Synopsis

Clinical Report Synopsis for Protocol 156-04-247

Name of Company: Otsuka Pharmaceutical Development & Commercialization, Inc.

Name of Product: Tolvaptan (OPC-41061)

Trial Title: A Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Effect of Single Oral Tolvaptan Tablets on Hemodynamic Parameters in Subjects with Heart Failure

Investigator(s) and Trial Center(s): Multicenter (48 centers); Multinational (US, Romania, and Bulgaria)

Publications: Udelson JE, Orlandi C, Ouyang J, Krasa H, Zimmer CA, Frivold G, et al. ECLIPSE: Acute Hemodynamic Effects of Tolvaptan, a Vasopressin V2 Receptor Blocker, in Patients with Symptomatic Heart Failure and Systolic Dysfunction: The ECLIPSE International, Multicenter, Randomized, Placebo-Controlled Trial. Presented at the 11th Annual Scientific Meeting of the Heart Failure Society of America - Symposium XXVII: Recent and Late Breaking Trials. 19 September 2007.

Studied Period:

Date of first signed informed consent: 01 Feb 2005

Date of last trial observation: 24 Dec 2006

Clinical Phase: 2

Objectives: The primary objective of this trial was to compare the effect of tolvaptan to placebo on the peak change from baseline in pulmonary capillary wedge pressure (PCWP) in subjects with heart failure. Secondary objectives were to compare:

- The effect of tolvaptan to placebo on the area under the curve (AUC) of the change from baseline in PCWP.
- The effect of tolvaptan to placebo on other pharmacodynamic (PD) variables including cardiac index, systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), right atrial pressure (RAP), urine output, free water clearance, and urine osmolality.

Methodology: This was a multicenter, randomized, double-blind, placebo-controlled, single dose trial to determine the hemodynamic effects of 3 doses of oral tolvaptan versus placebo in subjects with heart failure. Inclusion/exclusion criteria (excluding hemodynamic parameters) were assessed for up to 2 weeks prior to randomization. Suitable candidates underwent insertion of a balloon-floatation pulmonary artery catheter

to assess final eligibility criteria. Final doses of cardiac concomitant medications were administered at least 2 hours prior to catheter insertion. Following catheter insertion, subjects entered into a 2- to 20-hour stabilization period. Hemodynamic assessments were completed periodically during this period to determine final subject eligibility. Potential subjects then entered a 2-hour baseline period. If all criteria were met during the baseline period, subjects were randomized via an interactive voice response system (IVRS) to one of 4 groups and received either a single oral tablet of placebo or tolvaptan 15, 30, or 60 mg. Subjects were followed for up to 24 hours for PD assessments. A follow-up telephone call was made to all subjects 7 (+2) days after trial drug administration to collect safety information.

Number of Subjects: Target enrollment for this trial was 180 subjects. A total of 181 subjects were enrolled, all of whom received trial medication and were included in the evaluations of efficacy and safety.

Diagnosis and Main Criteria for Inclusion: Male or female subjects at least 18 years old with New York Heart Association (NYHA) Class III or IV heart failure for at least 3 months duration due to left ventricular systolic dysfunction were considered for screening. Additional eligibility requirements included a left ventricular ejection fraction ≤ 40% by any method (eg, 2D-Echo, radionuclide ventriculography, gated single proton emission computed tomography, cardiac catheterization) within 1 year of screening and two consecutive baseline PCWP measurements ≥ 18 mmHg within 2 hours of randomization. Subjects received standard background therapy for heart failure (eg, angiotensin converting enzyme inhibitor, angiotensin II receptor blocker, beta-blocker, aldosterone receptor antagonist) for at least 1 month prior to screening.

Test Product, Dose, Mode of Administration, Batch or Lot No(s): Tolvaptan 15, 30, or 60 mg tablets administered orally - lot numbers 02C80A015A, 04C77A015, and 05D73A015A for the 15-mg tablets; 02C80A030A, 03L73A030E, and 05D73A030A for the 30-mg tablets; and 02C80A060, 04L93A060, and 05D73A060 for the 60-mg tablets. Matching placebo tablets administered orally - lot numbers 02C80P000B, 04A95P000E, and 05D73P000A. The tolvaptan and placebo tablets used in this trial were manufactured by Otsuka Pharmaceutical Company, Ltd (Japan).

Reference Product, Dose, Mode of Administration, Batch or Lot No(s): None.

Criteria for Evaluation:
The primary outcome variable was the peak change from baseline in PCWP from 3 to 8 hours postdose. Pulmonary capillary wedge pressure was assessed during the baseline period and at 0.5, 1, 2, 3, 4, 5, 6, 7, and 8 hours postdose. (Prior to Amendment 1, PCWP was also collected at 9 and 12 hours postdose.) Additional assessments of PCWP and other hemodynamic parameters could have been obtained at 12- and 24-hours postdose if the pulmonary artery catheter was still in place due to medical necessity.

Secondary variables and their methods of determination were as follows:

Pharmacodynamic:

- AUC of the change from baseline in PCWP from 0 to 8 hours postdose was determined using the trapezoidal rule.
- Peak change from baseline in cardiac index, SVR, PVR, and RAP from 3 to 8 hours postdose was determined by subtracting baseline values from maximum (cardiac index) or minimum (SVR, PVR, and RAP) values from hemodynamic assessments performed from 3 to 8 hours postdose.
- Change from baseline in urine output was determined from hourly collection of urine beginning 1 hour prior to dosing and continuing to 8 hours postdose.
- Change from the 1 hour baseline interval in free water clearance was calculated from values for urine volume, urine osmolality, and plasma osmolality in 2-hour intervals up to 8 hours postdose.
- Change from baseline in urine osmolality was determined from samples taken from the hourly urine collections.

Pharmacokinetic (PK): Plasma samples for determination of maximum (peak) plasma concentration (C_{max}), time to maximum (peak) plasma concentration (t_{max}) and AUC from time 0 to 8 hours (AUC_{0-8h}) were obtained predose and at 1, 2, 3, 4, 5, 6, 7, and 8 hours postdose. Samples could have been obtained at 12 and 24 hours postdose, if hemodynamic measurements were obtained).

Safety: Subjects were monitored throughout the trial for the adverse events (AEs). Vital signs recorded at screening and discharge or early termination (ET) included supine blood pressure (BP), heart rate (HR), respiratory rate, and temperature. Supine BP and HR were measured after 5 minutes of supine rest at the time of hemodynamic samples (ie, 0.5, 1, 2, 3, 4, 5, 6, 7, and 8 hours postdose; 12 and 24 hours postdose, if applicable). Clinical laboratory samples obtained at screening and discharge/ET were shipped to a central laboratory for analysis.

Statistical Methods:

Demographics/Baseline Characteristics: Demographic characteristics, medical history, and other baseline data were summarized by descriptive statistics, as appropriate.

Efficacy/Pharmacodynamic Variables: The intent-to-treat (ITT) dataset for the primary analysis included data from all treated subjects who had observations for PCWP at baseline and at time points from 3 to 8 hours postdose, even if some data points were missing. Intent-to-treat datasets for the other hemodynamic variables were defined similarly. Due to the known technical issues associated with obtaining accurate and consistent hemodynamic measurements, individual subject data were assessed by an Independent Technical Review Committee (ITRC) in a blinded manner to determine evaluable datasets. The evaluable datasets were used in the primary analysis of the protocol, with the ITT dataset as a secondary analysis.

The baseline for PCWP, cardiac index, SVR, PVR, and RAP was defined as the average of the last two consecutive measures repeated within 10 minutes of each other prior to randomization. For PCWP, the lower reading was within ±10% of the higher reading.

An analysis of covariance (ANCOVA) model with terms of treatment, country, and baseline PCWP as covariates was applied to the data of the primary efficacy variable of the 60 mg, 30 mg, and placebo groups. A comparison between a tolvaptan dose (30 mg or 60 mg) versus placebo was significant if both the F-test of the treatment effect of the ANCOVA and the t-test of the contrast statement of the ANCOVA model between the tolvaptan dose and placebo were significant. No adjustments were made for multiple comparisons. The comparison between tolvaptan 15 mg and placebo was considered as secondary and was conducted by using the t-test in a contrast statement of ANCOVA.

For each treatment group, absolute values and changes from baseline were summarized for PCWP, cardiac index, SVR, PVR, RAP, urine volume, free water clearance, and urine osmolality using descriptive statistics including: number of subjects (n), median, mean, standard error (SE), minimum, and maximum. An ANCOVA model, using data of all 4 treatment groups, with terms of treatment, country, and baseline observation as covariates was used for the analyses of these secondary efficacy variables. Contrast statements under the linear model were constructed to make treatment comparisons for tolvaptan doses versus placebo. The alpha level was 0.05 for each contrast of a secondary efficacy/pharmacodynamic variables.

Safety: Safety analyses were conducted on the safety population consisting of all randomized subjects who received at least one dose of trial medication. Adverse events were coded by Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and summarized by frequency of occurrence for all events, treatment-related events, serious events, deaths, and withdrawals. Clinical laboratory data were summarized in tabular displays of change from baseline for each parameter and shift tables using a low-normal-high scale. Hematology and serum chemistry data were also examined for abnormalities of potential clinical significance. Vital signs were summarized in tabular displays of change from baseline and the incidence of potentially clinically significant vital sign results.

Pharmacokinetic Methods: Pharmacokinetic parameters were determined using a noncompartmental approach. For each treatment group, plasma concentrations by time point and PK parameters were summarized using descriptive statistics including: n, median, mean, SD, coefficient of variation, minimum, and maximum.

Efficacy/Pharmacodynamic Results:
The primary variable in this trial was the mean peak change in PCWP from 3 to 8 hours postdose. The largest treatment effect was seen in the tolvaptan 15 mg group (mean change, -6.38 mmHg compared with -4.16 mmHg in subjects receiving placebo). Mean values in $AUC_{0\text{-}8h}$ for change from baseline in PCWP were similar; the largest treatment effect was seen in subjects receiving 15 mg tolvaptan (mean change of -21.41 mmHg compared with -8.36 mmHg in subjects receiving placebo).

The primary statistical analysis for the overall comparison among the treatment groups of placebo and of 30 and 60 mg tolvaptan (pooled) approached statistical significance (F-test, p = 0.0563).

A posthoc analysis of peak change from baseline in PCWP was also conducted, excluding 4 subjects. For these 4 subjects (one tolvaptan and 3 placebo subjects), one of the baseline PCWP measurements was excluded by the blinded Independent Technical Review Committee, resulting in only one validated baseline PCWP measurement (rather than 2 baseline PCWP measurements within 10% of each other, as required by the protocol). With these 4 subjects excluded, the F-test for the analysis of peak change from baseline in PCWP yielded statistically significant results (p = 0.0101).

For all tolvaptan treatment groups, a decrease in PCWP was seen as early as 2 hours after dosing, with the largest decrease observed in subjects receiving 15 mg tolvaptan. However, only subjects receiving tolvaptan continued to have decreases in PCWP through the 8-hour time point. Over the 8-hour period, the largest mean change was 3.76 mmHg at 7 hours in subjects receiving tolvaptan 15 mg.

At approximately 2 hours postdose, significant differences in mean urine volume were seen between tolvaptan subjects (range, 240.6 mL to 283.4 mL) and placebo subjects (87.2 mL). As anticipated, a dose-response effect on urine volume was evident in the tolvaptan group: urine output was lowest in the 15 mg tolvaptan group and highest in the 60 mg tolvaptan group.

From 3 to 8 hours postdose, RAP showed mean changes of -3.49 to -4.35 mmHg for subjects in all treatment groups. These differences were statistically significant for the 15 mg group (p = 0.0030) and for the 30 mg group (p = 0.0173) compared with the placebo group. In a post-hoc analysis, PAP for the same time period (3 to 8 hours postdose) showed peak changes of 3.01 to -5.60 mmHg. These changes were statistically significant for all treatment groups when compared with placebo (p = 0.0050 for tolvaptan 15 mg, p = 0.0164 for tolvaptan 30 mg, and p = 0.0395 for tolvaptan 60 mg). No differences were seen between the tolvaptan and placebo groups in PVR, cardiac index, or SVR.

Pharmacokinetic Results:

Tolvaptan C_{max} and $AUC_{0\text{-}8h}$ increased linearly with increasing dose but variability in response was high; coefficients of variation ranged from 35 to 52%. A summary of PK parameters is presented in the table below. Many subjects in the 30 and 60 mg dose groups had plasma concentrations within the range of the 15 mg dose group.

Mean (SD) Tolvaptan Pharmacokinetic Parameters Following a Single Oral Dose of Tolvaptan to Heart Failure Subjects

PK Parameter	Tolvaptan 15 mg (N = 43)	Tolvaptan 30 mg (N = 43)	Tolvaptan 60 mg (N = 45)
C_{max} (ng/mL)	165 (57.8)	314 (146)	657 (302)
t_{max} (h)[a]	2.17 (0.95-12.02)	3.00 (0.93-8.00)	3.00 (0.92-8.03)
AUC_{0-8h} (ng ·h/mL)	761 (281)[b]	1480 (773)	3190 (1650)

[a]Median (minimum-maximum).
[b]n=42.

Pharmacokinetic/Pharmacodynamic Results:
No correlations were observed for plots of peak change in PCWP from 3 to 8 hours postdose or the AUC_{0-8h} of the change from baseline in PCWP plotted versus tolvaptan AUC_{0-8h} or for peak change from baseline in PCWP plotted versus cumulative urine volume, 0 to 8 hours postdose.

Safety Results:
Overall, 77/181 (42.5%) subjects experienced at least one TEAE during the trial. The incidence of TEAEs was highest in the tolvaptan 60 mg group (54.3%) and lowest in the placebo group (33.3%).

Two subjects died after trial participation, but during the 7-day follow-up period (Subjects [redacted] [30 mg tolvaptan] and [redacted] [60 mg tolvaptan]); neither of the events was considered related to trial drug. Overall, 10 subjects (5.5%) experienced SAEs: 1 in the 15 mg group (Subject [redacted]), 3 in the 30 mg group (Subjects [redacted], [redacted], and [redacted]), 5 in the 60 mg group (Subjects [redacted], [redacted], [redacted], [redacted], and [redacted]), and 1 in the placebo group (Subject [redacted]). Only 3 subjects with SAEs experienced events that were considered possibly or definitely related to trial drug: Subject [redacted] (60 mg tolvaptan) experienced severe atrial flutter, Subject [redacted] (60 mg tolvaptan) experienced severe diabetes insipidus, and Subject [redacted] (60 mg tolvaptan) experienced moderate renal failure. Seven subjects experienced TEAEs that were considered severe and 3 subjects discontinued from the trial because of TEAEs: 1 subject who received 60 mg tolvaptan (Subject [redacted]) and 2 subjects who received placebo (Subjects [redacted] and [redacted]).

No clinically meaningful changes were observed in vital signs or clinical laboratory tests.

Conclusions:
- Tolvaptan administration resulted in improvements in the hemodynamic profile of patients with severe congestive heart failure.
- Improvements were observed for PCWP, RAP, and PAP.
- No changes were observed for cardiac index or for pulmonary and systemic vascular resistance.

- Subjects receiving tolvaptan continued to experience decreases in PCWP after 2 hours; subjects treated with placebo had PCWP values fluctuating around the value observed at the 2-hour time point.
- Tolvaptan 15 and 30 mg produced statistically significant decreases in RAP compared with placebo.
- All tolvaptan doses (15 mg, 30 mg, and 60 mg) decreased PAP, and changes in PAP from baseline were statistically significant for all tolvaptan treatment groups when compared with placebo.
- Tolvaptan subjects experienced greater increases from baseline in urine volume and free water clearance and greater decreases in urine osmolality than did subjects receiving placebo.
- Tolvaptan, administered as a single oral dose of 15, 30, or 60 mg, was well tolerated.
- No clinically meaningful changes were observed in vital signs or clinical laboratory tests.
- No unexpected safety findings were reported.

Otsuka Pharmaceutical Development & Commercialization, Inc.

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