Synopsis

Clinical Report Synopsis for Protocol 263-102-00003

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, Non-inferiority Trial to Evaluate the Efficacy and Safety of OPC-61815 Injection Compared With Tolvaptan 15-mg Tablet in Patients With Congestive Heart Failure

Principal or Coordinating Investigator and Trial Centers: Multicenter (72 trial sites received investigational medicinal product [IMP], and screened and enrolled subjects; Japan)

Publications: None to date

Trial Period:

Date of first signed informed consent: 16 Jan 2019

Date of last trial observation: 29 Jul 2020

Clinical Development Phase: 3

Trial Interruption: There was no unplanned trial interruption.

Scientific Background and Explanation of Rationale: 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 noninferiority of the OPC-61815 16-mg injection formulation to the tolvaptan 15-mg tablet in subjects with congestive heart failure (CHF).

Objectives:
Primary: To confirm the noninferiority of the OPC-61815 16-mg injection to the tolvaptan 15-mg tablet, with the primary endpoint as the change in body weight following a 5-day intravenous administration of the OPC-61815 16-mg injection or 5-day oral administration of the tolvaptan 15-mg tablet to subjects with CHF and volume overload despite having received diuretics other than vasopressin antagonists.

Secondary: To evaluate other efficacy endpoints and the safety, pharmacodynamics (PD), and pharmacokinetics (PK) of the OPC-61815 16-mg injection in comparison with the tolvaptan 15-mg tablet.

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Methodology: This was an active-controlled, randomized, double-blind, parallel-group, multicenter design trial.

The 3 days before the start of IMP administration comprised the run-in period, during which the use of diuretics, change in body weight, and congestive symptoms were assessed. After the run-in period, only subjects who met the inclusion criteria for the run-in period entered into the treatment period during which the IMP was administered once daily for 5 days. The doses and dosage regimens of diuretics that were used since before the start of the run-in period were maintained until the end of the treatment period. The completion assessment was performed on Day 6, and the follow-up assessment was performed between Day 12 and Day 15.

This trial employed a double-dummy method to maintain blindness. Subjects received either a combination of the OPC-61815 16-mg injection and placebo tablet or a combination of the placebo injection and tolvaptan 15-mg tablet. Subjects were hospitalized from the day before start of the run-in period (Day −4) to the end of the treatment period (Day 6).

Number of Subjects: The number of subjects required for this trial was determined to be 288 subjects (144 subjects per group). A total of 362 subjects were screened for this trial. Of the subjects screened, a total of 294 subjects were randomized to 1 of the 2 treatment groups and received at least one dose of IMP (149 subjects OPC-61815 16 mg and 145 subjects tolvaptan 15 mg).

Diagnosis and Main Criteria for Inclusion: The trial included male and female subjects aged 20 to 85, inclusive, at the time of informed consent with CHF and in whom lower limb edema, pulmonary congestion, or jugular venous distension due to volume overload was present. Subjects were hospitalized during the trial and were taking any of the following oral 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

Investigational Medicinal Product, Dose, Dosage Regimen, Formulation, Mode of Administration, and Lot No.(s.): The IMPs administered to subjects in each treatment group are presented in the table below. The investigator or subinvestigator instructed subjects to ingest one tolvaptan 15-mg tablet or one placebo tablet with water once daily. Immediately after the intake of the tablet, the investigator or subinvestigator administered the OPC-61815 16-mg injection or placebo injection as a 1-hour (55 to 65 minutes was allowed) infusion once daily for 5 days according to the IMP administration procedures specified separately.

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Investigational Medicinal Products Used in Each Treatment Group	
Treatment Group	**IMPs (Per Day)**
OPC-61815 16-mg injection	One vial of OPC-61815 16-mg injection + one placebo tablet
Tolvaptan 15-mg tablet	One vial of placebo injection + one tolvaptan 15-mg tablet

The IMPs were provided to the IMP storage manager by the sponsor or designated agent. The IMPs for each subject were supplied as a packaged set composed of 6 vials containing either OPC-61815 16-mg injection (lot number: 18H97A016) or placebo injection (lot number: 18H91P000), and 1 small box containing 10 tolvaptan 15-mg tablets (lot number: 18B82A015) or 10 placebo tablets (lot number: 18A74P000).

Reference Product, Dose, Dosage Regimen, Formulation, Mode of Administration, and Lot No(s): Please see above for tolvaptan.

Duration of Treatment: The planned duration of trial participation for each subject was a maximum of 22 days (screening [4 to 7 days before start of IMP administration], 3 days for the run-in period, 6 days for the treatment period, and post-treatment follow-up at 7 to 10 days after final IMP administration).

Trial Assessments:
Efficacy: Body weight, congestive symptoms (lower limb edema, pulmonary congestion, jugular venous distension, hepatomegaly, cardiothoracic ratio, pulmonary rales, and cardiac third sound), and New York Heart Association (NYHA) classification.

Pharmacokinetic: Blood sampling for plasma concentrations of OPC-61815 free form and tolvaptan (OPC-41061).

Pharmacodynamics: Daily urine volume, daily fluid intake, serum sodium concentration, serum potassium concentration, serum osmolality, biomarker measurements (plasma concentrations of arginine vasopressin [AVP] and brain natriuretic peptide [BNP], plasma renin activity, and serum concentrations of N-terminal fragment of brain natriuretic peptide precursor [NT-proBNP] and troponin I), and urine osmolality.

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

Screening/Other: Medical and medication history, physical examination, laboratory tests, vital signs, body weight, urine pregnancy test, and deoxyribonucleic acid (DNA) storage.

Criteria for Evaluation:
Efficacy:
Primary: Change in body weight from baseline (before IMP administration on Day 1) at time of final IMP administration (day after final IMP administration).

Secondary: Congestive symptoms (lower limb edema, pulmonary congestion, jugular venous distension, hepatomegaly, cardiothoracic ratio, pulmonary rales, and cardiac third sound) and NYHA classification.

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Pharmacokinetics: Plasma concentrations of OPC-61815 free form and tolvaptan (OPC-41061).

Pharmacodynamics: Daily urine volume, daily fluid intake, daily fluid balance, serum sodium concentration, serum potassium concentration, serum osmolality, biomarker measurements (plasma concentrations of AVP and BNP, plasma renin activity, and serum concentrations of NT-proBNP and troponin I), daily urine sodium excretion, daily urine potassium excretion, and urine osmolality.

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

Pharmacokinetic Methods:
Bioanalytical: OPC-61815 free form and OPC-41061 in plasma were analyzed using a validated high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) method.

Pharmacokinetics: The plasma drug concentration data were summarized using descriptive statistics.

Statistical Methods:
Determination of Sample Size: The number of subjects required to confirm the noninferiority of OPC-61815 16-mg injection to the tolvaptan 15-mg tablet for the primary endpoint of change in body weight from baseline (before IMP administration on Day 1) at the time of final IMP administration was determined. The noninferiority margin for the present trial was set at 0.48. Setting the noninferiority margin at 0.48, the detection power at 90%, and the significance level at 5%, and using the value for up until the morning after Day 5 of treatment in the tolvaptan 15-mg tablet in the tolvaptan phase 3 trial to set the mean ± standard deviation (SD) change in body weight from baseline at time of final administration at −1.30 ± 1.25 for both the tolvaptan 15-mg tablet group and the OPC-61815 16-mg injection group, the number of subjects required for this trial was determined to be 288 (144 subjects per group).

Subject Samples: The full analysis set included all subjects who received at least one dose of IMP and had evaluable post-treatment body weight data.
The safety analysis set included all subjects who received at least one dose of IMP.
The PD analysis set included all subjects who received at least one dose of IMP and had evaluable post-treatment PD data.
Of the subjects in the safety analysis set, those with measured plasma drug concentration data were included in the PK analysis set.

Efficacy: The primary endpoint was the change in body weight from baseline (before IMP administration on Day 1) at the time of final IMP administration (day after final IMP administration), and the noninferiority of the OPC-61815 16-mg injection to the tolvaptan 15-mg tablet in the change from baseline in body weight was to be confirmed with a noninferiority margin of 0.48.

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The main analysis was an analysis of the primary endpoint using an analysis of covariance (ANCOVA) model with treatment as a fixed effect factor and baseline value body weight as a covariate. The least-squares (LS) mean difference and its two-sided 95% confidence interval (CI) between the OPC-61815 16-mg injection group and the tolvaptan 15-mg tablet group was calculated. The noninferiority of the OPC-61815 16-mg injection to the tolvaptan 15-mg tablet was to be confirmed when the upper limit of the CI did not exceed 0.48.

At each time point, the measured values, changes, and percent changes in body weight from baseline were summarized by treatment group using descriptive statistics.

For changes in body weight from baseline, a time course (mean ± SD) from Day 1 of the treatment period to follow-up was created for each treatment group.

For lower limb edema and pulmonary congestion, the improvement rate and the resolution rate (disappearance rate) at the time of final IMP administration was determined in each group, and the differences and their two-sided 95% CIs in the rates between the OPC-61815 16-mg injection group and the tolvaptan 15-mg tablet group were calculated.

The changes in jugular venous distension, hepatomegaly, and cardiothoracic ratio from baseline at the time of final IMP administration were analyzed using an ANCOVA model with treatment as a fixed effect factor and baseline as a covariate, and the LS mean differences and their two-sided 95% CIs between the OPC-61815 16-mg injection group and the tolvaptan 15-mg tablet group were calculated.

For the disappearance rates of pulmonary rales and cardiac third sound at the time of final IMP administration, the difference and its 95% CI between the OPC-61815 16-mg injection group and the tolvaptan 15-mg tablet group were calculated.

A shift table was prepared for the NYHA classification from baseline at the time of final IMP administration and each time point by treatment group. For Class II and higher subjects, the proportion of those who had improved from baseline by 1 or more NYHA class at the time of final IMP administration were calculated for each treatment.

Pharmacokinetics: The plasma drug concentration data were summarized using descriptive statistics as follows:

- At each time point, the plasma drug concentration data were summarized by compound and by treatment group using descriptive statistics.
- The descriptive statistics calculated included the number of subjects (N), arithmetic mean, SD, coefficient of variation, minimum, median, and maximum.

Pharmacodynamics: Measured values and changes from baseline at each time point were summarized by treatment group using descriptive statistics (N, mean, SD, minimum, median, and maximum). For changes from baseline in daily urine volume, daily fluid intake, and daily fluid balance after IMP administration on Day 1 and after IMP administration on Day 5, the mean difference ([OPC-61815 16-mg injection group] - [tolvaptan 15-mg tablet group]) and its 95% CI were calculated.

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Safety: The incidences of treatment-emergent adverse events (TEAEs) were summarized for all TEAEs, TEAEs by severity, IMP-related TEAEs, serious TEAEs, and TEAEs leading to the discontinuation of 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 135 of the 149 subjects (90.6%) randomized to OPC-61815 16 mg completed the trial and 14 subjects (9.4%) were discontinued; the most common reason for discontinuation in the OPC-61815 16 mg treatment group was AE (8 of 149 subjects [5.4%]). A total of 135 of the 145 subjects (93.1%) randomized to tolvaptan 15 mg completed the trial, and 10 subjects (6.9%) were discontinued; the most common reasons for discontinuation were AE and physician decision (3 of 145 subjects [2.1%] each). Adverse events leading to discontinuation included aspartate aminotransferase/alanine aminotransferase increased to 3 times the upper limit of normal or higher, serum or plasma sodium increased by 12 mEq/L or more within 24 hours after start of IMP administration, serum or plasma sodium increased to 155 mEq/L or higher, or other.

Overall, the subjects who were randomized and received at least one dose of IMP were predominantly male (210 of 294 subjects [71.4%]), with a mean age of 74.7 years, and the mean weight was 62.1 kg. The demographic and baseline characteristics were similar between the OPC-61815 and tolvaptan treatment groups.

Efficacy Results:

- The difference in the LS mean (95% CI) for body weight between the OPC-61815 16 mg treatment group and tolvaptan 15 mg treatment group was −0.31 kg (−0.68, 0.06). Since the upper limit of the 95% CI was below the predefined noninferiority margin of 0.48, the noninferiority of the OPC-61815 16-mg injection to the tolvaptan 15-mg tablet was confirmed.
- All congestive symptoms evaluated in this trial showed improvement from baseline at the time of final IMP administration for both the OPC-61815 16 mg and tolvaptan 15 mg treatment groups:
  - The improvement rate for lower limb edema at the time of final IMP administration was 68.9% in the OPC-61815 16 mg treatment group and 75.7% in the tolvaptan 15 mg treatment group. The disappearance rate for lower limb edema at the time of final IMP administration was 59.8% for the OPC-61815 16 mg treatment group and 58.6% for the tolvaptan 15 mg treatment group.
  - The LS mean change (95% CI) from baseline in jugular venous distension at the time of final IMP administration in subjects with baseline values was −2.89 cm (−3.45, −2.33) for the OPC-61815 16 mg treatment group and −3.15 cm (−3.68, −2.62) in the tolvaptan 15 mg treatment group.
  - The LS mean changes (95% CI) from baseline in hepatomegaly at the time of final IMP administration in subjects with baseline values were −0.93 cm (−1.44, −0.43) for the OPC-61815 16 mg treatment group and −0.88 cm (−1.43, −0.33) for the tolvaptan 15 mg treatment group.

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  - The improvement rate for pulmonary congestion at the time of final IMP administration was 56.1% for the OPC-61815 16 mg treatment group and 64.7% for the tolvaptan 15 mg treatment group. The disappearance rate for pulmonary congestion at the time of final IMP administration was 43.1% for the OPC-61815 16 mg treatment group and 52.9% for the tolvaptan 15 mg treatment group.
  - The disappearance rate of pulmonary rales at the time of final IMP administration was 74.3% for the OPC-61815 16 mg treatment group and 78.9% for the tolvaptan 15 mg treatment group.
  - The disappearance rate of the third cardiac sound at the time of final IMP administration was 31.7% for the OPC-61815 16 mg treatment group and 31.0% for the tolvaptan 15 mg treatment group.
  - The LS mean changes (95% CI) from baseline for cardiothoracic ratio at the time of final IMP administration was −2.06% (−2.62, −1.51) for the OPC-61815 16 mg treatment group and −1.99% (−2.56, −1.42) for the tolvaptan 15 mg treatment group.
- The improvement rates in NYHA classification, for subjects who improved by 1 or more grades at the time of final IMP administration compared with baseline, were 44.9% in the OPC-61815 16 mg treatment group and 42.5% in the tolvaptan 15 mg treatment group. The difference of improvement (95% CI) between the OPC-61815 and the tolvaptan treatment groups was 2.4% (−10.2, 14.6).

Pharmacokinetic Results:

- Following single intravenous administration of OPC-61815 16 mg, mean OPC-61815 free form plasma concentrations reached maximum values at 1 to 1.25 hours after start of administration and decreased thereafter.
- Following single intravenous administration of OPC-61815 16 mg, mean OPC-41061 plasma concentrations reached maximum values at 1 to 1.25 hours after start of administration and decreased thereafter. Following single oral administration of tolvaptan 15 mg tablet, mean OPC-41061 plasma concentrations reached maximum values at 4 to 6 hours after administration and decreased thereafter.

Pharmacodynamic Results:

- The greatest increase in daily urine volume from baseline was observed on Day 2 in both the OPC-61815 16 mg treatment group and tolvaptan 15 mg treatment group. Daily urine volume increased from baseline throughout the treatment period in both treatment groups. Changes from baseline for daily urine volume were similar for both treatment groups throughout the treatment period.
- Daily fluid intake increased from baseline throughout the treatment period in both the OPC-61815 16 mg treatment group and tolvaptan 15 mg treatment group. Changes from baseline for daily fluid balance showed negative values for both the OPC-61815 16 mg treatment group and tolvaptan 15 mg treatment group throughout the treatment period. Changes from baseline for daily fluid intake and daily fluid balance were similar for both treatment groups throughout the treatment period.

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- Urine osmolality decreased from baseline throughout the treatment period in both the OPC-61815 16 mg treatment group and tolvaptan 15 mg treatment group. The degree of changes was similar in both the OPC-61815 and tolvaptan treatment groups.
- Serum osmolality increased on Day 6 compared with baseline in both the OPC-61815 16 mg treatment group and tolvaptan 15 mg treatment group. Serum sodium concentrations increased on Day 2 compared with baseline in the OPC-61815 16 mg treatment group and tolvaptan 15 mg treatment group and remained around the same level throughout the treatment period. The degree of changes in serum osmolality and serum sodium was similar in both the OPC-61815 and tolvaptan treatment groups.
- Changes in each biomarker on Day 6 compared with baseline were similar in both the OPC-61815 16 mg and tolvaptan 15 mg treatment groups. For both the OPC-61815 and tolvaptan treatment groups, plasma AVP concentrations slightly increased and plasma BNP and serum NT-proBNP concentrations decreased. No notable changes from baseline were seen in plasma renin activity and serum troponin concentrations on Day 6 in either the OPC-61815 16 mg treatment group or tolvaptan 15 mg treatment group during the treatment period.

Safety Results:

- The overall incidence of TEAEs was similar in both the OPC-61815 16 mg treatment group and the tolvaptan 15 mg treatment group. A total of 163 TEAEs were reported for 83 of 149 subjects (55.7%) in the OPC-61815 16 mg treatment group and a total of 139 TEAEs were reported for 85 of 145 subjects (58.6%) in the tolvaptan 15 mg treatment group. No deaths were reported during the trial.
- The incidence of other serious adverse events (SAEs) was similar in both treatment groups. Other SAEs were reported for 6 of 149 subjects (4.0%) in the OPC-61815 16 mg treatment group and 5 of 145 subjects (3.4%) in the tolvaptan 15 mg treatment group. Of the SAEs reported, the investigator considered only the SAE of hyperkalaemia reported for a subject in the OPC-61815 16 mg treatment group to be IMP-related.
- The incidence of TEAEs leading to discontinuation of IMP was higher in the OPC-61815 16 mg treatment group compared with the tolvaptan 15 mg treatment group. Treatment-emergent AEs leading to discontinuation of IMP were reported for 8 of 149 subjects (5.4%) in the OPC-61815 16 mg treatment group and 3 of 145 subjects (2.1%) in the tolvaptan 15 mg treatment group. Of the TEAEs leading to discontinuation of IMP, the investigator considered all TEAEs to be IMP-related except for TEAEs of dehydration (2 subjects), congestive hepatopathy (1 subject), and blood creatinine increased (1 subject) reported for subjects in the OPC-61815 16 mg treatment group.
- Constipation, thirst, dry mouth, dehydration, and hyperkalaemia were reported as TEAEs that occurred in ≥ 5% of subjects in either treatment group. The TEAEs in which the OPC-61815 16 mg treatment group had a higher incidence than the tolvaptan 15 mg treatment group were dehydration and hyperkalaemia, and the TEAEs in which the tolvaptan 15 mg treatment group had a higher incidence than OPC-61815 16 mg treatment group were thirst and dry mouth. The majority of the TEAEs were mild or moderate in severity.

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- Of the TEAEs reported, IMP-related TEAEs were reported for 45 of 149 subjects (30.2%) in the OPC-61815 16 mg treatment group and for 44 of 145 subjects (30.3%) in the tolvaptan 15 mg treatment group. The most frequently reported IMP-related TEAEs (≥ 5% of subjects) were thirst and dehydration for the OPC-61815 16 mg treatment group and thirst and dry mouth for the tolvaptan 15 mg treatment group.
- The incidence of severe TEAEs was higher in the OPC-61815 treatment group compared with the tolvaptan treatment group.
- Dehydration, sodium-related AEs (blood sodium increased, hypernatraemia, and rapid correction of hyponatraemia), hyperkalaemia, and blood potassium increased were observed as notable TEAEs with higher incidences in the OPC-61815 16 mg treatment group compared with the tolvaptan 15 mg treatment group. Most of the TEAEs were considered by the investigator to be mild in severity.
- There were no clinically meaningful changes from baseline for clinical laboratory results, vital signs, or ECG findings.

Conclusions:

During this trial, an injection of OPC-61815 16 mg or a tablet of tolvaptan 15 mg was administered for 5 days to subjects with CHF (cardiac edema) who had excessive fluid retention even after treatment with existing diuretics, and the following results were obtained:

- The noninferiority of OPC-61815 16 mg to tolvaptan 15 mg was confirmed using the change in body weight after administration of OPC-61815 16 mg or tolvaptan 15 mg once daily for 5 days as the primary endpoint. Body weight decreased the most on Day 2 in each treatment group and continued to decrease gradually throughout the treatment period after Day 3. The OPC-61815 treatment group had improvement in congestive symptoms (lower limb edema, jugular venous distension, pulmonary congestion, pulmonary rales, third cardiac sound, and cardiothoracic ratio), and NYHA functional classification to the same extent as the tolvaptan treatment group.
- Daily urine volume increased from baseline in the OPC-61815 treatment group throughout the treatment period, and changes from baseline in daily urine volume were similar to those in the tolvaptan treatment group.
- No safety concerns were observed. The overall incidence of TEAEs was similar in both the OPC-61815 16 mg treatment group and the tolvaptan 15 mg treatment group. Constipation, thirst, dry mouth, dehydration, and hyperkalaemia were reported as TEAEs that occurred in ≥ 5% of subjects in either treatment group. The TEAEs in which the OPC-61815 16 mg treatment group had a higher incidence than the tolvaptan 15 mg treatment group were dehydration and hyperkalaemia, and the TEAEs in which the tolvaptan 15 mg treatment group had a higher incidence than the OPC-61815 16 mg treatment group were thirst and dry mouth. The majority of the TEAEs were mild or moderate in severity.

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