Synopsis

Clinical Report Synopsis for Protocol 156-09-284

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

Name of Product: Tolvaptan (OPC-41061)

Study Title: A Phase 2a, Single-center Study Investigating the Short-term Renal Hemodynamic Effects, Safety and Pharmacokinetics/Pharmacodynamics of Oral Tolvaptan in Subjects With Autosomal Dominant Polycystic Kidney Disease at Various Stages of Renal Function

Investigator and Study Center: [redacted], MD, PhD, [redacted] The Netherlands

Publications: None to date

Studied Period:

Date of first signed informed consent: 06 Oct 2010

Date of last study observation: 11 Nov 2011

Clinical Phase: 2a

Objectives:

Primary Objective: The primary objective was to determine the effect of maximally tolerated doses of tolvaptan at steady state on the measured glomerular filtration rate (mGFR), effective renal plasma flow (ERPF), and filtration fraction in subjects with autosomal dominant polycystic kidney disease (ADPKD), including those with severely impaired renal function.

Secondary Objectives:

- To determine the effect of tolvaptan on urine volume (2-hour and split 24-hour collections) and free water clearance (FWC).
- To characterize the plasma concentrations of tolvaptan.
- To determine short-term effects of tolvaptan on total kidney volume (TKV) as measured by changes from baseline.

Methodology: This was a single-center, sequential trial of the effect of multiple doses of tolvaptan on renal function to be conducted in up to 36 subjects diagnosed with ADPKD. Subjects were administered a daily split-dose regimen of tolvaptan for 3 weeks. The dose was up-titrated weekly, as tolerated. Renal assessments were conducted at Baseline (Day 0), the Final Treatment visit (Day 21), and 3 weeks after the last dose of trial medication.

Trial participation for each subject was up to 12 weeks, including a 2- to 42-day Screening period, 3-week treatment period, and 3-week post treatment period. The duration of this trial from first subject screened to last subject completed was approximately 13 months.

Number of Subjects: This trial planned to include up to 36 male and female subjects who had been diagnosed with ADPKD. Inclusion was stratified for estimated glomerular filtration rate using the 4-variable modification of diet in renal disease (MDRD) equation ($eGFR_{MDRD}$) (Levey AS, et al. Ann Intern Med. 1999;130:461-70), with 3 strata: > 60, 30 to 60, and < 30 mL/min/1.73 m^2 ($eGFR_{MDRD}$ > 60, 30 to 60, and < 30 groups, respectively). Each stratum was to contain a minimum of 6 subjects and up to 12 subjects.

This trial was started in subjects with $eGFR_{MDRD} \geq 30$ mL/min/1.73 m^2. Following determination of the effects in subjects with $eGFR_{MDRD} \geq 30$ mL/min/1.73 m^2, subjects with $eGFR_{MDRD} < 30$ mL/min/1.73 m^2 were entered as appropriate. If necessary, subjects withdrawn from the trial were to be replaced.

Overall, 29 subjects were enrolled in this trial as follows: 10 subjects were enrolled in the $eGFR_{MDRD}$ > 60 group, 9 subjects completed the trial, and 1 subject discontinued early due to an adverse event (AE); 10 subjects were enrolled in the $eGFR_{MDRD}$ 30 to 60 group, 9 subjects completed the trial, and 1 subject discontinued early due to an AE; and 9 subjects were enrolled in the $eGFR_{MDRD}$ < 30 group, and 9 subjects completed the trial.

All 29 subjects were included in the safety analysis. Twenty-seven subjects were included in the pharmacodynamic (PD) analysis. Subject [redacted] (> 60 mL/min/1.73 m^2) and Subject [redacted] (30 to 60 mL/min/1.73 m^2) had no postdose assessments and were excluded from the PD analysis. Subject [redacted] (< 30 mL/min/1.73 m^2) took a diuretic, during the post treatment period. Therefore, the PD analysis was also performed with Subject [redacted] excluded. In the analysis below, the mean post treatment values in the $eGFR_{MDRD}$ < 30 group are reported with Subject [redacted] excluded.

Diagnosis and Main Criteria for Inclusion: Subjects were male or female; between 18 and 70 years of age, inclusive, with a diagnosis of ADPKD by Ravine category. In addition, $eGFR_{MDRD}$, as assessed by the MDRD equation based on an average of 2 creatinine measurements, fell into one of the following strata:

- Group A: $eGFR_{MDRD}$ > 60 mL/min/1.73 m^2;
- Group B: $eGFR_{MDRD}$ 30 to 60 mL/min/1.73 m^2;
- Group C: $eGFR_{MDRD}$ < 30 mL/min/1.73 m^2.

Test Product, Dose, Mode of Administration, Batch or Lot No(s): Initially, each subject received an oral 45 mg AM/15 mg PM split dose regimen (45/15 mg) of tolvaptan for 1 week, with the larger dose upon awakening each day followed by the smaller dose approximately 8 hours later. If the subject tolerated this dose, the daily split dose was increased to a 60 mg AM/30 mg PM split dose regimen (60/30 mg) for 1 week, followed by a 90 mg AM/30 mg PM split dose regimen (90/30 mg) the successive week as tolerated.

Tolvaptan was manufactured by Otsuka Pharmaceutical Co., Ltd. and supplied as 15- and 30-mg tablets (lots 09I94A015A and 09J77A030A, respectively).

Reference Product, Dose, Mode of Administration, Batch or Lot No(s): Not applicable.

Criteria for Evaluation:
Primary Outcome Variables:
Pharmacodynamics: The primary outcome variables were mGFR as determined by iothalamate clearance, ERPF as determined by hippuran clearance, and filtration fraction (mGFR/ERPF).

Secondary Outcome Variables:
Pharmacokinetics of tolvaptan in plasma: Secondary pharmacokinetic (PK) variables were maximum (peak) plasma concentration (C_{max}), time to maximum (peak) plasma concentration (t_{max}), and area under the concentration-time curve calculated from zero to 5 hours postdose (AUC_{0-5h}) at the Final Treatment visit.

Pharmacodynamics: Secondary PD variables were urine volume (24-hour split urine sample and 2-hour urine collections), calculated FWC, and short-term changes in TKV as percent change from baseline at the Final Treatment visit (after approximately 3 weeks of treatment) and at the Post Treatment visit (after approximately 3 weeks off treatment) measured by magnetic resonance imaging.

Safety: The safety variables were AEs, vital signs, clinical laboratory test results, physical examinations, and electrocardiograms (ECGs).

Pharmacokinetic/pharmacodynamic Methods:
Bioanalytical: Plasma concentrations of tolvaptan and its metabolites, DM-4103 and DM-4107, were quantified by a validated assay using high performance liquid chromatography with tandem mass spectrometric detection. Serum and urine chemistries; iothalamate, hippuran, plasma renin, and serum cystatin C concentrations; and plasma aldosterone and copeptin concentrations were determined by the clinical chemistry laboratory according to their standard operating procedures.

Pharmacokinetics: Plasma concentrations of tolvaptan, DM-4107, and DM-4103 were analyzed using noncompartmental methods.

Pharmacodynamics: The mGFR was considered equivalent to iothalamate clearance. The ERPF was considered equivalent to hippuran clearance. Filtration fraction was calculated as mGFR divided by ERPF.

All clearances except FWC were determined as urine excretion rate of the analyte (mL/min) times amount excreted in urine divided by the average serum concentration over the urine collection interval; the duration of the collection interval was calculated using actual times, not nominal times. Urine flow rate minus osmolar clearance was used to determine FWC.

Pharmacokinetics/pharmacodynamics: Correlations of tolvaptan C_{max} and AUC_{0-5h} with mGFR were determined.

Statistics: The PK and PD variables were summarized by treatment group, visit, and time point using descriptive statistics. Changes from baseline for PD variables were also summarized using descriptive statistics. The Wilcoxon signed-rank test was used to determine the significance of the change from baseline and, in a separate analysis, the Wilcoxon rank-sum test was used to test if the percent change from baseline was different between $eGFR_{MDRD}$ groups.

Pharmacokinetic Results: A summary of tolvaptan PK parameters for subjects with evaluable concentrations is presented below.

Mean (SD) Tolvaptan Pharmacokinetic Parameters Following a 90 mg Tolvaptan Dose after 3 Weeks of Tolvaptan Treatment in ADPKD Subjects with Varying Degrees of Renal Function

Parameter	**$eGFR_{MDRD}$ > 60 mL/min/1.73 m^2 (N = 8)**	**$eGFR_{MDRD}$ 30 to 60 mL/min/1.73 m^2 (N = 9)**	**$eGFR_{MDRD}$ < 30 mL/min/1.73 m^2 (N = 9)**
C_{max} (ng/mL)	828 (297)	591 (235)	840 (355)
t_{max} (h)[a]	2.00 (1.00-3.00)	2.00 (1.00-3.00)	2.00 (1.00-5.00)
AUC_{0-5h} (ng·h/mL)	2850 (774)	2140 (863)	3100 (1060)

SD = standard deviation.

[a]Median (minimum-maximum).

Pharmacodynamic Results: A summary of the mean (standard deviation [SD]) percent change from baseline in the renal function parameters and TKV is presented in the table below.

Mean (SD) Values and Percent Change From Baseline in Renal Function Parameters and Total Kidney Volume Following a 90 or 60 mg Tolvaptan Dose After 3 Weeks of Tolvaptan Treatment in ADPKD Subjects With Varying Degrees of Renal Function

Parameter	$eGFR_{MDRD}$ > 60 mL/min/1.73 m^2 (N = 9)	$eGFR_{MDRD}$ 30 to 60 mL/min/1.73 m^2 (N = 9)	$eGFR_{MDRD}$ < 30 mL/min/1.73 m^2 (N = 9)
mGFR (mL/min)			
Final Treatment	104.3 (22.7)	60.1 (16.6)	28.6 (10.0)
Percent Change	−7.4 (8.7)	−8.4 (6.8)[a]	−2.1 (5.5)
ERPF (mL/min)			
Final Treatment	319.0 (77.6)	211.7 (47.0)	96.4 (28.6)
Percent Change	−5.7 (11.7)	−4.0 (7.5)	−1.1 (6.1)
Filtration Fraction			
Final Treatment	0.330 (0.024)	0.283 (0.023)	0.293 (0.029)
Percent Change	−1.372 (5.145)	−4.235 (5.253)	−3.265 (4.358)
Total Kidney Volume (mL)			
Final Treatment	1315.1 (703.5)	1735.3 (1093.8)	4276.2 (3187.0)
Percent Change from Baseline	−4.5 (3.7)[a]	−4.6 (2.7)[a,b]	−1.9 (1.9)[a]

Note: Subject [redacted] ($eGFR_{MDRD}$ < 30 group) was excluded from the post treatment analysis due to his use of the diuretic bumetanide after the Final Treatment visit; N = 8 for the $eGFR_{MDRD}$ < 30 group at the Post Treatment visit.

[a] P-value for assessment of significance for the change from baseline < 0.05.

[b] P-value for comparison of change in $eGFR_{MDRD}$ 30 to 60 group to change in $eGFR_{MDRD}$ < 30 group < 0.05.

A summary of the mean (SD) change from baseline in the other primary PD parameters is presented in the table below.

Mean (SD) Values and Change From Baseline in 24-hour Urine Volume, Total Urine Volume During Renal Function Testing, and Free Water Clearance Following a 90 or 60 mg Tolvaptan Dose After 3 Weeks of Tolvaptan Treatment in ADPKD Subjects With Varying Degrees of Renal Function

Parameter	$eGFR_{MDRD}$ > 60 mL/min/1.73 m^2 (N = 9)	$eGFR_{MDRD}$ 30 to 60 mL/min/1.73 m^2 (N = 9)	$eGFR_{MDRD}$ < 30 mL/min/1.73 m^2 (N = 9)
24-hour Collection (mL)			
Final Treatment	6532.8 (2036.9)	6233.9 (1307.1)	5024.4 (1767.5)
Change from Baseline	4551.1 (1792.7)[a,b]	3274.4 (1293.3)[a]	2215.0 (1142.0)[a,c]
2-hour Collections-Total (mL)			
Final Treatment	1948.9 (740.5)	1540.0 (322.8)	1187.8 (304.7)
Change from Baseline	888.9 (730.3)[a]	625.6 (478.5)[a]	356.7 (283.2)[a]

Parameter	$eGFR_{MDRD}$ > 60 mL/min/1.73 m^2 (N = 9)	$eGFR_{MDRD}$ 30 to 60 mL/min/1.73 m^2 (N = 9)	$eGFR_{MDRD}$ < 30 mL/min/1.73 m^2 (N = 9)
Free Water Clearance (mL/min)			
Final Treatment	5.219 (2.215)	4.069 (0.987)	2.673 (0.618)
Change from Baseline	4.334 (3.268)[a]	2.822 (1.715)[a]	1.701 (1.225)[a]

Note: Subject [redacted] ($eGFR_{MDRD}$ < 30 group) was excluded from the post treatment analysis due to his use of the diuretic bumetanide after the Final Treatment visit; N = 8 for the $eGFR_{MDRD}$ < 30 group at the Post Treatment visit.

[a] P-value for assessment of significance for the change from baseline < 0.05.

[b] P-value for comparison of change in $eGFR_{MDRD}$ > 60 group to change in $eGFR_{MDRD}$ 30 to 60 group < 0.05.

[c] P-value for comparison of change in $eGFR_{MDRD}$ > 60 group to change in $eGFR_{MDRD}$ < 30 group < 0.05.

Following tolvaptan treatment, filtration fraction was unchanged. There was a trend for negative changes in mGFR, ERPF, and TKV and positive changes in urine volumes and FWC with increasing renal function.

Blood copeptin, cystatin C, creatinine, osmole, sodium, and uric acid concentrations increased following tolvaptan administration while albumin, aldosterone, plasma renin, potassium, and urea concentrations did not.

Changes in creatinine clearance paralleled mGFR, though uric acid clearance was reduced by a greater than proportional extent.

Pharmacokinetic/pharmacodynamic Results: There was no correlation between tolvaptan C_{max} or AUC_{0-5h} and mGFR.

Safety Results: All 29 subjects enrolled in the trial received at least 1 dose of trial medication. The administration of titrated split doses of tolvaptan (45/15, 60/30, and 90/30 mg) over a 3-week period resulted in no clinically relevant changes in clinical laboratories, vital signs, ECGs, or physical examinations in and subject, regardless of renal function status. All subjects experienced at least 1 treatment-emergent adverse event (TEAE) during the trial. The most frequently-reported TEAEs in the $eGFR_{MDRD}$ > 60, 30 to 60, and < 30 groups, respectively, were Thirst (10/10 subjects, 100.0%; 10/10 subjects, 100.0%; and 8/9 subjects, 88.9%), Polyuria (10/10 subjects, 100.0%; 9/10 subjects, 90.0%; and 7/9 subjects, 77.8%), Nocturia (8/10 subjects, 80.0%; 6/10 subjects, 60.0%; and 6/9 subjects, 66.7%), and Dry Mouth (6/10 subjects, 60.0%; 5/10 subjects, 50.0%; and 5/9 subjects, 55.6%). There were fewer reports of these TEAEs in subjects with diminished renal function ($eGFR_{MDRD}$ < 30 group).

A TEAE of Angina pectoris was reported in Subject [redacted] on Day 9 and elevated to a serious TEAE because the subject was hospitalized for an angiogram on Day 34. The results of the exam showed no new coronary damage, and the serious TEAE was resolved on Day 36. A serious TEAE of Polyuria from Days 2 to 5 was reported in

Subject [redacted] that resulted in trial medication discontinuation on Day 4. A nonserious TEAE of Dry Mouth from Days 14 to 53 was reported in Subject [redacted] that resulted in discontinuation of trial medication on Day 14. This subject had been diagnosed with laryngeal carcinoma in 1998 and treated with radiation in the throat.

Small mean increases from baseline in serum chemistry values were observed in sodium, which is known to be an effect of the mechanism of action of tolvaptan. No clinically meaningful changes were observed in creatinine, potassium, uric acid, calcium, cholesterol, glucose, sodium, or liver function serum chemistry parameters. No notable mean changes from baseline or shifts relative to baseline were observed in urinalysis or hematology test values. Two subjects had TEAEs of Hypernatraemia related to serum chemistry results after trial medication administration. One subject had a TEAE of Anaemia related to hematology results.

No notable mean changes from baseline were observed for clinical measurements in this trial. One subject had a TEAE of Palpitations, 2 subjects had TEAEs of Pyrexia, and 1 subject each had TEAEs of Bradycardia and Weight Decreased. Four subjects had potentially clinically significant categorical changes in an ECG parameter. One subject had a new onset QT interval corrected for heart rate by Bazett's formula (QTcB) interval > 500 msec. Three subjects had an increase in QTcB interval between 30 and 60 msec.

Conclusions:

- Following a 90-mg dose, tolvaptan C_{max} and $AUC_{0\text{-}5h}$ were not affected by mGFR and were not correlated with any PD endpoint.
- While tolvaptan's effects decreased as renal function decreased, they remained significant even in the group having chronic kidney disease Stage 4 renal function despite the small sample size.
- Subjects receiving tolvaptan for 3 weeks had modest (approximately 8% for subjects with $eGFR_{MDRD}$ > 60 and 30 to 60 mL/min/1.73 m^2 and 2% for subjects with $eGFR_{MDRD}$ < 30 mL/min/1.73 m^2), reversible reductions in mGFR. These reductions strongly correlated with $eGFR_{MDRD}$ and were consistent with serum creatinine increases observed in prior clinical trials. The mean changes in mGFR were not clinically meaningful, even in subjects with low levels of renal function.
- The percent change from baseline in ERPF, as measured by clearance of hippuran, decreased as baseline mGFR decreased and was highly correlated with the percent change in mGFR.
- Filtration fraction appeared minimally reduced across groups.
- Tolvaptan-induced changes in urine output and FWC are lower as renal function decreases.
- Total kidney volume was slightly reduced after 3 weeks of tolvaptan treatment; mean changes were −4.6%, −4.5%, and −1.9% in subjects with $eGFR_{MDRD}$ > 60, 30 to 60, and < 30 mL/min/1.73 m^2, respectively. At 3 weeks post treatment, mean changes had returned toward baseline.

- Blood copeptin, cystatin C, creatinine, osmole, sodium, and uric acid concentrations were increased following tolvaptan administration while albumin, aldosterone, plasma renin, potassium, and urea concentrations were not. At 3 weeks post treatment, all concentrations were similar to baseline values.
- While changes in creatinine clearance paralleled mGFR, uric acid clearance was reduced by a greater than proportional extent.
- The administration of titrated split doses of tolvaptan from 45/15 to 90/30 mg over a 3-week period resulted in no clinically relevant changes in clinical laboratories, vital signs, ECGs, or physical examinations in subjects with ADPKD in this trial, regardless of renal function status.
- The most-frequently reported TEAEs (≥ 50% of subjects) were Thirst, Polyuria, Nocturia, and Dry Mouth, which are consistent with the pharmacologic action of tolvaptan.
- The incidence of TEAEs was similar across all stages of renal function.