Synopsis

Clinical Report Synopsis for Protocol 156-03-244

Name of Company: Otsuka Pharmaceutical Development & Commercialization, Inc

Name of Product: Tolvaptan (OPC-41061)

Trial Title: International, Multicenter, Study of One-year, Open-label, Titrated Oral Tolvaptan Tablet Administration in Patients with Chronic Hyponatremia: Extension to Studies 156-02-235 and 156-03-238 to Assess One-year Safety

Safety and sodium Assessment of Long-term Tolvaptan With hyponatremia: A year-long, open-label Trial to gain Experience under Real-world conditions ("SALT WATER")

Investigator(s) and Trial Center(s): Multicenter (33 centers; multinational)
Tomas Berl, MD, Coordinating Investigator

Publications: Berl T, Quittnat-Pelletier F, Verbalis JG, Schrier RW, Bichet DG, Ouyang J, et al. Oral tolvaptan is safe and effective in chronic hyponatremia. J Am Soc Nephrol. 2010 Feb 25. [Epub ahead of print].

Studied Period:

Date of first signed informed consent (trial initiation date): 26 May 2004
Date of last trial observation (trial completion date): 27 Oct 2009

Clinical Phase: 3

Objectives: To assess the safety of long-term tolvaptan use in subjects previously enrolled in shorter-term phase 3 trials and gather information on the natural history of hyponatremia in the context of tolvaptan therapy and underlying disease states.

Methodology: This was an international, multicenter, open-label hyponatremia trial designed to assess the long-term safety of titrated oral tolvaptan (15, 30, or 60 mg once daily [QD]) in subjects with chronic hyponatremia, conducted as an extension to 2 pivotal randomized, placebo-controlled, phase 3 hyponatremia trials. A total of 111 subjects were enrolled at 33 active trial centers in the United States (US), Canada, and European Union (EU).

Subjects provided informed consent and were screened up to 2 days prior to potential enrollment. Subjects eligible for enrollment must have had persistent or recurrent hyponatremia defined as having a sodium level < 135 mEq/L and been in a euvolemic or hypervolemic state at screening. Subjects with sodium levels fluctuating near this threshold may have been rescreened.

Subjects were not randomized for the extension trial. Enrolled subjects began treatment with 15 mg tolvaptan QD. A titration between target doses of 15 mg, 30 mg, or 60 mg of trial medication was based on the subject's change in serum sodium concentration and clinical tolerance of the trial medication. The dose titration scheme was designed to bring the subject into a stable, normal range of blood sodium over the initial introduction of therapy. Serum sodium levels were measured at screening, predose on Day 1, and 8 hours postdose (± 2 hours) on Day 1; during the titration phase on Days 2 to 14 (required on Day 2 and following each dose adjustment, and at the required clinic visit on Day 14); and at regularly scheduled visits for the duration of trial. As a guideline, titration to the next higher dosage proceeded if the subject's change in serum sodium level was < 5 mEq/L from the previous day's measurement and was ≤ 135 mEq/L. Titration to the next higher dose was not recommended if the subject's serum sodium level was > 135 mEq/L or the change in serum sodium level was ≥ 5 mEq/L from the previous day's measurement. Down-titration to the next lower dosage was to occur if the subject's serum sodium was between 140 and 145 mEq/L and the degree of urine output or other symptoms were problematic; if the subject's sodium was consistently > 145 mEq/L; or if the serum sodium level increased at too great a rate (either > 12 mEq/L/24 hours or > 8 mEq/L/8 hours on the first day). If the latter conditions occurred, the investigator was to confirm the results with a stat repeat test and if confirmed, the investigator was to contact the medical monitor for guidance. In contrast to the 2 pivotal parent trials, the absolute requirement for overnight observation was not required for this trial; the only requirements to assess response were postdose serum sodium measurements (initially within 6 to 10 hours postdose on Day 1) as well as clinical tolerance (overnight observation was required only if warranted in the investigator's medical judgment).

The dose level for each individual subject was determined at the end of the titration period and was to be maintained (administered orally QD) for the remainder of the trial. During the trial treatment period, subjects continued their current medications, and may have been offered standard therapies for hyponatremia as clinically indicated. Subjects who entered the trial with a sodium value < 130 mEq/L may have had their fluid restricted to 1 liter/day or less, if necessary, at the discretion of the investigator (if possible, fluid restriction was to be avoided for the first 24 hours of titration). The investigator may have periodically assessed the subject's clinical need to continue in the trial (particularly during assessment of participation in trial extensions at Week 58, Week 106, and Week 214). A safety follow-up visit was performed at least 7 days after the last day of trial medication. Subjects who were evaluated at the last scheduled visit during the treatment period (Week 58, Week 106, or Week 214 depending on which protocol amendment they were treated under) were defined as trial completers. Following the post-Week 214 follow-up visit, subjects may have entered an off-drug reassessment period for the final trial extension. This final trial extension provided tolvaptan on an outpatient basis to subjects who previously completed Week 214, while regulatory authority approval was pending.

Trial participation was up to 264 weeks followed by a 1-week follow-up assessment. The trial was to conclude the earlier of September 2009, or when the last subject terminated,

or when the sponsor terminated the trial in each region based on approval/non-approval status or other mechanisms of providing therapy.

Number of Subjects: Enrollment was limited to subjects previously enrolled in 1 of 2 tolvaptan phase 3 studies for hyponatremia (Trials 156-02-235 or 156-03-238). Although no predetermined sample size was calculated for this open-label trial, anticipated enrollment was up to 200 subjects.

A total of 111 subjects were enrolled in this open-label trial (included 56 subjects who previously received tolvaptan and 55 subjects who previously received placebo in the parent trials). A total of 47/111 subjects completed the trial at the following timepoints: Week 58 (6 subjects, 5.4%), Week 106 (3 subjects, 2.7%), Week 216 (38 subjects, 34.2%). Ten of the 38 subjects who completed at Week 216 enrolled in and completed the extension phase (up to Week 264/ET followed by the 7-day follow-up visit). A total of 64/111 subjects (57.7%) prematurely discontinued from the trial; the primary reason for discontinuation was AEs.

All 111 subjects were included in the ITT population. Of these, 110 (99.1%) were analyzed for efficacy (Subject 135-1011 in the prior placebo group did not have a postbaseline serum sodium measurement and therefore was excluded from the ITT efficacy analysis). All 111 subjects were included in the safety analysis.

Diagnosis and Main Criteria for Inclusion: Consenting adult subjects of either gender who had successfully completed participation in 1 of the 30-day, randomized, blinded, placebo-controlled trials within the tolvaptan phase 3 hyponatremia program (Trials 156-02-235 or 156-03-238) were considered for enrollment if they showed evidence of need for continued therapy. Subjects were required to present with persistent or recurrent hyponatremia (serum sodium concentration of < 135 mEq/L associated with a euvolemic (eg, syndrome of inappropriate antidiuretic hormone secretion [SIADH]) or hypervolemic (eg, congestive heart failure [CHF] or cirrhosis) condition. However, justification for enrollment of subjects whose sodium at entry was in the normal range (> 135 mEq/L) may have been given to, and accepted by, the medical monitor for the trial.

Test Product, Dose, Mode of Administration, Batch or Lot No(s): Tolvaptan was manufactured by Otsuka Pharmaceutical Co, Ltd (Japan) and supplied as15- and 30-mg oral tablets. Trial medication was administered as 15 mg (1 × 15-mg tablet), 30 mg (1 × 30-mg tablet) or 60 mg (2 × 30-mg tablets) QD.

Batch numbers used for tolvaptan tablets administered in the trial were:

- Tolvapatan 15-mg tablets: 02C80A015B, 04C77A015, 05D73A015A, and 07I96A015.
- Tolvapatan 30-mg tablets: 03L73A030E, 04C77A030A, 05I84A030C, and 08F80A030A.

Reference Product, Dose, Mode of Administration, Batch or Lot No(s): Not applicable, as this was an uncontrolled, open-label trial.

Criteria for Evaluation:

Primary Outcome Variables

Safety: Safety of long-term tolvaptan therapy was assessed by regular monitoring of adverse events (AEs), vital signs (weight, heart rate [HR], and blood pressure [BP]), electrocardiogram (ECG) measurements, and clinical laboratory parameters (including critical electrolytes, glucose, renal function, liver function tests, blood cell counts, and coagulation parameters) as obtained at baseline, during titration, and at regularly scheduled intervals throughout the remainder of the trial, including follow-up.

Other safety assessments included directed physical examination.

Secondary Outcome Variables

Efficacy: The secondary efficacy outcome variables were serum sodium levels, body weight, need for prescription treatment of hyponatremia (fluid restriction, hypertonic saline, or other medications), 12-Item Short-form (SF-12) Health Survey Physical Component Summary (PCS) and Mental Component Summary (MCS) scores, and the Hyponatremia Disease-specific Survey.

The protocol-specified secondary efficacy endpoints were as follows:

1) Sodium measurements obtained at designated intervals were compared to each subject's baseline sodium concentration at the beginning of placebo-controlled therapy in their original trial (parent trial) and from baseline on initiation of therapy in the open-label trial (current trial).
2) Percentage of subjects with varying degrees of hyponatremia ("severe" < 130 mEq/L, "mild" 130 to 135 mEq/L, "normal" > 135 mEq/L) at baseline and each trial visit.
3) Percentage of subjects requiring prescription of fluid restriction for the express purpose of treating hyponatremia during each period of the trial, assessed descriptively at each visit.
4) Percentage of subjects requiring prescription of hypertonic saline for the express purpose of treating hyponatremia during each period of the trial, assessed descriptively at each visit.
5) Percentage of subjects requiring prescription of other medicines for the express purpose of treating hyponatremia during each period of the trial, assessed descriptively at each visit.
6) Body weight at each visit (assessed only for those with clinical evidence of hypervolemia at baseline).
7) Change from baseline in the SF-12 Health Survey PCS and MCS scales at baseline, Day 31, Week 26, Week 34, Week 42, Week 50, Week 58, Week 70, Week 82, Week 94, Week 106, and Week 214/ET while on tolvaptan.

8) Change from baseline in the Hyponatremia Disease-specific Survey at baseline, Day 31, Week 26, Week 34, Week 42, Week 50, Week 58, Week 70, Week 82, Week 94, Week 106, and Week 214/ET while on tolvaptan.

Safety: Not applicable.

Statistical Methods:

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

Efficacy Methods: No primary efficacy analysis was planned. Secondary efficacy analyses were performed for the intent-to-treat (ITT) population, defined as all enrolled subjects. Two subsets of the ITT dataset included all enrolled subjects who had baseline serum sodium < 130 mEq/L (severe) or baseline serum sodium ≥ 130 mEq/L (mild). For a variable defined as a change from baseline in a clinical or laboratory measurement, only data from subjects who had observations for the measurement both at baseline and at least one postbaseline visit were analyzed.

For analyses by visit, 2 types of datasets were defined. The observed cases (OC) dataset consisted of only data points obtained from subjects who were evaluated at the visit, without missing trial medication consecutively for 14 days between the previous visit and the current visit. In the last observation carried forward (LOCF) dataset, missing data were filled in by the subject's preceding nonmissing value, except that baseline values were not carried forward.

Secondary efficacy analyses were performed on the following endpoints using the methods described for each. In general, descriptive statistics (eg, proportion, median, mean, standard deviation [SD], minimum and maximum) were calculated for efficacy variables and for prospectively-defined subgroups (eg, baseline sodium concentration, hyponatremia severity, hyponatremia etiology):

1) Sodium measurements obtained at designated intervals were compared to each subject's baseline sodium level at the beginning of placebo-controlled therapy in their original trial and from baseline on initiation of therapy in the open-label trial. Data were summarized for each protocol-specified visit as well as for subgroups of subjects with baseline serum sodium < 130 mEq/L (severe) and baseline serum sodium ≥ 130 mEq/L (mild) in the parent and current trials and baseline etiology of hyponatremia (CHF, cirrhosis, SIADH, other).
2) Percentage of subjects with varying degrees of hyponatremia ("severe" < 130, "mild" 130 to 135, "normal" > 135 mEq/L) at baseline and each trial visit. Data were summarized at each visit as well as for subgroups of subjects with baseline serum sodium < 130 mEq/L (severe) and baseline serum sodium ≥ 130 mEq/L (mild) in the parent and current trials at baseline and each trial visit. An additional analysis of this endpoint was performed to summarize normalization of

sodium levels (to collapse the 3 hyponatremia categories into 2 [≤ 135 and > 135 mEq/L]) using similar methods.

3) Percentage of subjects requiring a prescription of fluid restriction for the express purpose of treating hyponatremia during each period of the trial was determined by Kaplan-Meier analysis using time to first event as well as summary statistics for overall incidence.
4) Body weight at each visit (assessed only for those with clinical evidence of hypervolemia at baseline) was summarized using descriptive statistics.
5) Change from baseline in the SF-12 Health Survey PCS and MCS scales were summarized for all visits with SF-12 Health Survey data collection specified as well as for subgroups of subjects with baseline serum sodium < 130 mEq/L (severe) and baseline serum sodium ≥ 130 mEq/L (mild) in the parent and current trials.
6) Change from baseline in Hyponatremia Disease-specific Survey PCS and MCS scores were summarized for scheduled visits up to visit Week 106 (based on the original protocol). Analyses were performed separately on data collected under 2 different versions of the Hyponatremia Disease-specific Survey.

Variables 1, 2, 5, and 6 above were summarized using both LOCF and OC analysis at the protocol-defined visits. For variables 1 and 5, paired t-tests were performed for changes from baseline in both the parent and current trials for each scheduled visit. For variables 4 and 6, paired t-tests were performed for changes from baseline in the current trial (only) for each scheduled visit. All statistical testing used a significance level of 0.05, without making adjustment for multiplicity.

Secondary efficacy endpoints that were not formally analyzed in the final dataset included the percentage of subjects who required prescription hypertonic saline and the percentage of subjects requiring prescription of other medicines for the express purpose of treating hyponatrenia. Other minor modifications to the planned analyses of the secondary efficacy endpoints were also noted.

Pharmacokinetic/pharmacodynamic Methods: Not applicable.

Safety Methods: Safety analyses were conducted on the safety population, defined as all enrolled subjects who took at least one dose of trial medication. Safety was assessed both qualitatively and quantitatively and summarized using descriptive statistics, as appropriate. The incidences of treatment-emergent AEs (TEAEs) were summarized for the total population as well as by prior treatment group for all TEAEs, TEAEs by severity, potentially drug-related TEAEs, treatment-emergent serious adverse events (SAEs), and discontinuations due to TEAEs.

For continuous safety variables (clinical laboratory tests, vital sign measurements, and ECG parameters), descriptive statistics were used to summarize mean changes from baseline as well as the original value at each visit. Shift tables were also produced to assess changes from baseline relative to the normal range (low-normal-high at baseline to

low-normal-high at a postbaseline visit) for the clinical laboratory parameters (serum chemistry and hematology). Potentially clinically significant changes in clinical laboratory parameters, vital signs, and ECGs were identified using protocol-defined criteria.

Efficacy Results:
Statistically significant increases in serum sodium concentrations were observed from baseline (parent and current trial) at all on-treatment visits up to Week 214 in the total population using both LOCF and OC. By previous treatment group, statistically significant increases from baseline (parent and current trial) were observed up to Week 214 in the prior placebo group and up to Week 202 in the prior tolvaptan group. The increases in serum sodium concentration in the prior placebo group, which received tolvaptan for the first time in this open-label trial, were similar in magnitude to those observed in the group that had previously received tolvaptan. In the prior tolvaptan group, increases in serum sodium concentration were consistent over time, indicating no apparent loss of effect. Within 7 days following tolvaptan discontinuation (the follow-up visit), a decrease in serum sodium concentrations was observed in both the prior placebo and prior tolvaptan groups.

In the LOCF and OC analyses, statistically significant greater mean changes from baseline in serum sodium concentrations in the parent trial were observed at nearly all on-treatment visits past Day 1 in both the severe hyponatremia and mild hyponatremia subgroups. In the total population (OC), statistically significant greater mean changes in serum sodium concentration relative to baseline in the parent trial were consistently observed at all on-treatment visits from Day 1 postdose through Week 214 in subjects with CHF or SIAHD/Other, and after Day 1 postdose through Week 18, Week 42, Week 50, Week 82, and Week 94 in the cirrhosis subgroup. The changes from baseline in serum sodium concentrations were similar for both the hyponatremia subgroup and etiology analyses when referenced from baseline in the current trial. In the total population, a decrease in mean serum sodium concentrations was observed within 7 days following tolvaptan discontinuation (the follow-up visit) for subjects with SIADH/Other, and to a lesser degree for subjects with CHF. Subjects with cirrhosis however, generally did not rebound in response to treatment discontinuation.

In the LOCF and OC analyses, the percentage of subjects who had normalized serum sodium concentrations at each on-treatment visit from Day 31 through Week 214 in the total population was greater than the percentage of those who did not (achieve normalized serum sodium concentrations). This was especially evident for subjects in the severe hyponatremia subgroup, wherein the percentage with normalized concentrations ranged from 55.1% to 100.0% between Day 31 and Week 214.

Overall, very few subjects required additional fluid restriction (13/111 subjects, 11.7%). Although the percentage of subjects who required fluid restriction was comparable in the prior placebo group (7 subjects) compared with in the prior tolvaptan group (6 subjects), subjects in the prior placebo group had a shorter time to the first need for fluid restriction (mean = 71 days) compared with the prior tolvaptan group (mean = 146 days). During

this open-label trial, subjects with severe hyponatremia had a longer time to first fluid restriction than subjects with mild hyponatremia.

Mean changes from baseline in body weight were variable over time; in general, no statistically significant changes in body weight were observed in hypervolemic subjects in the total population or when evaluated by previous treatment group.

Changes from baseline in the SF-12 Health Survey PCS and MCS scores generally were variable over time, although the majority of changes from baseline in the parent trial were slight increases (improvement) in scores. Hyponatremia Disease-specific Survey PCS and MCS scores were variable over time with only nominal changes from baseline observed. Statistical significance was not reached for most time points for any of the analysis sets for either SF-12 Health Survey or Hyponatremia Disease-specific Survey PCS or MCS scores.

Safety Results:

Extent of Exposure:

All 111 subjects were exposed to tolvaptan and were included in the safety analysis. The mean daily dose of tolvaptan increased to approximately 30 mg/day over the first 12 to 16 weeks and remained at that level throughout the remainder of the trial. The majority of subjects were exposed to tolvaptan for a minimum of > 56 to 58 weeks (79/111, 71.2%) and nearly half were exposed to tolvaptan for a minimum of > 98 to 106 weeks (55/111, 49.5%). Twelve (of 111) subjects (10.8%) were exposed to tolvaptan for > 202 to 214 weeks and 6/111 subjects (5.4%) had > 214 weeks of exposure.

Adverse Events:

An overview of AEs is provided in the following table:

Summary of Adverse Events

Number of:	**Prior Treatment (Parent Trial)**		**Open-label Tolvaptan**
	Tolvaptan	**Placebo**	
Subjects treated, N[a]	56	55	111
Subject days of drug exposure	40,656	38,509	79,165
Subjects with AEs, n (%)	52 (92.9)	53 (96.4)	105 (94.6)
AEs, N	880	878	1758
Subjects with TEAEs, n (%)	52 (92.9)	53 (96.4)	105 (94.6)
TEAEs, N	681	654	1335
Subjects with treatment-emergent SAEs, n (%)	37 (66.1)	39 (70.9)	76 (68.5)
Subjects with severe TEAEs, n (%)	37 (66.1)	36 (65.5)	73 (65.8)
Subjects discontinued trial medication due to TEAE, n (%)	9 (16.1)	10 (18.2)	19 (17.1)
Subjects discontinued trial medication due to TEAE or death, n (%)	16 (28.6)	12 (21.8)	28 (25.2)
Subjects died, n (%)	12 (21.4)	7 (12.7)	19 (17.1)

SAE = serious adverse event;.TEAE = treatment-emergent adverse event.

Note: Parent trial = Trial 156-02-235 or Trial 156-03-238.

[a]Percentages based on number of subjects treated. Subjects are counted once per category.

Overall, TEAEs that occurred at a 10% or greater incidence in all subjects who received open-label tolvaptan were peripheral oedema and hyponatraemia (each 25/111, 22.5%); anaemia and diarrhoea (each 20/111, 18.0%); nausea and urinary tract infection (each 19/111, 17.1%); fatigue and headache (each 15/111, 13.5%); thirst and hypokalaemia (each 14/111, 12.6%); ascites, pneumonia, and hypotension (each 13/111, 11.7 %); and congestive cardiac failure, back pain, dizziness, and pollakiuria (each 12/111, 10.8%). Of the 25 subjects with a reported TEAE of hyponatraemia, 13 were not currently taking open-label therapy at the time of the event. The majority of all TEAEs were mild or moderate in intensity. Treatment emergent-adverse events classified as severe by 5% or greater incidence were hyponatraemia (9/111, 8.1%), pneumonia (9/111, 8.1%), cardiac failure (7/111, 6.3%), and congestive cardiac failure (7/111, 6.3%). The most frequently reported potentially drug-related TEAEs (by ≥ 5% incidence in the total population) were pollakiuria (12/111, 10.8%), thirst (11/111, 9.9%), and fatigue (6/111, 5.4%).

A total of 19 deaths were reported during the open-label trial (12 subjects in the prior tolvaptan group and 7 subjects in the prior placebo group). The causes of death appear to be mostly related to underlying conditions. TEAEs that resulted in death in 2 or more subjects were cardiac failure (5/111, 4.5%) and renal failure (2/111, 1.8%). One subject experienced a fatal TEAE of hepatorenal syndrome that was considered possibly drug-related by the investigator; all other deaths were considered not likely or unrelated to trial medication.

A total of 76/111 subjects (68.5%) reported at least one treatment-emergent SAE during the trial (37/56 subjects [66.1%] in the prior tolvaptan group and 39/55 subjects [70.9%] in the prior placebo group). The most common SAEs (5% or greater incidence) reported during the trial included pneumonia and hyponatraemia (each 10/111, 9.0%), followed by cardiac failure and congestive cardiac failure (each 7/111, 6.3%). While the incidence of hyponatraemia, cardiac failure, and congestive cardiac failure by prior treatment group was relatively balanced, pneumonia was reported as an SAE with greater frequency in the prior tolvaptan group (9/56 subjects [16.1%] compared with 1/55 subjects [1.8%] in the prior placebo group).

A total of 19/111 subjects (17.1%) discontinued open-label tolvaptan due to a TEAE (9 in the prior tolvaptan group and 10 in the prior placebo group). The only TEAE that led to discontinuation that occurred in more than 1 subject was cardiac failure (2/111 subjects, 1.8%), which was reported for 1 subject from each prior treatment group.

Clinical Laboratory Results:

None of the mean changes from baseline or shifts from baseline in serum chemistry (with exception of shifts towards normal sodium) or hematology clinical laboratory values was considered to be clinically significant. While potentially significant changes in several parameters were observed, in most cases, the respective baseline values were also outside the normal range. There were no apparent trends in potentially clinically significant abnormal serum chemistry or hematology results nor notable differences observed between subjects who had previously received either tolvaptan or placebo in the parent trial.

Several chemistry laboratory abnormalities were reported as TEAEs. The 3 most common serum chemistry abnormalities reported as TEAEs (by ≥ 5% of subjects) were hyponatraemia (25/111 subjects, 22.5%), hypokalaemia (14/111 subjects, 12.6%), and hyperkalaemia (7/111 subjects, 6.3%). Thirteen of the 25 subjects who reported a TEAE of hyponatraemia were not taking open-label therapy at the time of the event (the AE was reported during a temporary dose interruption, during the post-treatment follow-up period upon completion of the trial, or other circumstance where the subject was not consistently taking trial medication, eg, noncompliance). The following chemistry laboratory abnormalities were considered SAEs: hyponatraemia (10 subjects), hyperkalaemia (3 subjects), hypoglycaemia (2 subjects), and increased blood creatinine, hypocalcaemia, and hypokalaemia (1 subject each). Two subjects discontinued trial medication due to TEAEs of increased blood creatinine and increased blood sodium, respectively.

The rate of increase in serum sodium level was also assessed. Five subjects (2 in the prior tolvaptan group and 3 in the prior placebo group) had increases in serum sodium concentrations ranging from 1.08 to 1.47 mEq/L/h within 6 to 10 hours after the initial dose of tolvaptan on Day 1. None of the 9 subjects evaluated at 8 hours postdose on Extension Day 1 experienced a rapid increase in serum sodium. In addition, 12 subjects (8 previously on tolvaptan and 4 previously on placebo) had serum sodium concentrations ≥ 145 mEq/L at some point during the trial. Of these 12, 5 subjects (4 from the prior tolvaptan group and 1 from the prior placebo group) had potentially clinically significant abnormal concentrations that ranged from 147 and 150 mEq/L and 1 subject discontinued trial medication on Day 15 due to an AE of increased blood sodium (serum sodium value was 145 mEq/L on Day 14). There were no deaths or other SAEs due to increases in serum sodium concentrations.

Several hematology abnormalities were reported as TEAEs. The most common serum chemistry abnormalities reported as TEAEs (by 2 or more subjects) were anemia (20/111 subjects, 18.0%), international normalized ratio (INR) increased (4/111 subjects, 3.6%), thrombocytopenia (2/111 subjects, 1.8%), and increased white blood cell (WBC) count (2/111 subjects, 1.8%). The following hematology abnormalities were considered SAEs: anemia (4 subjects) and increased INR (1 subject). No hematology abnormalities reported as TEAEs led to discontinuation of trial medication.

Vital Signs:

There were no apparent trends between groups by prior therapy or by visit, with the exception of supine systolic blood pressure (SBP) (slight decreases) and HR (slight increases), primarily observed in the prior placebo group throughout the trial. While mean SBP values at baseline were relatively consistent in both prior treatment groups as well as overall (values ranged from 127.2 to 127.8 mmHg), it was noted that median values were approximately 4 mmHg lower in the prior tolvaptan group compared with the prior placebo group (124 and 128 mmHg, respectively). This small degree of imbalance in the regression to the mean may, at least in part, account for the more pronounced reduction in SBP observed in the prior placebo group. Overall, the trends

towards increased HR and decreased SBP values in the prior placebo were not considered to be of clinical concern.

Mean changes from baseline in body weight were variable over time.

Overall, the incidence rates of potentially clinically significant vital sign abnormalities were similar between the 2 prior treatment groups, with the exception of changes in supine HR (potentially clinically significant decreases in supine HR [≤ 50 + decrease ≥ 15 bpm] were observed in 6 subjects in the prior tolvaptan group and no subjects in the prior placebo group).

Vital sign abnormalities reported as TEAEs in > 5% of all subjects were hypotension (13/111 subjects, 11.7%); hypertension (8/111 subjects, 7.2%); and pyrexia (6/111 subjects, 5.4%). Of these, hypertension and hypotension were reported as SAEs in 1 subject each. No vital sign abnormalities reported as TEAEs led to discontinuation of trial medication.

ECGs:
There were no clinically relevant changes from baseline over time in ECG values in the open-label population. Overall, the incidences of potentially clinically significant ECG abnormalities were low and relatively similar between the 2 prior treatment groups, with exception of the following categories: 30 to 60 msec changes in QTcF and > 60 msec changes in both QTcB and QTcF. The incidence of > 60 msec changes in QTcB and QTcF was greater in the prior placebo group compared with the prior tolvaptan group (9 subjects versus 5 subjects, respectively, for QTcB; 8 subjects versus 4 subjects, respectively, for QTcF). Overall, the categorical changes in ECG parameters were not considered to be clinically significant.

ECG-related abnormalities were reported as TEAEs in > 2% of all subjects were atrial fibrillation (6/111 subjects, 5.4%); tachycardia (4/111 subjects, 3.6%); and atrial tachycardia (3/111 subjects). The following ECG-related abnormalities were reported as SAEs: atrial fibrillation (3/11 subjects, 2.7%); atrial flutter, atrial tachycardia, bradycardia, and sinus tachycardia (each 1/111 subjects); arrhythmia, tachycardia, and ventricular tachycardia (each 1/111 subjects). The SAE of ventricular tachycardia resulted in discontinuation of open-label tolvaptan on Day 3.

Conclusions:

- Statistically significant increases from baseline in serum sodium concentrations were observed at all on-treatment visits up to Week 214 for the total population; by prior therapy, increases were observed up to Week 214 in the prior placebo group and up to Week 202 in the prior tolvaptan group. A decrease in serum sodium concentrations was observed within 7 days following tolvaptan discontinuation (the follow-up visit). The increases in the prior placebo group, which received tolvaptan for the first time in this open-label trial, were similar in magnitude to those observed in the group that had previously received tolvaptan. In the prior tolvaptan group, increases were consistent over time, indicating no apparent loss of effect.

- By baseline hyponatremia severity, statistically significant mean changes from baseline in serum sodium concentrations were observed at nearly all on-treatment visits in both the severe (< 130 mEq/L) and mild (≥ 130 mEq/L) hyponatremia subgroups; the increases in serum sodium concentrations in subjects who had previously received placebo were similar to those in subjects who had previously received tolvaptan.
- By baseline etiology, statistically significant mean changes from baseline in serum sodium concentrations were observed at nearly all on-treatment visits for subjects with CHF and SIADH/other; the mean changes in subjects with cirrhosis were only consistently observed up to Week 18. Within 7 days following tolvaptan discontinuation (the follow-up visit), mean serum sodium concentrations were generally decreased in subjects with CHF and SIADH/Other; subjects with cirrhosis however, generally did not rebound in response to treatment discontinuation.
- By Day 31, 57.7% of subjects in the total population had normalized serum sodium concentrations (ie, > 135 mEq/L); this treatment effect was generally sustained for the duration of the trial, as percentages of normalized subjects ranged from 55.6% to 91.2% through Week 214.
- Very few subjects required the additional therapy of fluid restriction.
- In general, no statistically significant changes in body weight were observed in hypervolemic subjects during the trial.
- Scores on the 12-Item SF-12 Health Survey PCS and MCS scales were variable over time; however, most changes from baseline in the parent trial showed slight increases (improvement) from baseline. Hyponatremia Disease-specific Survey PCS and MCS scores were variable over time with only nominal changes from baseline observed. Statistical significance was not reached for most time points on either survey.
- Administration of open-label tolvaptan at titrated oral doses of 15, 30, or 60 mg daily was generally safe and well tolerated in hyponatremic subjects. The incidences of TEAEs, potentially drug-related TEAEs, discontinuations from trial medication due to AEs, and SAEs were similar between the 2 prior treatment groups (in the parent trials). The most common TEAEs (by ≥ 10% incidence in the total open-label tolvaptan population) were peripheral oedema, hyponatraemia, anaemia, diarrhoea, nausea, urinary tract infection, fatigue, headache, thirst, hypokalaemia, ascites, pneumonia, hypotension, congestive cardiac failure, back pain, dizziness, and pollakiuria. The majority of TEAEs were considered mild or moderate in intensity. The most common events classified as severe (by ≥ 5% incidence) were hyponatraemia, pneumonia, cardiac failure, and congestive cardiac failure.
- Overall, the slow, measured rise in serum sodium concentrations resulted in relatively few instances of a too-rapid rate of correction. Five subjects (2 in the prior tolvaptan group and 3 in the prior placebo group) had increases in serum sodium ranging from 1.08 to 1.47 mEq/L/h within 6 to 10 hours after the initial tolvaptan dose on Day 1. Twelve subjects (8 previously on tolvaptan and 4 previously on placebo) who had serum sodium concentrations ≥ 145 mEq/L at some point during the trial; of these, 1 subject was discontinued on Day 15 due to an AE of increased blood sodium

(145 mEq/L). There were no deaths or other SAEs due to these serum sodium concentration changes.

- Nineteen deaths resulting from TEAEs occurred during the open-label trial (12 subjects in the prior tolvaptan group and 7 subjects in the prior placebo group). The causes of death appeared to be mostly related to the underlying conditions. The TEAEs that resulted in death in 2 or more subjects were cardiac failure and renal failure. One subject experienced a fatal TEAE of hepatorenal syndrome that was considered possibly drug-related by the investigator; all other deaths were considered not likely or unrelated to trial medication.
- Treatment with open-label tolvaptan appeared to produce no clinically significant trends in the overall population of hyponatremia subjects with respect to laboratory test, vital sign, and ECG data. There were no apparent trends in abnormal serum chemistry or hematology clinical laboratory or ECG results between groups by prior therapy or by visit. The slight decreases in supine SBP and slight increases in HR observed primarily in the prior placebo group were not considered to be clinically significant; there were no other apparent trends for vital signs between groups by prior therapy or by visit.