 2019
Date of last trial observation: 30 Jun 2020

Clinical Development Phase: 3

Trial Interruption: There was no unplanned trial interruption.

Scientific Background and Explanation of Rationale: OPC-61815 provides an aquaretic intravenous treatment option for heart failure patients when oral administration is not feasible/desirable, eg, due to impaired consciousness, decreased absorption of oral tablets due to edema of the gastrointestinal tract associated with central venous pressure elevation caused by heart failure (gastrointestinal edema), oxygen therapy, or decreased swallowing function in elderly patients. OPC-61815 is being developed with an expectation to be effective for the treatment of volume overload in heart failure when adequate response is not obtained with other diuretics (eg, loop diuretics).

This phase 3 trial was conducted to confirm the tolerability of intravenous administration of OPC-61815 once daily for a maximum of 5 days to congestive heart failure (CHF) patients who have difficulty with or are incapable of oral intake.

Objectives:
To confirm the tolerability of intravenous administration of OPC-61815 at 8 or 16 mg once daily for a maximum of 5 days to CHF patients with volume overload despite having received diuretics (injection) other than vasopressin antagonists and who have difficulty with or are incapable of oral intake.

This trial had no secondary objectives.

Methodology: This was a multicenter, uncontrolled, open-label trial to confirm the tolerability of intravenous administration of OPC-61815 at 8 or 16 mg once daily for a maximum of 5 days to CHF patients with volume overload despite having received diuretics (injection) other than vasopressin antagonists and who have difficulty with or are incapable of oral intake.

Number of Subjects: A total of 40 subjects were planned for enrollment into the trial. A total of 54 subjects were screened for the trial and 45 subjects received at least one dose of investigational medicinal product (IMP); 38 subjects with dose maintained at 8 mg, and 7 subjects with dose increased to 16 mg.

Diagnosis and Main Criteria for Inclusion: The trial population included consenting Japanese male or female CHF patients with volume overload despite having received diuretics (injection) other than vasopressin antagonists and who have difficulty with or are incapable of oral intake.

- Subjects who were currently receiving loop diuretics injection at a dose equivalent to furosemide 20 mg/day or higher
- Subjects with CHF in whom lower limb edema, pulmonary congestion, or jugular venous distension due to volume overload was present
- Male or female subjects aged 20 to 85 years, inclusive, at time of informed consent
- Subjects who were judged by the investigator or subinvestigator to have difficulty or be incapable of oral intake, including patients who were judged by the investigator or subinvestigator to require nothing by mouth management
- Subjects who were currently hospitalized or who were able to be hospitalized from the time of informed consent until the end of the treatment period

Investigational Medicinal Product, Dose, Dosage Regimen, Formulation, Mode of Administration, and Lot No(s):
The IMPs for each subject were supplied as a kit box composed of 6 vials containing either OPC-61815 16-mg injection (lot number 18H97A016) or OPC-61815 8-mg injection (lot number 18L82A008).

The investigator or subinvestigator administered OPC-61815 once daily as 1-hour infusion (55 to 70 minutes allowable) according to the IMP administration procedures specified separately. OPC-61815 treatment started with 8 mg, and eligibility for dose escalation was assessed on Day 2 of the treatment period (and again on Day 3 of the treatment period, if applicable). If the dose escalation criteria were met, the dose was increased to 16 mg; if the criteria were not met, administration continued at 8 mg.

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

Reference Product, Dose, Dosage Regimen, Formulation, Mode of Administration, and Lot No(s):
The reference product is not applicable for this trial.

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

Trial Assessments:
Pharmacokinetics: No pharmacokinetic (PK) assessments were performed in this trial.

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, jugular venous distension, pulmonary congestion confirmed by cardiothoracic ratio by chest X-ray, pulmonary rales, cardiac third sound, dyspnea [respiratory rate, paroxysmal nocturnal dyspnea, orthopnea, and subject-assessed dyspnea], 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:
Efficacy: Descriptive statistics and two-sided 95% confidence intervals (CIs) were calculated for measured values and changes from baseline at the time of final IMP administration, and descriptive statistics were calculated for the percent changes.

The efficacy endpoints were:
- Body weight
- Congestive symptoms (lower limb edema, jugular venous distension, hepatomegaly, pulmonary rales, cardiac third sound, cardiothoracic ratio, and pulmonary congestion)
- Dyspnea (respiratory rate, paroxysmal nocturnal dyspnea, orthopnea, and subject-assessed dyspnea)
- NYHA classification

Rationale: Body weight was selected as a measure that objectively reflects the general state of volume overload. Congestive symptoms and dyspnea were selected as symptoms or findings that reflect the volume overload state in patients with CHF. The NYHA classification is selected as a measure that assesses subjective physical activity in patients with CHF.

Pharmacodynamics: urine volume, fluid intake, fluid balance, serum sodium concentration, serum potassium concentration, serum osmolality, urine sodium excretion, urine potassium excretion, urine osmolality, and biomarker measurements (plasma concentrations of arginine vasopressin [AVP] and brain natriuretic peptide [BNP],

plasma renin activity, and serum concentrations of N-terminal pro-brain natriuretic peptide [NT-proBNP] and troponin I).

Rationale: Urine volume, urine osmolality, urine sodium excretion, urine potassium excretion, serum osmolality, serum sodium concentration, and serum potassium concentration were selected as endpoints to evaluate the aquaretic effect of OPC-61815. Fluid intake and fluid balance were selected to evaluate the impact of aquaresis by OPC-61815 on fluid balance. Tolvaptan, which is the active ingredient of OPC-61815, is an AVP V_2 antagonist and affects the plasma osmolality; therefore, plasma AVP concentration was selected to evaluate the effect on the release of AVP into the circulation. Plasma renin activity was selected to evaluate the impact of aquaresis by OPC-61815 on the renin-angiotensin system. The plasma concentrations of BNP, serum concentrations of NT-proBNP and troponin I were selected to evaluate the impact of the aquaretic effect of OPC-61815 on cardiac function.

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

Rationale: Adverse events, clinical laboratory tests, physical examination, vital signs (blood pressure, pulse rate, and body temperature), and 12-lead ECG are commonly used as endpoints of general safety.

Pharmacokinetic Methods:
None were employed in this trial.

Statistical Methods:
Determination of Sample Size: The primary objective of this clinical trial was to confirm the tolerability of intravenous administration of OPC-61815 at 8 or 16 mg once daily for a maximum of 5 days to CHF patients with volume overload despite having received diuretics (injection) other than vasopressin antagonists and who have difficulty with or are incapable of oral intake. The number of subjects required for this purpose was determined to be at least 40 subjects (number of subjects started on OPC-61815). For the target sample size of 40 subjects, the probability of AE occurring at an incidence of 5% and 4% is respectively 87% and 80%.

Subject Samples: Subject samples identified for this trial included the safety analysis set (ie, all subjects who received at least one dose of IMP), the efficacy analysis set (ie, all subjects who received at least one dose of IMP and had postdose efficacy data), and the pharmacodynamic (PD) analysis set (ie, all subjects who received at least one dose of IMP and had postdose PD data).

Efficacy: For body weight, some endpoints of the congestive symptoms (ie, jugular venous distention, hepatomegaly cardiothoracic ratio), and respiratory rate, descriptive statistics and two-sided 95% CIs were calculated for measured values and changes from baseline at the time of final IMP administration, and descriptive statistics were calculated for the percent changes. At each time point, descriptive statistics were calculated. The

number and proportion with the two-sided 95% CIs were calculated for the improvement rate and the disappearance rate at the time of final IMP administration for endpoints other than those listed above. For NYHA classification, the proportion with two-sided 95% CIs were calculated for subjects who have improved from baseline by 1 class or more at the time of final IMP administration. A shift table was also prepared at each time point and at the time of final IMP administration.

The same analysis was conducted for subjects categorized by the presence or absence of dose escalation (ie, subjects with dose increased to 16 mg and subjects with dose maintained at 8 mg without dose escalation) based on the dose escalation criteria (excluding analysis regarding the day of IMP dose escalation).

Pharmacokinetics/pharmacodynamics: There were no PK data in this trial. The PD data were summarized by descriptive statistics.

Measured values and changes from baseline were summarized at each time point for the following parameters: urine volume, fluid intake, fluid balance, serum sodium concentration, serum potassium concentration, serum osmolality, biomarkers (plasma AVP concentration, plasma renin activity, plasma BNP concentration, serum NT-proBNP concentration, and serum troponin I concentration), urine sodium excretion, urine potassium excretion, urine osmolality.

Safety: The AE data were summarized by safety analysis set. The incidences of treatment-emergent adverse events (TEAEs) were summarized for all TEAEs, TEAEs by severity, TEAEs with an outcome of death, serious TEAEs, and TEAEs leading to discontinuation of the IMP.

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 54 subjects were screened for this trial, and 45 were administered IMP: 38 subjects with dose maintained at 8 mg, and 7 subjects with dose increased to 16 mg. None of the subjects reduced the dose after the dose was increased to 16 mg. All 45 subjects received at least one dose of IMP and thus were included in the safety analysis set. They also had at least one postdose data point to qualify for the efficacy analysis set and PD analysis set. Overall, 41 subjects completed the trial (34 of those subjects completed the trial early), and 4 subjects were discontinued from the trial. Of the 34 subjects who completed the trial early 30 (88.2%) became capable of fluid management by oral intake alone, and 4 (11.8%) had all congestive findings resolve, requiring no further improvement of volume overload. The total mean duration for all subjects in the safety analysis set was 2.4 days (median: 2.0 days).

Just over half the subjects were male (51.1%) aged ≥ 65 years (86.7%). The mean age of subjects was 73.7 years (range 39 – 85 years) and a mean body weight of 64.5 kg (range 28.0 – 124.5 kg).

Efficacy Results:
The change in body weight decreased at the time of final IMP administration compared with baseline for all subjects treated with OPC-61815 by 3.01 kg (−3.79, −2.23 [mean (95% CI)]), by 3.14 kg (−4.03, −2.24 [mean (95% CI)]) in subjects with dose maintained at 8 mg, and by 2.20 kg (−3.12, −1.28 [mean (95% CI)]) in subjects with dose increased to 16 mg.

Results of all congestive and dyspnea symptoms considered in the trial for all subjects administered OPC-61815 follow.

- Lower limb edema was present in 38 subjects at baseline. The lower limb edema improvement rate was 73.7% (95% CI: 56.9, 86.6). The lower limb edema disappearance rate was 50.0% (95% CI: 33.4, 66.6).
- Jugular venous distension was present in 19 subjects at baseline. Jugular venous distension was decreased by 4.06 cm (95% CI: −5.20, −2.93) for all subjects who had a baseline value.
- Hepatomegaly was present in 4 subjects, and it decreased by 2.13 cm (95% CI: −4.91, 0.66) for all subjects who had a baseline value.
- Pulmonary congestion was present in 44 subjects at baseline. The pulmonary congestion improvement rate was 81.8% (95% CI: 67.3, 91.8), and the pulmonary congestion disappearance rate was 22.7% (95% CI: 11.5, 37.8).
- Pulmonary rales were present in 36 subjects. The pulmonary rales disappearance rate was 72.2% (95% CI: 54.8, 85.8).
- Cardiac third sound was present in 18 subjects at baseline. The cardiac third sound disappearance rate was 72.2% (95% CI: 46.5, 90.3).
- Cardiothoracic ratio was measured in 45 subjects at baseline. The cardiothoracic ratio decreased by 2.29% (95% CI: −3.55, −1.02).
- Respiratory rate was measured in 45 subjects at baseline. The respiratory rate decreased by 3.24 breaths/minute (95% CI: −4.72, −1.77).
- Paroxysmal nocturnal dyspnea was present in 29 subjects at baseline. The paroxysmal nocturnal dyspnea disappearance rate was 93.1% (95% CI: 77.2, 99.2).
- Orthopnea was present in 33 subjects at baseline. The orthopnea disappearance rate was 84.8% (95% CI: 68.1, 94.9).
- Subject-assessed dyspnea was evaluated as present in 36 subjects at baseline. The subject-assessed dyspnea improvement rate was 97.2% (95% CI: 85.5, 99.9).

The percentage of subjects in NYHA classification who improved by 1 or more grades at the time of final IMP administration compared with the baseline was 70.7% (95% CI: 54.5, 83.9) for all subjects treated with OPC-61815. Of the 29 subjects who showed improvement at the time of final IMP administration from baseline,

1 subject improved by 3 grades, 12 subjects improved by 2 grades, and 16 subjects improved by 1 grade. The results in subjects with dose maintained at 8 mg and subjects with dose increased to 16 mg for all congestive, dyspnea symptoms and NYHA were similar.

Pharmacodynamic Results:

- Mean changes from baseline of daily urine volume was increased on Day 1 and Day 2 for overall subjects treated with OPC-61815.
- The mean change from baseline of daily fluid balance showed negative values on Day 1 for overall subjects treated with OPC-61815.
- Mean changes from baseline of serum sodium concentration increased overall in subjects treated with OPC-61815 at 4 hours after Day 1 administration and continued to increase through Day 5 predose.
- The mean change from baseline of plasma AVP concentration slightly increased, and the mean change from baseline of plasma BNP concentration, serum NT-proBNP concentration, and serum troponin concentration decreased at the time of final IMP administration for overall subjects treated with OPC-61815.

Safety Results:

- The incidence of TEAEs was 77.8% (35/45 subjects). Severe AEs occurred in 3 subjects (6.7%) overall. Ventricular tachycardia and pleural effusion (1 subject each 2.2%) were reported for a total of 1 subject each (2.6%) who maintained a dose of 8 mg and decreased hemoglobin reported for 1 subject (14.3%) who increased dose to 16 mg. All the other AEs were mild or moderate in severity.
- The most frequently reported TEAE among all subjects in the safety analysis set was constipation by 12 subjects (26.7%). The most frequently reported TEAE in subjects who maintained a dose of 8 mg was constipation (11 subjects [28.9%]) and in subjects who increased to a dose of 16 mg was hypokalaemia (2 subjects [28.6%]).
- The most frequently reported IMP-related TEAE among all subjects in the safety analysis set was dry mouth (2 subjects [4.4%]), who were also subjects who maintained a dose of 8 mg (2 subjects [5.3%]).
- There were no deaths. Serious TEAEs were reported overall in 2 subjects (4.4%), and these 2 subjects (5.3%) were subjects who maintained a dose of 8 mg. The SAEs were ventricular tachycardia and pleural effusion in 1 subject each. Ventricular tachycardia was an AE leading to treatment discontinuation and was considered to be related to the IMP. Pleural effusion was concluded to be unrelated to the IMP. Both serious TEAEs resolved.
- Hypernatremia was an AE of interest and occurred in 1 subject overall (2.2%), and this 1 subject (2.6%) maintained a dose of 8 mg. The severity was mild. A relationship to the IMP could not be ruled out.
- No clinically relevant changes from baseline were found in laboratory parameters, ECG parameters, or vital signs.

Conclusions:

The efficacy and safety of OPC-61815 administered intravenously to subjects where oral administration was judged to be difficult or impossible were confirmed by the decreases in body weight, increased daily urine volume, disappearance or improvement rates of congestive symptoms and dyspnea, and improvements in NYHA classifications compared to the baseline. There was no unacceptable safety issues at the starting dose of 8 mg nor were there any marked differences in tolerability between subjects who maintained the dose at 8 mg or who increased dose to 16 mg. No clinically significant problems were observed.