Synopsis

Clinical Report Synopsis for Protocol 156-14-003

Name of Sponsor: Otsuka Pharmaceutical Co., Ltd.

Name of Investigational Medicinal Product: Tolvaptan (OPC-41061)

Protocol Title: A Multicenter, Uncontrolled, Open-label, Dose-titration Trial to Investigate the Efficacy and Safety of Tolvaptan Tablets in Patients With Hyponatremia in Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)

Principal or Coordinating Investigator and Trial Centers: This trial was conducted in 16 subjects at 13 sites in Japan. [redacted]

Publications: None to date.

Trial Period:

Date of first signed informed consent: 02 Mar 2017

Date of last trial observation: 19 Mar 2019

Clinical Development Phase: Phase 3

Trial Interruption: There was no unplanned trial interruption.

Scientific Background and Explanation of Rationale: Tolvaptan is an oral arginine vasopressin (AVP) receptor antagonist with a high affinity for the V_2 receptor and has been shown to produce aquaresis resulting in the increased excretion of free water. In the United States (US) and European Union (EU), tolvaptan is approved for the treatment of hyponatremia secondary to SIADH. However, the efficacy and safety of tolvaptan have not been demonstrated in Japanese patients. The present clinical trial was planned to demonstrate the appropriateness of the proposed dosage regimen (the efficacy and safety of tolvaptan administered at the proposed dosage regimen), and to confirm the safety and other characteristics of the drug under a specified monitoring. This protocol was prepared based on the agreement reached with Pharmaceutical and Medical Devices Agency regarding the appropriateness of the trial plan at the consultation after completion of the phase 2 trial (19 Apr 2016, Application Number P3962). In the view of the above, the conduct of this trial was scientifically and ethically appropriate.

Objectives: To determine the efficacy and safety of tolvaptan based on the change in serum sodium concentration following administration of tolvaptan oral tablets at 7.5 to 60 mg/day for up to 30 days in Japanese patients with hyponatremia in SIADH.

Methodology: This clinical trial was a multicenter, uncontrolled, open-label, dose-titration trial to investigate the efficacy and safety of tolvaptan administered for up to 30 days at a dose of 7.5 to 60 mg/day, based on the change in serum sodium concentration in Japanese subjects with hyponatremia secondary to SIADH.
The trial consisted of a screening period, pretreatment observation period, treatment period, and follow-up period.
After written informed consent was obtained, the investigator or subinvestigator performed the screening examination to confirm the eligibility of the subject within 14 to 2 days before start of investigational medicinal product (IMP) administration, and the subject was admitted to the trial site 2 days before start of IMP administration, at which eligibility for trial entry was confirmed during the pretreatment observation (the day before start of IMP administration) and predose on Day 1 of the treatment period.
From Day 1, the IMP was orally administered once daily after breakfast, and the specified observations, examinations, and investigations were performed for the efficacy and safety evaluations. The starting dose of the IMP was 7.5 mg/day, which was increased to 15 mg/day, followed by 30 mg/day then 60 mg/day on or after Day 2, to determine the maintenance dose in each subject. Once the maintenance dose had been determined, the IMP was administered continuously at that dose throughout the period.
If the subject became less responsive to the IMP due to exacerbation of the underlying disease or other causes, and the investigator or subinvestigator concluded that dose escalation was needed and this increase would raise no safety problems, the dose may have been increased. When increasing the dose beyond the maintenance dose once it had been determined, the subject was hospitalized at the trial site to determine a new maintenance dose.
To prevent a too rapid increase in serum sodium concentration, fluid restriction was avoided within 24 hours after IMP administration on Day 1 of the treatment period, based on safety considerations. From Day 2 of treatment period and onward, the investigator or subinvestigator defined the upper limit of daily fluid intake according to fluid intake the subject took on Day 1 for each subject and instructed the subject to take fluids depending on his/her condition.
From the day after the maintenance dose had been determined and onward, a decision regarding switching the subject to outpatient treatment would have been made as specified in the protocol.
The maximum treatment duration was 30 days. If the serum sodium concentration had normalized (≥ 135 mEq/L), the subject had no subjective symptoms associated with hyponatremia, and the investigator or subinvestigator concluded that the serum sodium concentration was unlikely to decrease on withdrawal of the IMP, the treatment may have been completed before the duration of treatment reached 30 days.
The subject was to have visited the trial site 7 to 10 days after the completion of IMP treatment to undergo the follow-up examination. Since serum sodium concentration was expected to decrease due to the withdrawal of treatment, serum sodium concentration was measured 3 to 5 days after completion of IMP treatment.
If hyponatremia had recurred after treatment with the IMP was completed before the duration of treatment reached 30 days (except treatment discontinuations as specified in the protocol), and it was judged by the investigator or subinvestigator that

readministration with the IMP was necessary, treatment may have been resumed within 30 days after the initial IMP administration (from protocol version 6.0).
The trial participation period for each subject was from the date of signed informed consent to the trial completion date.

Number of Subjects: A total of 31 subjects were screened for entry into the trial, 16 subjects received IMP, and 11 (68.8%) subjects completed the trial. There was 1 subject (6.3%) who was readministered IMP.

Diagnosis and Main Criteria for Inclusion: In this trial, male and female Japanese subjects with hyponatremia secondary to SIADH, aged from 20 to 85, inclusive at the time of consent were eligible. The trial population was required to include 16 subjects who were evaluable for the primary endpoint, the percentage of subjects with normalized serum sodium concentration (ie, subjects whose predose serum sodium concentration centrally measured on Day 1 was < 135 mEq/L).

Investigational Medicinal Product, Dose, Dosage Regimen, Formulation, Mode of Administration, and Lot No.(s.): Subjects were administered tolvaptan tablets once daily after breakfast with water. The starting dose of tolvaptan was 7.5 mg/day (one 7.5 mg tablet), which was increased to 15 mg/day (one 15 mg tablet) on or after Day 2 of treatment period, followed by 30 mg/day (one 30 mg tablet) and then 60 mg/day (two 30 mg tablets), to determine the maintenance dose for each subject. Once the maintenance dose had been determined, the IMP was administered continuously at that dose throughout the period.
The dose could be reduced at any time during the treatment period, if any safety problem arose and the investigator or subinvestigator concluded that a dose reduction was necessary. Dose reduction was to be performed as 1 dose level per day.

The lot numbers and expiration dates used in this trial were as follows:
Tolvaptan (OPC-41061) 7.5 mg tablets: Lot#16D77A0075, expiration date 07 Apr 2019, Lot#18E79A0075, expiration date 09 May 2021
Tolvaptan (OPC-41061) 15 mg tablets: Lot#15L77A015A, expiration date 07 Dec 2019, Lot#18B82A015, expiration date 12 Feb 2022
Tolvaptan (OPC-41061) 30 mg tablets: Lot#15L86A030A, expiration date 16 Dec 2019, Lot#18B83A030A, expiration date 13 Feb 2022

Reference Product, Dose, Dosage Regimen, Formulation, Mode of Administration, and Lot No(s): Not applicable.

Duration of Treatment: The maximum duration of treatment was set as 30 days.

Trial Assessments:
Efficacy: Serum sodium concentration and clinical symptoms associated with hyponatremia

Pharmacokinetics (PK): Plasma concentrations of tolvaptan and its metabolites DM-4103 and DM-4107

Pharmacodynamics (PD): Daily urine volume, daily fluid intake, daily fluid balance, urine osmolality, serum osmolality, daily urinary sodium excretion, and plasma AVP concentration

Safety: Adverse events (AEs), clinical laboratory tests, body weight, vital signs, 12-lead electrocardiography, liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and serum total bilirubin), and pregnancy test

Criteria for Evaluation:

Efficacy:

Primary endpoint:

- Percentage of subjects with normalized serum sodium concentration (≥ 135 mEq/L) on the day after final IMP administration

Secondary endpoints:

- Change in serum sodium concentration
- Time course of serum sodium concentration
- Changes in clinical symptoms associated with hyponatremia

Pharmacokinetics: The plasma concentrations of tolvaptan and its metabolites (DM-4103 and DM-4107)

Pharmacodynamics:

- Daily urine volume
- Daily fluid intake
- Daily fluid balance
- Serum osmolality
- Urine osmolality
- Daily urinary sodium excretion
- Plasma AVP concentration

Safety: AEs, clinical laboratory tests, body weight, vital signs, 12-lead electrocardiography, and liver function tests.

Pharmacokinetic/Pharmacodynamic Methods:

Bioanalytical: Tolvaptan, DM-4103, and DM-4107 in plasma were analyzed by Toray Research Center using a validated high performance liquid chromatography with tandem mass spectrometry method.

Pharmacokinetics: Blood samples were collected to measure the plasma concentrations of tolvaptan and its metabolites, DM-4103 and DM-4107.

Pharmacodynamics: Details on PD analyses are provided in the Statistical Analysis Plan (SAP).

Statistical Methods:

Determination of Sample Size: The target sample size was determined with respect to the percentage of subjects with a normalized serum sodium concentration (≥ 135 mEq/L) at the final administration of tolvaptan.

Sample size determination was based on the results from patients with SIADH as the underlying disease of hyponatremia ("the SIADH subpopulation") in the efficacy analysis sets of 2 overseas phase 3, placebo-controlled, randomized, double-blind trials in patients with hyponatremia due to SIADH and other causes (Trials 156-02-235 and 156-03-238, with an optional up-titration of 15, 30, and 60 mg for 30 days). To determine the sample size of this trial, a threshold percentage was set based on the results of the placebo group in the SIADH subpopulation of the overseas trials. Considering the distribution of the point estimates which are calculated based on multiple sample sizes, in the percentage of subjects with a normalized serum sodium concentration after the final IMP administration in the tolvaptan group, a sample size for which the probability of obtaining a point estimate exceeding the threshold percentage was kept at ≥ 80% was sought. In addition, since this trial intended to evaluate the efficacy and safety of tolvaptan in subjects with SIADH due to a variety of etiologies, and to investigate the appropriateness of the dose-titration approach adopted as the dosage regimen, the various etiologies of SIADH and the expected number of subjects at each maintenance dose level were also taken into consideration in determination of the sample size.

In the SIADH subpopulation of the 2 overseas phase 3 trials, the percentage of subjects with a normalized serum sodium concentration (Day 30, Last Observation Carried Forward) was 64.6% (31 of 48 subjects) in the tolvaptan group and 30.2% (16 of 53 subjects) in the placebo group. Therefore, the threshold percentage was set at 44.3% (the upper limit of the exact 95% confidence interval (CI) for the percentage of normalized subjects in the placebo group). When a binomial distribution with a parameter of 64.6% (the point estimate of the percentage of normalized subjects in the tolvaptan group) is assumed, the probability that the expected point estimate of the percentage of normalized subjects will exceed the threshold percentage is kept at ≥ 80% with a sample size of ≥ 8 subjects.

The underlying diseases of SIADH are diverse, and it is difficult to evaluate the efficacy of tolvaptan for each of all SIADH etiologies. Therefore, patients with SIADH will be divided into those with SIADH due to ectopic vasopressin producing tumors and those due to other etiologies to evaluate the efficacy of tolvaptan. Since the prevalence of these 2 categories of patients is presumed to be nearly equivalent, a sample size of 16 subjects (8 subjects × 2) for the entire trial would enable an efficacy evaluation by SIADH etiology.

In this trial, the following 4 maintenance dose levels had been established: 7.5, 15, 30, and 60 mg/day. A sample size for which the probability of obtaining at least 1 subject for each maintenance dose level is kept at ≥ 80% was calculated by applying the multinomial distribution. Since the proportion of subjects with each maintenance dose level in the trial was unpredictable, the subjects were assumed to be equally distributed to the 4 maintenance dose levels. By applying a polynomial distribution with a common parameter of 25% across the 4 maintenance dose levels, the sample size required to obtain at least 1 subject at each maintenance dose level with a ≥ 80% probability was 11 subjects. Based on the above results, the target sample size was set as 16 subjects.

Subject Samples:

The datasets analyzed for the trial are as follows:

Efficacy Analysis Set: The efficacy analysis set consists of all subjects who received at least 1 dose of the IMP and have postdose serum sodium concentration data.

Maintenance Dose-setting Set: Of the efficacy analysis set, the subpopulation comprised of the subjects for whom maintenance doses of the IMP were determined is defined as the maintenance dose-setting set.
Safety Analysis Set: The safety analysis set consists of all subjects who received at least 1 dose of the IMP.
PK Analysis Set: The PK analysis set consists of all subjects who received at least 1 dose of the IMP and have postdose drug concentration data.
PD Analysis Set: The PD analysis set consists of all subjects who received at least 1 dose of the IMP and have postdose PD data.
Efficacy: The primary endpoint was the percentage of subjects with normalized serum sodium concentration the day after the final IMP administration.
The percentage of subjects with normalized serum concentration, defined as ≥ 135 mEq/L, on the day after final IMP administration was calculated versus the number of subjects with serum sodium concentration of < 135 mEq/L at baseline (predose on Day 1 of the treatment period).
Pharmacokinetics: In the PK analysis set, the plasma concentrations of tolvaptan and its metabolites, DM-4103 and DM-4107 on Day 21 and the day after the final IMP administration was adjusted for the dose administered immediately before each timepoint to calculate descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) by timepoint and by compound.
Pharmacodynamics: PD analyses were performed in the PD analysis set. Measured values and changes from baseline (at predose on Day 1 of the treatment period for serum osmolality and plasma AVP concentration or at 24 hours predose on Day 1 of the treatment period for other parameters) at each timepoint were summarized using descriptive statistics.
Safety: Safety analyses were performed on the safety analysis set using descriptive statistics.

Summary of Results:

Disposition, Demographics, and Baseline Characteristics:

A total of 31 subjects were screened for entry into the trial, 16 subjects received IMP, and 11 (68.8%) subjects completed the trial. There was 1 subject (6.3%) who was readministered IMP. There were 5 (31.3%) subjects who discontinued from the trial, and the most common reason for discontinuation was "continuation of treatment became difficult due to an AE," which occurred in 2 (12.5%) subjects. The majority of subjects were male (13 [81.3%] subjects), with an average age of 71.9 ± 6.1 years. There were 10 (62.5%) subjects with ectopic antidiuretic hormone-producing tumors and 6 (37.5%) subjects with other causes.

Efficacy Results:

- The percentage of subjects with normalized serum sodium concentration on the day after final IMP administration showed a high rate of 13/16 (81.3%) subjects.
- The percentage of subjects with normalized serum sodium concentration on the day after final IMP administration showed high efficacy across all administered doses.

- The serum sodium concentration increased after IMP administration in all subjects, which tended to be decreased after completion of IMP administration in most subjects, whereas it was maintained at a high level throughout the treatment period.
- The percentage of subjects with normalized serum sodium concentration on the day after final IMP administration showed high efficacy in underlying cause leading in SIADH and serum sodium concentration at predose on Day 1 of the treatment period.

Pharmacokinetic/Pharmacodynamic Results:

- There was large variability in the plasma concentrations of OPC-41061, DM-4103, and DM-4107.
- An increase of urine volume and fluid intake and decrease of fluid balance were observed after administration of IMP.
- A decrease of urine osmolality was observed after administration of IMP and urinary sodium excretion did not show any obvious trends.
- Increases of serum osmolality and plasma AVP concentration were observed after administration of IMP and tended to decrease after completion of IMP administration.

Safety Results:

- The mean duration of exposure was 22.6 ± 10.1 days and 11 (68.8%) subjects were exposed to IMP for 22-30 days.
- Overall, 15 (93.8%) subjects experienced 78 treatment-emergent adverse events (TEAEs), and 10 (62.5%) subjects reported TEAEs that were considered to be IMP-related. One (6.3%) subject died in the trial treatment period, 5 (31.3%) subjects had serious TEAEs, and 5 (31.3%) subjects had TEAEs leading to discontinuation.
  - The most frequently reported TEAEs that were considered by the investigator to be related to IMP were thirst (reported in 3 [18.8%] subjects), blood creatinine increased, and weight decreased (reported in 2 [12.5%] subjects each).
  - The serious adverse event (SAE) of lung adenocarcinoma that resulted in death was considered by the investigator to be unrelated to IMP.
  - The SAEs of ventricular and supraventricular extrasystoles were considered related to the IMP, however the hospitalization was due to patient monitoring rather than the event clinical severity.
  - Other SAEs were considered by the investigator to be unrelated to IMP.
- No significant changes were observed in clinical laboratory tests and no significant changes were observed in liver function tests.

Overall Conclusions:

- Administration of tolvaptan to Japanese subjects with SIADH normalized serum sodium concentration and showed high efficacy (13/16 [81.3%] subjects).
- The effectiveness was confirmed regardless of SIADH etiology and the serum sodium concentration before administration.
- No significant safety concerns were observed during the trial.