

### 7.3.4 Significant Adverse Events

#### 7.3.4.1 Pulmonary Embolism

In the phase 3 HF trial, pulmonary embolism was reported in 1.3% of tolvaptan and 0.8% of placebo-treated subjects. To further explore this relationship, the incidence of treatment-emergent PEs, DVTs and pulmonary infarcts was determined in the phase 3 HF trial, the all HF and hyponatremia subjects dataset and in the dataset of all HF subjects enrolled in trials other than the phase 3 HF trial. As shown in the table below, the incidence of treatment-emergent PEs was low but slightly greater in tolvaptan than placebo-treated subjects across the datasets analyzed. The incidence of AEs of isolated DVT (without reported PE or pulmonary infarct) was similar across the treatment arms. The number of subjects with PEs at doses other than 30 mg was too small to allow exploration of dose-dependency (1 PE occurred at each of the following doses: 15mg titrated to 60 mg, 45 mg and 90mg).

<b>Table 7.3.4.1-1 Treatment-emergent pulmonary embolism and DVTs*</b>		
	<b>Tolvaptan</b>	<b>Placebo</b>
<b>All Subjects from Multiple-Dose Placebo-Controlled Heart Failure and Hyponatremia Trials</b>		
	<b>N=3294</b>	<b>N=2716</b>
Pulmonary embolism, DVT, embolism, pulmonary infarct	1.4% (45)	1.1 % (31)
Pulmonary embolism	0.9% (31)	0.7% (18)
Pulmonary Infarct	0%	0.1% (2)
<b>DVT †</b>	<b>0.4% (14)</b>	<b>0.4% (11)</b>
<b>Phase 3 Heart Failure Trial</b>		
	<b>N=2063</b>	<b>N=2055</b>
Pulmonary embolism, DVT, pulmonary infarct	1.8% (37)	1.4% (29)
PE	1.3% (27)	0.8% (17)
Pulmonary Infarct	0%	0.1% (2)
<b>DVT †</b>	<b>0.5% (10)</b>	<b>0.5% (10)</b>
<b>Heart Failure Subjects from Multiple-Dose Placebo-Controlled Trials Excluding the Phase 3 HF Trial</b>		
	<b>N=951</b>	<b>N=464</b>
Pulmonary embolism, DVT, pulmonary infarct	0.7% (7)	0.2% (1)
PE	0.4% (4)	0.2% (1)
Pulmonary Infarct	0	0
<b>DVT†</b>	<b>0.3 (3)</b>	<b>0</b>

† DVT and no reported AE of pulmonary embolism or infarct

\*The CRFs of subjects with an AE pt\_text term of "Embolism" were reviewed. Based on the CRFs, none of these events appeared to represent a PE or DVT.

*Reviewer's comment: Stimulation of V1 receptors on platelets is thought to facilitate thrombosis and hence a biologically plausible mechanism for this association exists. Nonetheless, it cannot be determined from the data if this association is real or simply an artifact.*

#### 7.3.4.2 Stroke and atrial fibrillation

In the adjudicated dataset of the phase 3 HF trial, treatment emergent stroke hospitalization were observed in 2.0% and 1.1% of tolvaptan and placebo treated subjects, respectively. Similarly AEs suggestive of stroke and/or ischemic events were reported at a greater incidence in tolvaptan than placebo subjects in the unadjudicated AE database of the phase 3 HF trial. Based on AE terms, very few of these events were clearly identifiable as hemorrhagic (7 subjects or 0.3% in the tolvaptan arm and 5 subjects or 0.2% in the placebo arm) and the majority of events appeared to be ischemic. In HF participating in other trials, the incidence of stroke and/or ischemic events was not different in the tolvaptan and placebo arms and in the all subjects database, the treatment difference was lost. To further explore a possible association between ischemic events and tolvaptan use, the incidence of myocardial infarction was determined in the phase 3 HF trial. Adjudicated myocardial infarctions hospitalizations and deaths were not more common in tolvaptan-treated subjects.

Population		Tolvaptan	Placebo
<b>Phase 3 Heart Failure Trial</b>		<b>N=2063</b>	<b>N=2055</b>
Adjudicated dataset	Stroke death	0.7% (14)	0.3% (7)
	Stroke hospitalization †	2.0% (41)	1.1 % (23)
AE dataset	All strokes and/or ischemic AEs‡	4.3% (89)	3.4% (69)
<b>All Heart Failure Subjects from Multiple-Dose Placebo Controlled Trials Excluding the Phase 3 HF Trial</b>		<b>N=951</b>	<b>N=464</b>
All strokes and/or ischemic AEs		0.6% (6)	0.7% (3)
<b>All Heart Failure and/or Hyponatremia Subjects in Multiple-Dose Placebo-Controlled Trials</b>		<b>N=3294</b>	<b>N=2716</b>
All strokes and/or ischemic AEs		2.9% (96)	2.7% (74)

†Source= Email correspondence from sponsor April 15, 2008

‡Terms pooled: cerebral hypoperfusion, cerebrovascular disorder, cerebrovascular insufficiency, cerebral infarction, cerebral ischemia, cerebrovascular accident, embolic stroke, ischemic stroke, thromboembolic stroke, Wallenberg syndrome, lacunar infarction, reversible ischemic neurologic deficit, transient ischemic attack, vertebrobasilar insufficiency, subarachnoid hemorrhage, hemorrhagic stroke, hemorrhage intracranial, cerebral haemorrhage

Because atrial fibrillation can lead to thromboembolic strokes, the incidence of atrial arrhythmias was also explored. As shown in the table below, no clear association between atrial fibrillation and tolvaptan use was observed across the various datasets. This contrasts with **the findings in conivaptan's development program** in which a greater incidence of atrial fibrillation was observed in conivaptan as compared to placebo-treated subjects.

Population	Atrial Arrhythmias		Atrial Fibrillation	
	Tolvaptan	Placebo	Tolvaptan	Placebo
All Heart Failure and Hyponatremia subjects multiple-dose placebo-controlled trials	5.7% (188)	5.6% (151)	4.5% (147)	5.0% (135)
Phase 3 Heart Failure Trial	7.1% (147)	6.6% (136)	5.6% (116)	5.9% (122)
Phase 3 Hyponatremia Trials	2.2% (5)	0.5% (1)	1.8 % (4)	0.5% (1)

### 7.3.4.3 Coma

In the phase 3 HF and hyponatremia trials, TEAEs of “unresponsiveness” and/or “coma” was reported in 9 tolvaptan and no placebo-treated subjects. The table below provides a further description of these AEs. As shown in the table, many of these episodes of coma and/or unresponsiveness represented primary cardiac events culminating in coma and/or episodes of unresponsiveness. **Two subjects had an “unresponsive” episode approximately 8 and 9 days post study medication termination and these events were not associated with a marked change/drop in serum sodium levels measured 8 to 9 days after study drug termination.**

<b>Table 7.3.5.1-3 AEs of Coma and Unresponsiveness in Tolvaptan-Treated Subjects</b>	
<b>PID (Indication)</b>	<b>Comments</b>
02235-039-2020 (Hyponatremia)	<b>“Unresponsive” on post-treatment day 8. Event described as mild, resolving and felt by investigator to be unrelated to study medication. Subject had h/o squamous cell carcinoma of head and neck and had a percutaneous endoscopic gastrostomy and tracheostomy. Upon completing treatment phase (8 days earlier), sodium was 138 mEq/L. On day of AE, serum sodium was 132 mEq/L.</b>
02235-083-1031 (Hyponatremia)	<b>“Unresponsive” on post-treatment day 9. Event described as moderate (duration not given though reported to have resolved the same day with AE of moderate altered mental status persisting to the next day). Event coincided with AEs of serious and severe hypokalemia and moderate anxiety and nervousness. Notable (and possible contributing) concurrent medications included hydrocodone bitartrate and digoxin. Upon completing the 30-day treatment phase, sodium was 137 mEq/L. Post-treatment day 9, sodium was 132 mEq/L.</b>
03236-122-6786 (HF)	<b>“Inresponsiveness” during hospitalization for worsening heart failure marked by increasing respiratory distress and death. AE of “inresponsiveness” reported day before death.</b>
03236-007-3489 (HF)	<b>“Unresponsiveness” approximately 4 and 14 days post early termination (terminated from medication after 2 days due to AEs of poor appetite and elevated creatinine). First episode described as mild and coincided with AE of moderate hypotension. Second episode described as severe and coincided with AEs of anterior wall MI, complete heart block and cardiogenic shock</b>
03236-122-6143 (HF)	<b>“Unresponsiveness” approximately 6 weeks after initiating study medication. Event described as severe and coincided with AEs of respiratory failure and death attributed to cardiac failure.</b>
03236-828-2396 (HF)	<b>“Coma” approximately 7 months after initiating study medication. Death 9 days later attributed to worsening heart failure (onset approximately 7 days prior to start of coma).</b>
03236-633-4582 (HF)	<b>“Coma” approximately 1 year after initiating study medication. Event coincided with AEs of ventricular fibrillation and cardiac arrest</b>
03236-563-4929 (HF)	<b>“Coma” approximately 10 days after last dose of study medication (medication stopped on study day 5 in setting AE of worsening heart failure). Death same day as AE of coma and attributed to worsening HF</b>
03236-194-4505 (HF)	<b>“Non responsive” approximately 3- 3 ½ months after initiating study medication Event described as mild and coincided with AE of serious and severe ventricular arrhythmia.</b>

*Reviewer’s comment: These events do not appear to represent osmotic demyelination or cerebral edema arising from a rapid change in serum sodium levels. A possible association between tolvaptan, ventricular arrhythmias, cardiac arrest and sudden death is discussed elsewhere in this review.*

### 7.3.5 Submission Specific Primary Safety Concerns

#### 7.3.5.1 Overly rapid correction of serum sodium

Though the goal of treating hyponatremia is to raise serum sodium levels, overly rapid correction can be associated with significant morbidity and mortality. Osmotic demyelination, characterized by dysarthria, dysphagia, paraparesis, quadraparesis, coma and seizures, has been reported with rapid rates of serum sodium correction. To minimize this risk, current guidelines recommend rates of correction of < 10-12 mEq/L over 24 hours.

In the phase 3 hyponatremia trials, serum sodium measurements were to be made at 8 hours post-dose on Study Day 1 and daily (pre-dose) until discharge. At the 8 hour post-dose measurement, 5.3% of tolvaptan-treated subjects had an increase in serum sodium greater than 8 mEq/L, while 1.1% had an increase greater than 12 mEq/L at a mean of 21 hours after the first dose. In contrast, less than 1% of placebo-treated subjects had a rise greater than 8 mEq/L at 8 hours and no placebo-treated subject had a rise greater than 12 mEq/L at a mean of 21 hours after the first dose. As shown in the table below, overly rapid rates of correction were more common in subjects with SIADH/Other and those with a baseline serum sodium < 130 mEq/L. Of these 12 subjects, only one was reported to be on fluid restriction (and based on fluid intake records, this patient was not adhering to fluid restriction at that time). Of the 11 patients with a rise in serum sodium > 8 mEq/L at the 8 hour measurement, a similar or greater change from baseline was noted in 7 subjects at the 24 hour measurement.

Population		Rise > 8 meq/L at 8 hour measurement		Rise >12 at 24 hour measurement	
		Tolvaptan	Placebo	Tolvaptan	Placebo
<b>All subjects</b>		5.3% (11)	0.5% (1)	1.1% (2)	0
<b>Baseline hyponatremia</b>	Serum sodium ≥ 130	2.9% (3)	0	0	0
	Serum sodium <130	7.5% (8)	1.0% (1)	2.1% (2)	0
<b>Disease*</b>	SIADH/other	9.6% (8)	0	1.4% (1)	0
	HF	3.1% (2)	0	1.7% (1)	0
	Cirrhosis	1.6% (1)	1.8% (1)	0	0

\*Disease etiology based on origin as determined by sponsor.

Of those with an overly rapid rise in serum sodium, adverse events were reported by four of the subjects in the period surrounding the rise. One subject (PID 02235-035-2002) developed AEs of hypotension, dehydration, ataxia, and slurred speech concomitant with the rise (9 mEq/L increase by approximately 9 ½ hours after tolvaptan initiation). AEs of thirst, lightheadedness, hypokalemia, increase in hypertension and changes in urination (increase and “strong urge”) were also reported. One subject withdrew consent.

In searching the database, an additional **subject with an AE text of “sodium rise 13 point in 24 hours”** was also identified. The subject (PID 03238-137-3021) developed a rapid rise in serum sodium, hypernatremia, acute renal failure and ultimately died. A brief narrative is provided below.

PID 03238-137-3021. 80 year-old man with a history of NYHA Class IV HF and baseline serum sodium 131 mEq/L who developed an increase in serum sodium of 13 mEq/L on study day 3 (study day 2 sodium =128mEq/L; study day 3=142 mEq/L). Study medication was withdrawn following dosing on study day 2. Sodium rose to 153-160 on Day 5 and then reportedly fell to 130 on Day 6. According to the submitted narrative, the subject developed acute renal failure (Cr rise from 1.7 to 2.1, BUN rise from 53 to 83) concurrent with the event. The subject died on Day 6 and death was assessed by the investigator as due to end stage congestive heart failure and as “unrelated to study drug.”

**Reviewer’s comment:** *Tolvaptan’s role in this death and the precipitation of acute renal failure (suspected prerenal) cannot be excluded.*

The safety database of multiple-dose placebo-controlled trials was also searched to determine the incidence of AE terms associated with osmotic demyelination and/or overly rapid rates of serum sodium correction. Terms searched included dysarthria, dysphagia, coma, mutism, quadraparesis, dystonia, parkinsonism, ataxia, seizure and epilepsy. In the all hyponatremia subjects data set, 0.8% of tolvaptan and 0.2% of placebo subjects were identified as having one of these AEs (3 tolvaptan **treated subjects had AEs of “coma”, 2 tolvaptan-treated subjects had AEs of dysarthria, and 1 placebo subject had an AE of parkinsonism**). Coma as an AE is discussed further under section 7.3.4. Brief narratives for the AE of dysarthria are provided below.

PID 02235-035-2002. 59 year-old woman with hyponatremia attributed to severe chronic obstructive pulmonary disease and a history of hypertension, allergic conjunctivitis, arteriosclerotic cardiovascular disease, asthma, constipation, generalized aches and pain, gastrointestinal upset, left pleural effusion, mild cerebral atrophy, osteoporosis, schizoaffective disorder and seasonal allergic rhinitis. Subject experienced mild dysarthria on Study Day 2 in the setting of a rapid rise in serum sodium (9 mEq/L increase at approximately 9 ½ hours after tolvaptan initiation). AEs of moderate ataxia, mild dehydration and hypotension were also reported and all AEs (including dysarthria) resolved on the same day.

PID 03238-119-1001. 77 year-old man with hyponatremia attributed to ischemic congestive heart failure (reported NYHA Class III) and a history of hypertension, hypercholesterolemia, peripheral vascular disease, severe chronic obstructive pulmonary disease, mild mitral regurgitation, bladder cancer, gastroesophageal reflux disease, insomnia, leg cramps and respiratory infection. Subject experienced dysarthria, depressed level of consciousness and weakness on Study Day 29. On exam the subject was noted to be drowsy with mild slurring and decreased muscle strength. The event occurred 1 week following **a reported serious and severe AE of “exacerbation of HF.” The serum sodium was 141 and had been 135 one week prior. According to the sponsor’s submitted narrative, “The family of the subject stated that this was his baseline condition.”**

*Reviewer’s comment: No clear cases of osmotic demyelination were observed during tolvaptan’s clinical development program.*

#### 7.3.5.2 Hypernatremia

While an overly rapid rate of correction is one risk associated with tolvaptan use, overcorrection and the resulting development of hypernatremia is another concern. Because hypernatremia is associated with intense thirst, in healthy subjects, hypernatremia is typically prevented by increased water consumption. Populations with impaired thirst and/or impaired access to free water **are at particular risk. In tolvaptan’s clinical development program, thirst was a common adverse event associated with tolvaptan use. In the phase 3 hyponatremia trials, thirst was reported as an AE in 14.4% of tolvaptan and 4.6% of placebo-treated subjects. In the phase 3 heart failure trial, which enrolled subjects without regard to baseline serum sodium levels, TEAEs of thirst were approximately 8 times more common in tolvaptan than placebo-treated subjects (16.0% tolvaptan and 2.1% placebo).**

Although thirst was common, TEAEs of hypernatremia were reported infrequently. In the all heart failure and hyponatremia subjects database, 1.8% of tolvaptan and 0.4% of placebo subjects reported an AE of hypernatremia. As shown in the table below, in the phase 3 hyponatremia trials, TEAE of hypernatremia was reported in only one subject. In the open label extension study of these trials, hypernatremia was slightly more common (3.6% or 4 subjects). Analyses of laboratory values similarly revealed a low incidence of serum

sodium values > 146 mEq/L in this population. While TEAEs of hypernatremia were also uncommon in the phase 3 heart failure study, analyses of laboratory values suggest a high incidence of hypernatremia and an association between tolvaptan use and the development of an elevated serum sodium. In the phase 3 heart failure study, 48.4% and 27 % of tolvaptan and placebo-treated subjects respectively had a serum sodium > 146 at some time during the trial. Of subjects with a normal baseline serum sodium 54.8% and 32.2 of tolvaptan and placebo-treated subjects had a serum sodium > the upper limit of normal during the study. Though some of these captured events may not represent persistent or even reproducible rises in serum sodium, the marked discrepancy between treatment arms suggests that tolvaptan use is associated with an increased risk of hypernatremia and that this risk is likely greater than suggested by analyses of TEAE reports.

	TEAEs of hypernatremia		Sodium > 146 mEq/L		Shift to Sodium > ULN*	
	Tolvaptan	Placebo	Tolvaptan	Placebo	Tolvaptan	Placebo
All heart failure subjects	1.8%	0.4%			41.1%	26.8%
All hyponatremia subjects	0.7%	0.6%	1.7%	0.8%	NA	NA
Phase 3 heart failure trials	1.7%	0.5%	48.4%	27%	54.8%	32.2%
Phase 3 hyponatremia trials	0.5%	0%	1.4%	0%	NA	NA

Source: Sponsor's Table 1.2.10.2 (page 1672), Table 2.5.4.2 (page 4059), Table 11.5.4.2 (page 12383), Table 3.12.2.1 (page 7677), Table 3.12.2.3 (page 7681), Table 12.17.1.1 (page 19765), Table 2.15.3 (page 6816) and Table 11.20.1 (page 16402) of ISS

\*Shift to > upper limit of normal in subjects with normal baseline

Table 7.3.5.2-2 below shows the incidence of treatment emergent hypernatremia by dose in the all heart failure subjects population and in trial 156-98-213, the largest dose ranging study in subjects with worsening heart failure. The incidence of treatment-emergent hypernatremia appears to increase with increasing tolvaptan dose.

Population	Tolvaptan Dose (mg)									Placebo
	<15	15	30	45	60	90	120	15-60	Any dose	
<b>All Heart Failure Subjects</b>										
	N=11	N=119	N=2527	N=91	N=235	N=82	N=7	N=75	N=3147	N=2571
Hypernatremia	0	0	1.5% (39)	0	3.8% (9)	9.8% (8)	0	0	1.8% (56)	0.4% (11)
<b>Subjects Hospitalized for Worsening Heart Failure (Trial 156-98-213)</b>										
			N=78		N=60	N=90			N=238	
Hypernatremia			3.8% (3)		9.5% (8)	10.5% (8)			8.0% (19)	0%

Source: Sponsor's Table 14-1 page 878 ISS

**Reviewer's comment :** *Hypernatremia may be a dose-limiting adverse event that defines the upper range of dosing in non-hyponatremic subjects.*

7.3.5.3 Renal Failure

In the sponsor’s analyses of AEs, the AE term “blood creatinine increased” was reported by 3.49% and 2.89% of tolvaptan and placebo-treated subjects respectively. However many different terms were used in the safety database to indicate renal failure. To further explore a possible association between tolvaptan and renal failure, AE Terms indicative of renal failure were pooled. No increase in renal failure was noted in tolvaptan treated subjects in the phase 3 heart failure trial (all subjects and sub-group with heart failure and hyponatremia). Similarly no increase in renal failure was noted in the phase 3 hyponatremia trials (all subjects and sub-group with hyponatremia and cirrhosis). The sponsor’s analyses of the all heart failure and hyponatremia subjects dataset, in which slightly different terms indicative of renal failure were pooled, also revealed no marked difference in the incidence of AEs of renal failure in tolvaptan and placebo-treated subjects (25.1% all tolvaptan doses, 24.9% tolvaptan doses 15 to 60 mg and 24.3% placebo).

Upon review of narratives for other AEs, episodes of acute renal failure were noted that were never reported as AEs on CRFs or appeared in the AE database. Review of a small sample of narratives/adverse reaction reports in tolvaptan and placebo-treated subjects revealed that underreporting occurred in both groups. Changes in renal function were further explored using data on changes in laboratory measures of renal function.

Mean changes (Table 7.4.5.3-1) and shift changes (7.4.5.3-2) in creatinine and BUN are shown below. The sponsor’s analyses of data from the all heart failure subjects dataset produced similar results to analyses performed in the all subjects population and hence are not shown separately. A numerically small greater mean increase in creatinine was seen in tolvaptan-treated subjects in the all heart failure and hyponatremia subjects, all heart failure subjects and all hyponatremia subjects datasets. This difference was statistically significant in the all subjects and all heart failure subjects dataset given the large sample size. In analyses of shift changes, the incidence of an increased in creatinine was also slightly greater in tolvaptan than placebo subjects in the all subjects and all heart failure subjects datasets. In contrast a greater mean increase in BUN and greater incidence of elevated BUN was seen in placebo treated subjects in the all subjects dataset and all heart subjects dataset.

<b>Table 7.4.5.3-1 Changes in BUN and Creatinine on Laboratory Tests in All Heart Failure and Hyponatremic Subjects in Multiple-Dose Placebo-Controlled Trials.</b>				
	Baseline		Mean Change	
	Tolvaptan	Placebo	Tolvaptan	Placebo
<b>All heart failure and hyponatremia subjects in multiple-dose placebo-controlled trials</b>				
Creatinine (mg/dL)	1.31	1.33	0.06 (N=3101)	0.03 (N=2619)
BUN (mg/dL)	28.8	29.2	0.25 (N=3120)	1.63 (N=2625)
<b>All hyponatremia subjects in multiple-dose placebo-controlled trials</b>				
Creatinine (mg/dL)	1.25	1.29	0.06 (N=562)	0.02 (N=490)
BUN (mg/dL)	29.5	31.9	0.28 (N=579)	0.14 (N=495)

Source: Table 28.4.1.1 (page 29315) and Table 28.6.1.1 (page 29336) ISS

<b>Table 7.4.5.3-2 Shift Changes in BUN and Creatinine on Laboratory Tests</b>		
	Tolvaptan	Placebo
<b>All heart failure and hyponatremia subjects in multiple-dose placebo-controlled trials</b>		
Increased Creatinine	18.4% (576/3126)	16.9% (445/2627)
Increased BUN	34.3% (1073/3127)	41.0% (1077/2626)
<b>All hyponatremia subjects in multiple-dose placebo-controlled trials</b>		

Increased Creatinine	17.0% (99/582)	17.7% (88/497)
Increased BUN	28.7% (167/581)	26.7% (132/495)

Source: Table 28.4.2.1 (page 29321) and Table 28.6.2.1 (page 29343) ISS

*Reviewer’s comment: No clear association between tolvaptan use and renal failure is seen. There is evidence that vasopressin regulates urea transporters and the lower incidence of increased BUN in the tolvaptan-treatment arm may be explained by an off-target drug effect.*

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

Tables 7.4.1-1 and 7.4.1-2 below show AEs occurring in >2% of tolvaptan-treated subjects in the phase 3 HF and phase 3 hyponatremia trials, respectively. Thirst and dry mouth were among the most common AEs among tolvaptan-treated subjects and occurred with much greater frequency in the tolvaptan than the placebo treatment arm. Polyuria and pollakiuria also occurred at a greater incidence in tolvaptan than placebo-treated subjects. Hyperglycemia, hyperkalemia, hypokalemia, and hyperuricemia are discussed further in Section 7.4.2, dizziness and dehydration in Section 7.3.2, pyrexia in Section 7.4.3, blood creatinine increased in Section 7.3.5 and encephalopathy in Section 7.5.4.1.

<b>Table 7.4.1-1. Adverse Reactions Occurring in <math>\geq</math> 2% of Tolvaptan-treated Subjects and at an Incidence Greater than that Observed in Placebo-Treated Subjects in the Phase 3 Heart Failure Trial</b>		
<b>MedDRA Preferred Term</b>	<b>Tolvaptan (N = 2063) % (n)</b>	<b>Placebo (N = 2055) % (n)</b>
<b>Gastrointestinal Disorders</b>		
Dry mouth and/or throat	9(177)	2(46)
Constipation	10(199)	9(191)
<b>General Disorders and Administration Site Conditions</b>		
Thirst	17(350)	2(45)
Fatigue	4(86)	3(67)
<b>Investigations</b>		
Blood creatinine increased	4(72)	3(62)
<b>Metabolism and Nutrition Disorders</b>		
Hyperuricemia	10(211)	8(167)
Hyperkalemia	9(187)	8(155)
Hypoglycemia	5(99)	4(73)
Diabetes mellitus*	8(168)	7(141)
Gout or podagra	5(102)	4(83)
<b>Nervous System Disorders</b>		
Dizziness	9(179)	8(161)
<b>Renal and Urinary Disorders</b>		
Polyuria or Pollakiuria†	6(118)	2(36)

\* Also includes hyperglycemia, diabetes mellitus inadequate control, diabetes mellitus insulin-dependent, diabetes mellitus non-insulin-dependent, glucose tolerance impaired, blood glucose fluctuation

† Also includes urine output increased, micturation urgency, nocturia

Source: Sponsor's Figure 10-1 page 804 ISS

**Table 7.4.1-2. Adverse Reactions Occurring in  $\geq 2\%$  of Tolvaptan-treated Subjects and at an Incidence Greater than that Observed in Placebo-Treated Subjects in the Phase 3 Hyponatremia Trials**

MedDRA Preferred Term	Tolvaptan (N = 223) % (n)	Placebo (N = 220) % (n)
<b>Gastrointestinal Disorders</b>		
Dry mouth	13(28)	4(9)
Nausea	9(19)	8(17)
Constipation	7(16)	2(4)
<b>General Disorders and Administration Site Conditions</b>		
Thirst	16(35)	5(11)
Asthenia	9(19)	4(9)
Pyrexia	4(9)	1(2)
<b>Metabolism and Nutrition Disorders</b>		
Hyperglycemia†	6(14)	1(2)
Hypokalemia	5(11)	4(9)
Anorexia	4(8)	1(2)
Dehydration	2(5)	1(1)
Hyperuricemia	2(4)	1(3)
<b>Nervous System Disorders</b>		
Dizziness	7(15)	6(12)
Encephalopathy	3(6)	1(2)
Coordination abnormal	2(5)	1(1)
<b>Psychiatric Disorders</b>		
Insomnia	5(12)	3(7)
Anxiety	3(7)	2(4)
<b>Renal and Urinary Disorders</b>		
Pollakiuria or Polyuria*	11(25)	3(7)
<b>Skin and Subcutaneous Tissue Disorders</b>		
Pruritus	4(8)	2(4)
Ecchymosis	3(7)	2(4)

\* Also includes urine output increased, micturation urgency, nocturia

† Also includes diabetes

Source: Sponsor's Figure 10-2 page 805 ISS

## 7.4.2 Laboratory Findings

### Chemistry

Analyses of laboratory findings focused on likely **laboratory abnormalities given the drug's mechanism of action** and experience with other members of this class and laboratory abnormalities identified during the

**sponsor’s review of the data. Emphasis below** is given to hypokalemia, hypomagnesemia, hyperuricemia, hyperglycemia and hypoglycemia. Hyponatremia is discussed in section 7.3. Changes in serum creatinine are discussed further under section 7.3.5.

Tables 7.4.2-1 and 7.4.2-2 show the results of analyses of mean changes and shift changes in variables of interest in multiple-dose, placebo-controlled trials in the all HF and hyponatremia subjects population and all **hyponatremia subjects population. The sponsor’s analyses** of the all HF subjects population produced similar results to those shown below for the all HF and hyponatremia subjects population and hence are not shown separately. These analyses suggest that tolvaptan may be associated with increases in blood glucose and uric acid levels, in addition to its effect on serum sodium and osmolality. In the subgroup of subjects with hyponatremia, the incidence of increased potassium was slightly greater in tolvaptan than placebo-treated subjects, however analysis of mean changes in potassium levels revealed no difference in this subgroup and analyses conducted in the larger population of all hyponatremia and heart failure subjects did not produce a similar result.

<b>Table 7.4.2-1 Mean Changes in laboratory variables of interest</b>				
	<b>Baseline</b>		<b>Mean Change</b>	
	<b>Tolvaptan</b>	<b>Placebo</b>	<b>Tolvaptan</b>	<b>Placebo</b>
<b>All heart failure and hyponatremia subjects in multiple-dose placebo-controlled trials</b>				
Glucose (mg/dL)	138.61	136.47	1.85 (N=3073)	0.08 (N=2578)
Magnesium (mg/dL)	2.03	2.04	0.08 (N=2303)	0.02 (N=2304)
Potassium (mEq/L)	4.33	4.32	0.17 (N=3056)	0.14 (N=2571)
Uric Acid (mg/dL)	8.54	8.71	0.02 (N=3116)	-0.42 (N=2619)
Sodium	138.59	138.58	1.85 (N=3126)	-0.14 (N=2630)
Serum Osmolality	294.29	293.18	4.30 (N=2338)	1.66 (N=2140)
<b>All hyponatremia subjects in multiple-dose placebo-controlled trials</b>				
Glucose (mg/dL)	150.12	147.64	-6.7 (N=569)	-9.9 (N=483)
Magnesium (mg/dL)	1.96	1.98	0.09 (N=449)	0.02 (N=437)
Potassium (mEq/L)	4.39	4.39	0.08 (N=541)	0.09 (N=496)
Uric Acid (mg/dL)	7.71	8.22	0.27 (N=575)	-0.37 (N=495)
Sodium	130.47	130.09	5.02 (N=587)	2.08 (N=505)
Serum Osmolality	284.24	282.98	7.49 (351)	2.77 (326)

Source: ISS Table 28.4.1.1 (page 29315) and Table 28.6.1.1 (page 29336)

<b>Table 7.4.2-2 Shift Changes in laboratory variables of interest</b>			
		<b>Tolvaptan</b>	<b>Placebo</b>
<b>All heart failure and hyponatremia subjects in multiple-dose placebo-controlled trials</b>			
Glucose	Increased	39.1% (1205/3080)	34.1% (879/2579)

	Decreased	2.7% (82/3080)	2.9% (75/2579)
Magnesium	Increased	1.8% (41/2305)	1.3% (30/2304)
	Decreased	0.6% (13/2305)	0.7% (16/2304)
Potassium	Increased	19.5% (598/3063)	19.2% (493/2570)
	Decreased	1.8% (46/3093)	2.2% (57/2585)
Uric Acid	Increased	36.9% (1153/3123)	32.3% (845/2620)
All hyponatremia subjects in multiple-dose placebo-controlled trials			
Glucose	Increased	31.5% (180/571)	30.0% (145/483)
	Decreased	3.5% (20/571)	3.7% (18/483)
Magnesium	Increased	1.8% (8/449)	1.6% (7/437)
	Decreased	1.1% (5/449)	1.4% (6/437)
Potassium	Increased	17.3% (94/542)	15.6% (73/467)
	Decreased	2.6% (15/572)	2.7% (7/437)
Uric Acid	Increased	28.9% (167/577)	25.1% (124/495)

Source: ISS Table 28.4.2.1 (page 29321)

A possible association between hyperglycemia, hyperuricemia, gout, changes in serum potassium levels and tolvaptan use was further explored using the AE database. Table 7.4.2-3 shows the incidence of AEs reported for these laboratory abnormalities in the tolvaptan and placebo arms of the phase 3 hyponatremia trials and phase 3 HF trial. A slightly greater incidence of hyperkalemia/blood potassium increased and hyperglycemia AEs were observed in tolvaptan-treated subjects in the phase 3 heart failure trials. Though the sample size was small, a marked difference in the incidence of hyperglycemia AEs was noted in the phase 3 hyponatremia studies. While no AE reports suggestive of elevations in uric acid were found, AEs of gout were slightly more common in tolvaptan treated subjects in the phase 3 heart failure trial.

Adverse Event	Phase 3 heart failure trial		Phase 3 hyponatremia trials	
	Tolvaptan N=2063	Placebo N=2055	Tolvaptan N=223	Placebo N=220
Hyperkalemia/blood potassium increased	9.1% (187)	7.5% (155)	5.8% (13)	5.9% (13)
Hypokalemia/blood potassium decreased	8.3% (172)	10.1 (207)%	5.4% (12)	5.0% (11)
Hyperglycemia	4.2% (86)	3.6% (73)	5.4% (12)	0.9% (2)
Hyperglycemia, diabetes *	8.2% (169)	7.1% (145)	6.3% (14)	0.9% (2)
Gout	4.7% (96)	3.9% (81)	0.45% (1)	0

\* Terms pooled: Hyperglycemia, diabetes mellitus, glucose tolerance impaired, glucose urine, glycosuria, diabetes mellitus insulin-dependent, diabetes mellitus, diabetes mellitus inadequate control

**Reviewer’s comment:** *Tolvaptan use may be associated with hyperglycemia, elevations in uric acid levels and gout and the label should carry an appropriate warning. The relationship between tolvaptan use and hyperkalemia is less clear.*

**Hematology**

In multiple-dose, placebo-controlled trials of subjects with HF and/or hyponatremia, increased activated partial thromboplastin times were observed in 9.7% of tolvaptan and 9.1% of placebo-treated subjects; increased prothrombin times were observed in 16.6% of tolvaptan and 14.1% of placebo-treated subjects. In the sponsor’s analyses of AEs associated with coagulation/hemostatic disorders and increased bleeding, no difference was seen between the tolvaptan and placebo treatment arms.

**7.4.3 Vital Signs**

Radial artery pulse, erect and supine systolic and diastolic blood pressure and body weight measurements were made during clinical studies and are of particular interest given tolvaptan’s aquaretic effects and the association between conivaptan and hypotension and atrial arrhythmias.

Analyses of vital signs data from multiple-dose, placebo controlled trials suggest that tolvaptan is associated with a slight mean increase in heart rate (see Table 7.4.3-1). Similarly, in analyses focused on potentially clinically significant heart rate abnormalities in heart failure and hyponatremia subjects from multiple-dose, placebo controlled trials, a slightly greater incidence of rapid heart rate (defined as a HR ≥ 120 beats per minute and increase of ≥ 15 beats per minute) was seen across all heart rate categories (sitting, standing and supine). In subset analyses of data from all heart failure subjects, sitting and supine heart rate were also slightly greater in tolvaptan than placebo-treated subjects (not shown). In the subset of subjects with hyponatremia, this difference was further magnified. Adverse events related to cardiac arrhythmias are discussed further under Section 7.3.2.

<b>Table 7.4.3.1. Vital Sign Changes- Heart Rate</b>			
		<b>Tolvaptan</b>	<b>Placebo</b>
<b>All heart failure and hyponatremia subjects in multiple dose placebo-controlled trials</b>			
Mean Change (beats/min)	Supine	-2.65 (N=3057)	-3.63 (n=2573)
	Standing	0.4 (N=893)	0.1 (N=423)
Shift to Abnormally High*	Sitting	1.9% (4/212)	0.7% (1/150)
	Standing	4.5% (40/892)	3.3% (14/423)
	Supine	4.5% (138/3057)	3.7% (96/2573)
<b>All hyponatremia subjects from multiple dose-placebo controlled trials</b>			
Mean Change (beats/min)	Supine	1.4 (N=133)	-1.2 (N=64)
	Standing	-0.8 (N=600)	-1.6 (N=514)
Shift to Abnormally High*	Sitting	0% (0/3)	0% (0/3)
	Standing	13.5% (18/133)	6.3% (4/64)
	Supine	5.8% (35/600)	3.5% (18/600)

Source: Source: ISS Table 28.7.1 (page 29347), Table 28.7.2 (page 29350), Table 28.8.1 (page 29352), Table 28.8.2 (page 29355), Table 28.9.1 (page 29357)

\*Shift to Abnormally High defined by the Sponsor as ≥ 120 beats per minute and increase of ≥ 15 beats per minute

With respect to mean changes in blood pressure (sitting, standing and supine, systolic and diastolic), no consistent difference between treatment arms was noted in analyses conducted on the all HF and hyponatremia subjects population, all HF subjects population and all hyponatremia subjects population. Similarly, in analyses focused on potentially clinically significant blood pressure abnormalities, no consistent difference was observed between treatment arms in the all HF and hyponatremia subjects population and all HF subjects population. In the all hyponatremia subjects population, there was no greater incidence of marked drops in blood pressure ( $\leq 90$  mmHg and decreased by  $\geq 20$  mmHg) in tolvaptan than placebo-treated subjects. No greater incidence of TEAEs suggestive of hypertension was observed in tolvaptan compared to placebo subjects. TEAEs suggestive of hypotension and/or hypovolemia are discussed further in Section 7.3.2.

**Reviewer's comment:** *Tolvaptan does not appear to have as marked an effect on blood pressure as conivaptan. This may be due to tolvaptan's more selective blockade of the V2 receptor.*

Mean weight loss was greater in tolvaptan treated subjects (-2.1 kg and -1.6 kg tolvaptan and placebo, respectively) and a dose response in this relationship was noted in the all HF and hyponatremia subjects population. A similar difference in weight loss between treatment arms was observed in both the all HF population and all hyponatremia population. Increases in weight ( $\geq 7\%$ ) were slightly more common in placebo than tolvaptan-treated subjects (14.2% or 461/3253 and 16.3% or 440/2704 in tolvaptan and placebo-treated subjects respectively in the all HF and hyponatremia subjects dataset). This difference between treatment arms was also seen in analyses of the all HF subjects dataset but not in the all hyponatremia subjects dataset.

No difference in mean temperature or incidence of abnormal elevations in temperature was observed between the tolvaptan and placebo arms in the all HF and hyponatremia subjects population or the all HF subjects population. In contrast, in the all hyponatremia subjects population, a very small but statistically significant difference ( $P=.005$ ) in the mean change in temperature was observed between treatment arms (mean change 0.04 and -0.03 °C, tolvaptan and placebo respectively). Similarly, in this dataset, the incidence of an increase in temperature to  $\geq 1.1$  °C to  $\geq 38.3$  °C was slightly greater in tolvaptan than placebo treated subjects (18/599 or 3.0% tolvaptan and 8/511 or 1.6% placebo). While TEAEs of pyrexia were more common in conivaptan than placebo subjects in conivaptan's development program, no marked difference in incidence of this TEAE was observed across treatment arms in the tolvaptan development program.

**Reviewer's comment:** *The clinical significance of this difference in temperature in subjects with hyponatremia is unclear.*

#### 7.4.4 Electrocardiograms (ECGs)

A thorough QT study was conducted by the Sponsor and reviewed by the Interdisciplinary Review Team for QT Studies Consultation. According to their review, the study was adequately designed and conducted to exclude a clinically significant QTc prolongation over the tolvaptan dose range studied (30 to 300mg QD). Compared to placebo-treated subjects, a slight shortening of the mean QRS interval, a smaller increase in the mean PR interval, a slightly greater shortening of the mean QT interval, a smaller decrease in ventricular rate and a smaller increase in RR interval were observed in tolvaptan-treated subjects in multiple-dose, placebo-controlled trials. The clinical significance of these finding is unclear. In analyses of ECGs outliers from subjects with heart failure and/or hyponatremia enrolled in multiple-dose placebo-controlled trials, the incidence of

notable changes, including arrhythmias, RBB and LBB was similar or slightly lower in tolvaptan than placebo-treated subjects.

#### 7.4.5 Special Safety Studies

As reported under Section 7.4.4, a thorough QT study did not show a clinically significant QTc prolongation over the tolvaptan dose range studied (30 to 300mg QD).

#### 7.4.6 Immunogenicity

Tolvaptan is a nonpeptide V2 receptor antagonist and is expected to have little immunogenic potential. In an antigenicity study, anaphylaxis was not observed in guinea pigs sensitized to tolvaptan. A non-serious anaphylactic reaction was reported in one subject with autosomal dominant polycystic kidney disease (ADPKD) enrolled in a long-term trial of tolvaptan as a treatment for ADPKD. The narrative and CRF for this subject have been requested. According to the Sponsor, several weeks are needed to translate the CRF. In multiple-dose placebo-controlled trials, urticaria was reported in 0.4% (14/3294) of tolvaptan and 0.2% (5/2738) of placebo-treated subjects. All events were considered non-serious.

### 7.5 Other Safety Explorations

#### 7.5.1 Dose Dependency for Adverse Events

Exploration for the dose dependency of AEs was limited by the small number of subjects exposed to doses outside those proposed for the heart failure indication (30 mg) and hyponatremia indication (15 mg titrated up to 60 mg as needed). This was particularly true for explorations for dose dependency of AEs in the all hyponatremia subjects population. To address this issue, analyses for dose dependency were also attempted using a weight-adjusted dose. The results of analyses conducted using data from the phase 3 HF trial raised concern for confounding by weight and this approach was not explored further. For significant AEs including ventricular tachycardia, cardiac arrest and hypotension/hypovolemia, analyses for dose dependency are addressed in Section 7.3.2. The dose dependency of hyponatremia is addressed in Section 7.3.5.

Table 7.5.1-1 below shows AEs identified by the sponsor as increasing in incidence with increasing tolvaptan dose in the all HF subjects dataset and in the largest dose-ranging study in subjects with worsening HF (trial 156-98-213). Given the small number of subjects receiving doses other than 30 mg, the data are somewhat difficult to interpret. There may be a dose dependency in the relationship between pollakiuria, nausea and diarrhea and tolvaptan use.

<b>Table 7.5.1-1. Incidence of Treatment Emergent Adverse Events with Increasing Tolvaptan Dose in Multiple-Dose Trials</b>										
Population	Tolvaptan Dose (mg)									Placebo
	<15	15	30	45	60	90	120	15-60	Any dose	
<b>All Heart Failure Subjects</b>										
	N=11	N=119	N=2527	N=91	N=235	N=82	N=7	N=75	N=3147	N=2571
Nausea	0	5.9%	10.7%	2.2%	11.1%	12.2%	28.6%	9.3%	10.3%	11.3%

		(7)	(271)	(2)	(26)	(10)	(2)	(7)	(325)	(290)
Diarrhea	0	6.7%	7.3%	2.2%	7.7%	11%	14.3%	9.3%	7.3%	7.5%
		(8)	(184)	(2)	(18)	(9)	(1)	(7)	(229)	(192)
<b>Subjects Hospitalized for Worsening Heart Failure (Trial 156-98-213)</b>										
			N=78		N=60	N=90			N=238	N=79
Nausea			7.7%		10.7%	11.8%			10.1%	13.9%
			(6)		(9)	(9)			(24)	(11)
Diarrhea			7.7%		8.3%	9.2%			8.4%	2.5%
			(6)		(7)	(7)			(20)	(2)
Abdominal Pain			2.6%		4.8%	6.6%			4.6%	6.3%
			(2)		(4)	(5)			(11)	(5)
Hypokalemia			2.6%		4.8%	3.9%			3.4%	1.3%
			(2)		(4)	(3)			(8)	(1)
Pollakiuria			1.3%		3.6%	5.3%			3.4%	2.3%
			(1)		(3)	(4)			(8)	(1)
Hypotension			5.1%		6.0%	11.8%			7.6%	13.9%
			(4)		(5)	(9)			(18)	(11)

Source: Sponsor's Table 14-1 page 878 ISS

### 7.5.2 Time Dependency for Adverse Events

In general the small difference in incidence between the tolvaptan and placebo treatment arms limited the ability to perform meaningful explorations of the time dependency for serious AEs.

Table 7.5.2-1 shows the incidence of hypernatremia in the two long-term studies of tolvaptan 30 mg in HF subjects. As shown in the table, the greatest relative increase in incidence of hypernatremia occurred within the first month of starting tolvaptan, though the incidence of hypernatremia remains higher in tolvaptan compared to placebo-treated subjects up to approximately 6 months of therapy.

	Placebo		Tolvaptan	
	N	n (%)	N	n (%)
Within 1 month	2175	2 (0.09)	2183	20 (0.92)
>1 to 6 months	1967	4 (0.20)	1966	13 (0.66)
>6 to 12 months	1398	2 (0.14)	1369	3 (0.22)
>12 months	798	1 (0.13)	617	1 (0.12)

Source: Sponsor's Table 1.3.1 page 2831 ISS

N=number of subjects who had exposure in a given period

### 7.5.3 Drug-Demographic Interactions

The sponsor performed subgroup analyses of TEAEs by age (< 65 years old or ≥ 65 years old), gender, and race (Caucasian or non-Caucasian). In the all HF subjects population and all hyponatremia subjects population, the number of subjects reporting ≥ 1 adverse events was not markedly affected by age, gender or race. As shown in

Table 7.5.3-1 below, in the all HF subjects population, possible drug-demographic interactions were seen for race and thirst and dry mouth. In analyses of TEAEs in subjects with hyponatremia occurring with an incidence of greater than or equal to 10%, no marked drug-demographic interaction was seen between tolvaptan AEs and age and gender. As in the all HF subjects population, a possible drug-demographic interaction was seen for thirst and race in subjects with hyponatremia.

<b>Table 7.5.3-1 Drug Demographic Interactions by Age, Gender and Race</b>						
<b>All Heart Failure Subjects in Multiple-Dose Placebo-Controlled Trials</b>						
	Tolvaptan 30 mg		Any Dose		Placebo	
Race	Caucasian N=2053	Non-Caucasian N=473	Caucasian N=2444	Non-Caucasian N=702	Caucasian N=2135	Non-Caucasian N=436
Thirst	381 (18.6%)	48 (10.1%)	479 (19.6%)	91 (13.0%)	52 (2.4%)	12 (2.8%)
Dry Mouth	211 (10.3%)	13 (2.7%)	264 (10.8%)	26 (3.7%)	56 (2.6%)	6 (1.4%)
<b>All Hyponatremia Subjects in Multiple-Dose, Placebo-Controlled Trials</b>						
	Tolvaptan Any Dose		Placebo			
Race	Caucasian N=498	Non-Caucasian N=109	Caucasian N=427	Non-Caucasian N=91		
Thirst	76 (15.3%)	9 (8.3%)	16 (3.7%)	4 (4.4%)		

Source: Sponsor's Tables 8.1.4.6-1 to 8.1.4.6-3 and 9.1.4.7.4.1-1 to 9.1.4.7.6-1 pages 388-393 and 636-639 ISS

## 7.5.4 Drug-Disease Interactions

### 7.5.4.1 Cirrhosis and Hyponatremia

Cirrhotics comprised approximately 15% of subjects in the all subjects hyponatremia dataset and 27% of subjects enrolled in the phase 3 hyponatremia trials. Hence unique safety signals arising in cirrhotics may be overshadowed in analyses of these larger hyponatremic populations. Safety analyses in cirrhotics focused on AEs which occurred at a greater incidence in cirrhotics treated with tolvaptan than cirrhotics treated with placebo. Safety analyses also addressed **possible AEs based the drug's mechanism of action and what is known about vasopressin's effects. In this regard, bleeding events (given V2 receptor's role in von Willebrand factor release and the high baseline risk of bleeding in cirrhotics), renal failure and volume depletion/hypotension were of particular interest.**

Controlled safety data in cirrhotics are derived from the phase 3 hyponatremia trials and a dose ranging study (156-96-203). Though cirrhotics were also enrolled in trial 156-97-204, a dose titration study that was terminated early, the sponsor does not provide sufficient demographic data to identify cirrhotics in this trial. (Subjects were classified as HF or non-HF; based on AE reports at least 2 of 23 subjects had cirrhosis). Safety data from this study are hence not discussed in this section.

The incidence of adverse events occurring in cirrhotics with hyponatremia is shown in Table 7.5.4.1-1 below. Death rates were similar in tolvaptan and placebo-treated subjects with cirrhosis. While serious AEs and all AEs were slightly more common in subjects with cirrhosis treated with tolvaptan in the phase 3 hyponatremia trials, the reverse was observed in the phase 2 dose-ranging study in cirrhotics.

Adverse Event	Phase 3 Hyponatremia Trials		Phase 2 Dose-Ranging Study in Cirrhotics		
	Tolvaptan N=63	Placebo N=57	Tolvaptan		Placebo N=15
			5 to 60 mg N=30	15 to 60 mg N=18	
Death	7.9% (5)	7.0% (4)	6.7% (2)	5.6% (1)	6.7% (1)
Serious Adverse Events	38.1% (24)	29.8% (17)	33.3% (10)	16.7% (3)	46.7% (7)
All Adverse Events	92.1% (58)	82.5% (47)	83.3% (25)	77.8%	93.3% (14)

Serious AEs occurring in 2 or more cirrhotics treated with tolvaptan and at an incidence greater than placebo in the phase 3 hyponatremia trials are shown in the table below. The incidence of serious AEs was not markedly different between the two study arms and of these serious AEs; the greatest difference in incidence was seen for encephalopathy (4.8% versus 0%).

Serious Adverse Events	Tolvaptan N=63	Placebo N=57
Ascites	4.8% (3)	1.8% (1)
Encephalopathy	4.8% (3)	0
Abdominal Pain	3.2% (2)	0
Hepatic Failure	3.2% (2)	1.8% (1)
Respiratory Failure	3.2% (2)	1.8% (1)
Upper GI Hemorrhage	3.2% (2)	0

To further explore an association between encephalopathy and tolvaptan use, similar terms were pooled. Table 7.3.1.8-1 shows a slightly greater incidence of mental status changes/ encephalopathy in tolvaptan compared to placebo subjects with cirrhosis enrolled in the phase 3 hyponatremia trials. This trend is not seen in the phase 2 dose-ranging study in cirrhotics.

Population		Changes in Mental Status		
		Tolvaptan	Placebo	
All Subjects Phase 3 hyponatremia trials	Serious	3.6% (8/223)	2.3% (5/220)	
	Severe	2.7% (6/223)	1.8% (4/220)	
	All	7.2% (16/223)	5.5% (12/220)	
Cirrhotics	Phase 3 hyponatremia trials	Serious	11.1% (7/63)	7% (4/57)
		Severe	7.9% (5/63)	7.0% (4/57)
		All	25.4% (16/63)	21.1% (12/57)
	Phase 2 dose-ranging study in cirrhotics†	Serious	5.6% (1/18)	13.3% (2/15)
		Severe	5.6% (1/18)	6.7% (1/15)
		All	22.2% (4/18)	27% (4/15)
	Open label extension study	Serious	30% (6/20)	NA
		Severe	30% (6/20)	NA
		All	45% (9/20)	NA

\*Terms pooled: confusional state, abnormal behavior, agitation, encephalopathy, hepatic encephalopathy, mental status change, somnolence, coma, depressed level of consciousness, disorientation, delirium, metabolic encephalopathy, stupor  
 †Includes subjects receiving tolvaptan doses  $\geq$  15 mg

Given tolvaptan’s mechanism of action, the incidence of bleeding events, renal failure and volume depletion/hypotension were also of particular interest. Table 7.5.4.1-4 below explores the incidence of these AEs. As shown, the incidence of GI bleeding was slightly greater in tolvaptan compared to placebo-treated cirrhotics. Analyses of trial 156-96-203, a dose-ranging study in cirrhotics, produced similar results. GI bleeding was reported in 2 out of 30 subjects (6.6%) treated with any dose of tolvaptan and 2 out of 18 subjects (11.1%) receiving doses of 15 mg or greater in this trial. In contrast, no GI bleeding episodes were reported in placebo-treated cirrhotics. A slightly greater incidence of hematoma/ecchymosis was also noted in tolvaptan compared to placebo-treated subjects in the phase 3 hyponatremia trials. Pooling AE reports of GI bleeding with AEs of hematoma/ecchymosis substantially magnified the difference in incidence between treatment arms. Other than GI bleeding, no other severe or serious bleeding occurred in cirrhotics in the phase 3 hyponatremia trials. In the sponsor’s analyses of laboratory data, decreased platelet counts were noted in 22% (10/45) and 16.7% (8/48) of tolvaptan and placebo-treated cirrhotics, respectively. As shown in the table below, renal failure and hypotension/hypovolemia were not more common in tolvaptan-treated subjects.

**Table 7.5.4.1-4. Treatment Emergent Adverse Events of Interest in Cirrhotics**

Terms Pooled	Phase 3 hyponatremia Trial		Open Label Extension Study
	Tolvaptan N=63	Placebo N=57	Tolvaptan N=20
GI Bleeding*§	9.5% (6)	1.8% (1)	20% (4)
<b>Hematoma/ecchymosis†•</b>	<b>9.5% (6)</b>	<b>0</b>	<b>20% (2)</b>
GI Bleed and/or hematoma/ecchymosis	17.5% (11)	1.8% (1)	30% (6)
Hypotension/hypovolemia**	9.5% (6)	8.8% (5)	10% (2)
<b>Renal Failure†</b>	<b>6.4% (4)</b>	<b>14.0% (8)</b>	<b>25% (5)</b>

§Analyses including all subjects in the phase 3 hyponatremia trials also showed a greater incidence of GI bleeding in the tolvaptan than the placebo treatment arm. The majority of these events, however, occurred in cirrhotics.

\*Terms pooled: upper gastrointestinal hemorrhage, esophageal varices hemorrhage, gastrointestinal hemorrhage, anal hemorrhage, gastric hemorrhage, hematochezia, hematemesis, diarrhea hemorrhagic, rectal hemorrhage

†Terms pooled: ecchymosis, hematoma, implant site bruising, implant site hematoma, injection site bruising, injection site Hematoma, periorbital hematoma, post procedural hematoma, scrotal hematoma, spontaneous hematoma, subcutaneous Hematoma, subdural hematoma, extradural hematoma, catheter site hematoma, breast hematoma.

•While many terms were pooled, the only AEs reported in cirrhotics were “ecchymosis” and “hematoma”

\*\*Terms pooled: blood pressure decreased, blood pressure orthostatic, blood pressure systolic decreased, cardiogenic shock, circulatory collapse, dizziness, dizziness postural, hypotension, volume blood decreased, vasodilation, procedural hypotension, orthostatic hypotension, hypovolemia, hypovolemic shock, hemodynamic instability, dehydration

†Terms pooled: renal failure acute, acute prerenal failure, blood creatinine increased, hepatorenal syndrome, oliguria, urine output decreased, urine flow decreased, renal tubular necrosis, renal function test abnormal, renal impairment, renal failure chronic, renal failure, renal disorder, hypercreatininemia, hepatorenal failure, creatinine renal clearance decreased, blood urea increased, blood creatinine increased, azotemia

**Reviewer’s comment: Tolvaptan may be associated with an increased risk of GI bleeding in cirrhotics.**

#### 7.5.4.2 SIADH and Hyponatremia

Subjects with SIADH/other comprised approximately 17 % of subjects enrolled in the hyponatremia development program and approximately 42% of subjects enrolled in the phase 3 hyponatremia trials. The phase 3 hyponatremia trials were the only multiple-dose, placebo-controlled trials to enroll a significant number of subjects with SIADH/other. Table 7.5.4.2-1 below shows AEs occurring in subjects with SIADH/other enrolled in this trial. Death, serious AEs and severe AEs were slightly more common in placebo than tolvaptan-treated subjects. In tolvaptan-treated subjects with SIADH, no single serious AE occurred in more than one subject. In tolvaptan-treated subjects with SIADH/other, one serious AE (dehydration) occurred in more than one subject (two tolvaptan versus one placebo-treated subject). As in the dataset of all subjects with HF and/or hyponatremia, dry mouth, thirst and constipation occurred at a greater incidence in tolvaptan than placebo-treated subjects with SIADH/other.

Adverse Event	SIADH		SIADH/other	
	Tolvaptan N=51	Placebo N=58	Tolvaptan N=90	Placebo N=97
Death	2.0% (1)	5.2 % (3)	1.1% (1)	4.1% (4)
Serious Adverse Events	5.5% (6)	13.8% (15)	6.4% (12)	13.4% (25)
Severe Adverse Events	9.8% (5)	24.1% (14)	11.1% (10)	19.6% (19)

Because vasopressin has been implicated in stress responses and this population included subjects with underlying psychiatric illnesses, an association between tolvaptan use and psychiatric AEs was also explored. AE terms identified in this dataset and searched included agitation, psychotic disorder, anxiety, depression, panic attack, and restlessness. Rates of psychiatric disorders were also **compared using the “Psychiatric Disorders” soc primary category**. No association between tolvaptan use and psychiatric AEs was found in this population.

*Reviewer’s comments: As discussed in Section 7.3.5, overly rapid rates of serum sodium correction occurred at a slightly greater incidence in subjects with SIADH than in subjects with HF or cirrhosis. Though the database is small, no other unique concerning safety signals were identified in this subgroup of subjects.*

#### 7.5.4.3 Heart Failure and Hyponatremia

HF subjects comprised the majority of subjects in the all hyponatremia subjects population and approximately 33% of subjects enrolled in the phase 3 hyponatremia trials. In comparison to placebo-treated subjects, mortality was slightly greater in subjects with HF and hyponatremia treated with tolvaptan (see Section 7.3.1). In the adjudicated dataset for the phase 3 heart failure trial, slightly greater mortality in tolvaptan-treated subjects was driven by a slightly greater incidence of fatal strokes, other cardiovascular mortality, and heart failure (see Table 7.5.4.3-1 below). However the absolute difference in the number of events between the two treatment arms was small and the significance of these findings is unclear. Moreover adjudicated cardiovascular hospitalizations were not more common in tolvaptan than placebo-treated subjects. As in the larger dataset of all subjects with HF, a slightly greater incidence of hospitalizations for stroke and arrhythmias was observed in

tolvaptan compared to placebo-treated subjects with HF and hyponatremia. Again, the absolute difference in the number of events between the two treatment arms was small.

<b>Table 7.5.4.3-1. Adjudicated Treatment Emergent Death and Hospitalizations in Subjects with hyponatremia in the Phase 3 HF Trial</b>		
<b>Cause of Death</b>	<b>Tolvaptan N=242</b>	<b>Placebo N=232</b>
Heart Failure	23.6% (57)	22.4% (52)
Acute Myocardial Infarction	0.4% (1)	0.9% (2)
Other Cardiovascular Mortality	2.1% (5)	1.3% (3)
Stroke	0.8% (2)	0
Sudden Cardiac Death	7.9% (19)	7.8% (18)
<b>Adjudicated Hospitalizations</b>		
All CV Hospitalizations	44.6% (108)	48.3% (112)
Arrhythmia	4.1% (10)	3.0% (7)
MI	0.8% (2)	1.7% (4)
Stroke	1.2% (3)	0.4% (1)
HF hospitalization	38.8% (94)	39.7% (92)
Other Cardiovascular morbidity	7.4% (18)	9.5% (22)

As shown in Table 7.5.4.3-1, TEAEs of hypotension and/or hypovolemia were observed at a similar or slightly greater incidence in tolvaptan compared to placebo-treated subjects in the all HF and hyponatremia population. Analyses revealed no difference in the incidence of renal failure.

<b>Table 7.5.4.3-1 The incidence Treatment Emergent hypotension and/or hypovolemia in subjects with heart failure and hyponatremia†</b>		
<b>Population</b>	<b>Tolvaptan</b>	<b>Placebo</b>
<b>All Subjects with Heart Failure and Hyponatremia</b>	<b>N=418</b>	<b>N=349</b>
Serious	6.7% (28)	6.0% (21)
All	26.3% (110)	25.5% (89)
<b>Phase 3 HF trial</b>	<b>N=242</b>	<b>N=232</b>
Serious	9.9% (24)	6.9% (16)
All	28.9% (70)	29.3% (68)
<b>Phase 3 Hyponatremia Trials</b>	<b>N=74</b>	<b>N=72</b>
Serious	4.1% (3)	4.2% (3)
All	23.0% (17)	19.4% (14)

†Terms pooled= blood pressure decreased, blood pressure orthostatic, blood pressure systolic decreased, cardiogenic shock, circulatory collapse, dizziness, dizziness postural, volume blood decreased, vasodilation, procedural hypotension, orthostatic hypotension, hypotension, hypovolemia, hypovolemic shock, hemodynamic instability, dehydration.

### 7.5.5 Drug-Drug Interactions

Tolvaptan is a substrate of CYP3A4 isoenzymes and hence the experience with concomitant tolvaptan and CYP3A4 inhibitor administration is of particular interest. The association between CYP3A4 inhibitor use and death and serious AEs in the all heart failure and/or hyponatremia subject population and in the phase 3 HF and hyponatremia trials was explored. Table 7.5.5-1 shows the incidence of death and serious AEs in tolvaptan and placebo subjects by category of CYP inhibitor use. As shown in the table, no clear association between the use

of CYP3A4 inhibitors and mortality or serious AEs in tolvaptan-treated subjects is suggested by these analyses. One death, however, was reported in a subject who developed markedly elevated levels of tolvaptan associated with concomitant administration of the CYP3A4 inhibitor clarithromycin. This case is described in further detail below.

<b>Table 7.5.5-1. Effect of Concomitant CYP3A4 Inhibitor Use and Treatment-Emergent Adverse Events*</b>				
AE	CYP3A4 inhibitor		No CYP3A4 Inhibitor	
	Tolvaptan	Placebo	Tolvaptan	Placebo
<b>All Multiple-Dose, Placebo-Controlled Trials in Subjects with Heart Failure and/or Hyponatremia</b>				
	N=688	N=570	N=2606	N=2146
Death	18.9%	20.9%	15.1%	18.3%
Serious AEs	61.1%	59.0%	41.3%	37.7%
<b>Phase 3 Heart Failure Trials</b>				
	N=466	N=452	N=1597	N=1603
Death	24.9%	24.8%	21.1%	22.1%
Serious AEs	67.6%	68.4%	55.3%	55.3%
<b>Phase 3 Hyponatremia Trials</b>				
	N=30	N=34	N=193	N=186
Death	6.7%	8.8%	6.2%	5.4%
Serious AEs	20.0%	41.2%	30.1%	27.4%

\*And no CYP3A4 inducer also present.

The subject (PID 03238-225-1027) was a 73 year-old man with hyponatremia in the setting of non-ischemic congestive heart failure (NYHA Class IV) and also a history of atrial fibrillation, diabetes, COPD, PVD, aortic stenosis, hyperuricemia and reported chronic kidney disease (per labs Cr=0.9). The subject was started on clarithromycin on study day 4 with follow-up labs approximately 10 days later revealing a rise in sodium from 127 to 136 mEq/L and increase in BUN and uric acid levels (see Table 7.5.5-2 below). The subject was withdrawn from the study on Day 28 and died on hospital day 32 in the setting of acute renal failure, respiratory insufficiency and increased bilirubin. The investigator attributed the cause of death to acute renal failure. The subject's last dose of study medication was on Day 27.

<b>Table 7.5.5-2 Tolvaptan trough levels, laboratory values and vital signs in subject 03238-225-1027</b>								
Study Day	Trough Tolvaptan Levels (ng/mL)*	Na	Cr	BUN	Uric Acid	BP (mmHg)	Pulse (bpm)	Wt (kg)
1	NA	126	0.9	29	3.5	105/60	64	67
2	NA	124	0.9	29	3.6	100/65	64	67
3	NA	129	0.9	27	3.6	105/70	60	65
4**	NA	127	1	28	3.8	110/70	60	66
14	1668 (reported as Week 1) 2109 (reported as Week 2)	136	1	46	4.5	110/70	68	70
21	2315 (reported as Week 3)	131	1.1	45	4.4	110/70	60	69
28	NA	131	1.8	61	4.6	100/70	72	71

Source for trough tolvaptan levels: Email correspondence from sponsor dated April 14, 2008 (per sponsor typographical error in trough levels as given in section 17.3.3, page 1459 of submitted report CSR 156-03-238). According to the sponsor, expected steady state trough of tolvaptan at 60 mg dose=40ng/mL.

\*\*Clarithromycin started.

**Reviewer's comment:** *Tolvaptan's role in this death cannot be excluded. As discussed in Section 4.4, coadministration of tolvaptan and potent CYP3A4 inhibitors should be contraindicated.*

According to the sponsor, in multiple-dose, placebo-controlled trials, only 4.5% of tolvaptan-treated subjects took CYP3A4 inducers. Given the small number of subjects, it is difficult to draw meaningful conclusions about **the effect of such inducers on tolvaptan's efficacy.**

## 7.6 Additional Safety Explorations

### 7.6.1 Human Carcinogenicity

Early in the chemistry review, concern was raised that toluene sulfonic acid methyl ester, a potential genotoxic carcinogen, could be formed during the final recrystallization step. The sponsor has agreed to provide residual levels of this potential impurity in the manufactured drug substance batches, however the results of this testing are not available at this time. The preclinical toxicology/carcinogenicity review is not yet finalized, but according to FDA reviewer, Dr. Xavier Joseph, the preclinical carcinogenicity studies were felt to be adequately designed and conducted and revealed no carcinogenic potential in animals. An analysis, using the primary SOC term **“Neoplasms benign, malignant and unspecified”**, revealed that such AEs were uncommon and occurred at no greater incidence in tolvaptan compared to placebo subjects in multiple-dose, placebo-controlled trials.

### 7.6.2 Human Reproduction and Pregnancy Data

No studies have been conducted in pregnant woman. According to the sponsor, there is no experience with tolvaptan in pregnant subjects in clinical trials to date. The preclinical toxicology review is not yet finalized, but according to Dr. Joseph, at very high doses, tolvaptan was associated with adverse effects on embryo/fetal development in rats and rabbits (162 to 324 times the maximum human dose on a mg/m<sup>2</sup> basis). In pregnant rats, oral administration of tolvaptan resulted in delayed fetal ossification at doses approximately 162 times the maximum human dose. Lower doses did not produce any adverse effects on the fetus in rats. In pregnant rabbits, oral administration of tolvaptan resulted in an increased incidence of post-implantation loss, and fetal microphthalmia, open eyelids, cleft palate, brachymelia, and hypoplasia of the radius, ulna, tibia and fibula and fused phalanx and sternebrae at doses 324 times the maximum human dose. Administration of doses approximately 97 times the maximum recommended human dose produced no adverse effect on the fetus in these rabbits.

In the rat fertility study, tolvaptan doses approximately 162 times the maximum human dose caused a reduction in the number of corpora lutea and implantations.

*Reviewer's comment: Based on the available data, a Pregnancy Category C classification seems appropriate.*

### 7.6.3 Pediatrics and Effect on Growth

Tolvaptan has not been studied in pediatric patients and the effects of growth in children are not currently known.

#### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

According to the sponsor, one case of tolvaptan overdose has been reported. A subject (PID 03236-680-4828) **reported taking an unknown number of “extra pills” on day 6 of treatment.** Though the amount of the overdose cannot be determined, based on drug dispensing and return information, the maximum possible 1 day dose was 210 mg. According to the sponsor, laboratory results reportedly showed an increase in creatinine, serum magnesium, sodium, BUN, uric acid and increased INR, trace urinary protein and an elevated AVP. No significant hypotension was reported. In one subject taking clarithromycin and tolvaptan concomitantly, markedly elevated levels of tolvaptan were noted, likely due to inhibition of tolvaptan’s **metabolism.** **This case is discussed further in section 7.5.5 (Drug-Drug Interactions).** In this subject an increase in creatinine was also reported, followed by death attributed to worsening heart failure.

Based on in vitro testing, there is no reason to suspect abuse potential. **The concepts of “withdrawal” and “rebound” are discussed further in this review only with respect to changes in serum sodium following drug discontinuation (see section 6.1.9).**

#### 7.7 Additional Submissions

The 120-Day Safety Update was submitted on February 22, 2008. No additional Submissions have been received.

### 8 Postmarketing Experience

Tolvaptan is not currently marketed in any country.

### 9 Appendices

#### 9.1 Literature Review/References

1. Ellison DH, Berl T. The Syndrome of Inappropriate Antidiuresis. NEJM. 2007; 356: 2064-72.
2. Garofeanu C. et al. Causes of Reversible Nephrogenic Diabetes Insipidus. A Systematic Review. Am J Kidney Dis. 2005; 45: 626-37.
3. Holmes CL, Landry DW, Granton JT. Science Review : Vasopressin and the Cardiovascular System Part 1- Receptor Physiology. Critical Care. 2003; 7: 427-34.
4. Laurenco R, Karp BI. Myelinolysis after Correction of Hyponatremia. Annals of Internal Medicine. 1997; 126 (1):57-62.
5. Klein JD, Frohlich O, Blount MA et al. Vasopressin Increases Plasma Membrane Accumulation of Urea Transporter UT-A1 in Rat Inner Medullary Collecting Ducts. J Am Soc Nephrol. 2006; 17 (10): 2680-86.
6. Sands JM. Renal Urea Transporters. Curr Opin Nephrol Hypertens. 2004; 13 (5): 525-32.
7. Conivaptan Package Insert, March 2007.

## 9.2 Labeling Recommendations

Because approval is not recommended at this time, no formal labeling recommendations are made. The review by the Division of Medication Errors and Technical Support (DMETS) has not yet been finalized. The sponsor has asked the Agency to consider “Samsca” and “Samsa” as potential alternative trade names to “Samska.”

## 9.3 Advisory Committee Meeting

An advisory committee meeting is scheduled for June 24-25, 2008. The purpose of this meeting is to obtain guidance from the Cardiovascular and Renal Drugs Advisory Committee on how best to approach products such as tolvaptan where efficacy has been demonstrated by a change in a laboratory value and not via a clear improvement in clinical outcome. The results of this meeting will be provided in a separate addendum to this review.

## 9.4 Discussion of Individual Studies

### 9.4.1 Hyponatremia Indication

#### 9.4.1.1 Study 156-02-235

Title: Multicenter, Randomized, Double-blind, Placebo-controlled, Efficacy and Safety Study of the Effects of Titrated Oral Tolvaptan Tablets in Patients with Hyponatremia “SALT TRIAL” (Sodium Assessment with Increasing Levels of Tolvaptan in Hyponatremia)

Duration of Study: Initiation: April 11, 2003; Completion: December 20, 2005.

#### Study Design and Objectives:

Study 156-02-235 was a multi-center, randomized, double-blind, placebo-controlled efficacy and safety study in patients with hyponatremia. (SPA- received 1/21/03). The study’s primary objective was to demonstrate the efficacy and safety of tolvaptan for achieving and maintaining an increase in serum sodium in patients with nonhypovolemic hyponatremia due to a variety of causes. The treatment indication (as stated in the synopsis) is given as: “Treatment of patients with non-acute hyponatremia associated with euvolemic and hypervolemic states.”

*Reviewer’s comments: Though the sponsor narrowed the stated treatment indication to “subjects with non-acute hyponatremia”, the inclusion/exclusion criteria did not ensure that the study population was in fact non-acute. The exclusion criteria excluded some particular causes of acute hyponatremia (e.g. acute and transient hyponatremia associated with head trauma or postoperative state), however based on the submitted protocol, hyponatremia could be established by a single serum sodium measurement made prior to randomization.*

#### Study Sites and Investigators:

Subjects were enrolled from 42 active study centers in the United States.

Inclusion Criteria:

1. Age greater than or equal to 18 years.
2. Hyponatremia in euvolemic or hypervolemic states, defined as serum sodium < 135 mEq/L prior to randomization. Hypervolemia is defined as: excess extracellular fluid volume manifesting as dependent edema or ascites. Euvolemia is defined as: absence of clinical and historical evidence of extracellular fluid volume depletion or sequestration; and absence of edema and ascites.
3. Ability to provide informed consent.

Exclusion Criteria:

1. Women who are breast feeding and females of childbearing potential who are not using acceptable contraceptive methods (such as barrier contraceptives or methods that result in a failure rate of less than 1%). All females of child-bearing potential must have a negative urine pregnancy test with results available prior to receiving Study Drug. All females of child-bearing potential must use two methods of contraception or remain abstinent. Non-childbearing potential shall be defined as either post-menopausal (12 consecutive months without menses) or surgically sterile.
2. Hyponatremia in hypovolemic states. Hypovolemic hyponatremia is defined as the presence of clinical and historical evidence of extracellular fluid volume depletion. Examples of clinical hypovolemic hyponatremia states include conditions where restoration of plasma volume results in correction and maintenance of normal plasma sodium concentration or those associated with critically low central venous pressure (< 5 cm H<sub>2</sub>O) or pulmonary capillary wedge pressure (< 5 mm Hg); but do not include conditions such as HF or cirrhosis where there is evidence of fluid overload (e.g., ascites or dependent edema) despite an inappropriate homeostatic response to perceived intravascular volume depletion.
3. Acute and transient hyponatremia associated with head trauma or postoperative state.
4. Hyponatremia due to uncontrolled hypothyroidism or uncontrolled adrenal insufficiency.
5. Cardiac surgery within 30 days of potential study enrollment, excluding percutaneous coronary interventions.
6. History of a myocardial infarction within 30 days of potential study enrollment.
7. History of sustained ventricular tachycardia or ventricular fibrillation within 30 days, unless in the presence of an AICD.
8. Severe angina including angina at rest or at slight exertion and/or unstable angina.
9. History of a CVA within the last 30 days.
10. Subjects with psychogenic polydipsia (however subjects with other psychiatric illness may be included)
11. Systolic arterial blood pressure < 90 mmHg.
12. History of hypersensitivity and/or idiosyncratic reaction to benzazepine or benzazepine derivatives (such as benazepril).
13. History of drug or medication abuse within the past year, or current alcohol abuse.
14. Uncontrolled DM defined as fasting glucose > 300mg/dL.
15. Urinary tract obstruction except BPH if non-obstructive.
16. Previous participation in another clinical drug trial within the past 30 days. Investigators may call the medical monitor to discuss potential inclusion if no impacts on safety or efficacy are anticipated
17. Previous participation in this or any other tolvaptan clinical trial.
18. Terminally ill or moribund condition with little chance of short term survival.
19. Serum creatinine > 3.5 mg/dL.
20. Serum sodium < 120 mEq/L with associated neurologic impairment, ie, symptoms such as apathy, confusion, seizures.

21. Patients with progressive or episodic neurologic disease such as multiple sclerosis or history of multiple strokes.
22. Child-Pugh score greater than 10. Patients with higher scores may be allowed to enroll if the patient has been stable for 30 days. Investigators must contact the medical monitor for approval.
23. Patients receiving intravenous fluids at a rate greater than KVO.
24. Hyponatremia due to lab artifacts (e.g., high glucose level > 300). Patients with prior normal and borderline sodium levels should be confirmed prior to randomization. Diabetic patients must have qualifying sodium draw after correction for elevated glucose levels.
25. Patients receiving AVP or its analogs for treatment of any condition.
26. Patients receiving within 7 days of randomization, other medications for treatment of hyponatremia specifically: demeclocycline, lithium carbonate or urea.
27. Patients likely requiring IV saline for correction of symptomatic or asymptomatic severe hyponatremia during the course of the study.
28. **Severe pulmonary artery hypertension: patient who's** condition could be expected to deteriorate with sudden shifts in fluid volumes and pressures.
29. Hyponatremia should not be the result of any medication that can safely be withdrawn

Study Plan:

Figure 9.4.1.1-1 below provides an overview of the trial design. Subjects were enrolled within 2 days of the screening period and were randomized in a 1:1 ratio to placebo or 15 mg tolvaptan for 30 days with forced titration up to 30 mg and 60 mg as need for clinical effect (see Figure 6.1.1-1 in the Review of Efficacy for hyponatremia). Subjects were followed for an additional 7 days after the 30 days of treatment. For subjects with a serum sodium < 130 mEq/L, fluid restriction to 1 L/day could be initiated at the **investigator's discretion**, however investigators were advised to hold fluid restriction for at least 24 hour after the first dose. Serum sodium was assessed on screening, pre-dose and 8 hours post dose on day 1, daily on days 2-4 or until discharge, on discharge, weeks 1, 2 and 3, day 30 (or early termination) and on follow up visit. The medical monitor was to be contacted if a subject had a rapid rise in serum sodium (defined as an increase in serum sodium by more than 8 mEq/L in any ten hour period following dosing on Day 1 or an increase by more than 12 mEq/L in the 24 hour period following dosing) or if a subject had a rise in serum sodium level exceeding 145 mEq/L.

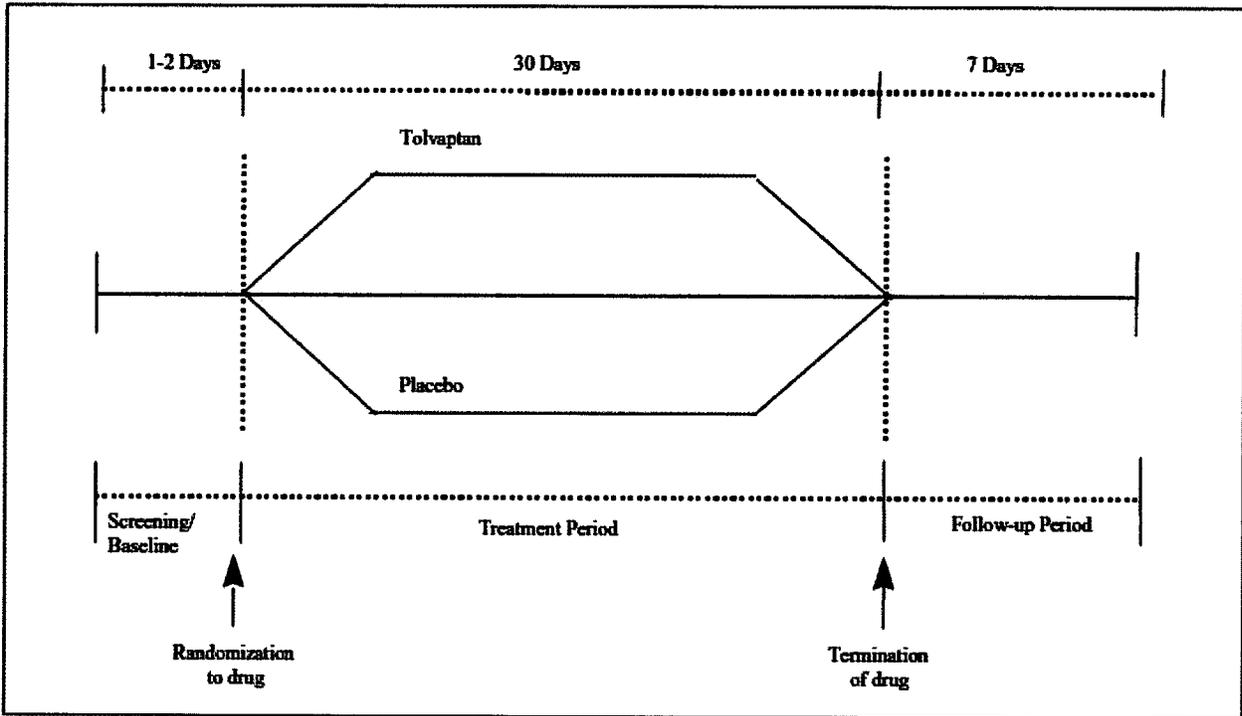


Figure 9.4.1.1-1. Sponsor's Figure of Study Design.

Statistical Analysis Plan:

See the Review of Efficacy for hyponatremia.

Amendments, Post Hoc Changes and Protocol Violations:

Amendments were made on June 27, 2003, May 24, 2004 and January 12, 2005. In general, these amendments modified and/or clarified exclusion and inclusion criteria. In Amendment 1 on June 27, 2003, 2 months after the first consent form was signed, the primary outcome variable was changed to include analysis of the AUC of the change from baseline in serum sodium up to Days 4 and 30. This modification was made in response to the recommendation made by FDA to focus on these co-primary endpoints. The Amendment also changed the treatment indication in the **protocol synopsis** from "Treatment of patients with hyponatremia associated with **euvolemic and hypervolemic states**" to "Treatment of patients with **non-acute** hyponatremia associated with **euvolemic and hypervolemic states.**" **The only change made** to the inclusion criteria by this amendment that also appeared to address this modification was to change exclusion criteria #3 from "**Hyponatremia associated with head trauma or post-operative state,** to "**Acute and transient hyponatremia associated with head trauma or postoperative state**". In Amendment 3 on January 12, 2005, the proposed study sample size was increased based on a sample size re-estimation using blinded data on the first 100 patients.

**Reviewer's comments:** See comments above under "Study Design and Objectives."

Clinically significant protocol deviations were reported in 89.8% of subjects and were comprised of the following: 159/205 (77.6%) procedural deviations, 88/205 (42.9%) dosing deviations, 22/205 (10.7%) entry criteria deviations, and 79/205 (38.5%) other. Table 9.4.1.1-1 below provides further details on these protocol violations.

**Table 9.4.1.1-1. Protocol Violations in Study 156-02-235**

Types of Protocol Violations	Frequency	Types
Procedural deviations	159/205 (77.6%)	Assessments that were either not done, or were not done within the protocol specified timeframe; Dose titrations outside the guidelines of the protocol; Subjects dosed with incorrect study medication.
Dosing deviations	88/205 (42.9%)	Dosing times being outside the protocol-specified window; An interruption in dosing of > 7 days; Subjects who were randomized but never received a dose of study medication
Entry criteria deviations	22/205 (10.7%)	Sodium level outside specified range Blood pressure outside specified range Uncontrolled diabetes Receiving fluids faster than KVO Unable to provide informed consent Serum creatinine >3.5 Informed consent obtained after first study procedure History of drug or alcohol abuse Hyponatremia associated with head trauma Participation in another clinical trial within 30 days
Other	79/205 (38.5%)	

According to the sponsor, irregularities in data collection were noted at two sites (Centers 004 and 006). Data from these centers were felt to be unreliable and these centers were excluded from the primary and secondary efficacy analyses (8 subjects from center 004 and 7 subjects from center 006).

Disposition

205 subjects were randomized and 202 subjects were treated: 100 with tolvaptan and 101 with placebo. The study was completed by 79/102 subjects in the tolvaptan group and 65/103 subjects in the placebo group. Among subjects with severe hyponatremia, the study was completed by 40 subjects (75.5%) in the tolvaptan group and 30 subjects (57.7%) in the placebo arm. The disposition of study subjects is shown in the sponsor's table below (page 107, CSR156-02-235).

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<b>Table 8.1-1 Subject Disposition</b>			
<b>Subjects</b>	<b>Tolvaptan N (%)</b>	<b>Placebo N (%)</b>	<b>Total N (%)</b>
Screened	--	--	244
Randomized	102 (100.0)	103 (100.0)	205 (100.0)
Treated	100 (98.0)	101 (98.1)	201 (98.0)
Completers <sup>a</sup>	79 (77.5)	65 (63.1)	144 (70.2)
Discontinued:	23 (22.5)	38 (36.9)	61 (29.8)
Adverse experience	9 (8.8)	17 (16.5)	26 (12.7)
Withdrew consent	9 (8.8)	10 (9.7)	19 (9.3)
Lost to follow up	2 (2.0)	6 (5.8)	8 (3.9)
Withdrawn by investigator	2 (2.0)	4 (3.9)	6 (2.9)
Met withdrawal criteria	1 (1.0)	0 (0.0)	1 (0.5)
Protocol deviation	0 (0.0)	1 (1.0)	1 (0.5)
Intent-to-treat <sup>b</sup>	97 (95.1)	93 (90.3)	190 (92.7)
Analyzed for safety <sup>c</sup>	100 (98.0)	101 (98.1)	201 (98.0)
Analyzed for efficacy <sup>d</sup>	95 (93.1)	89 (86.4)	184 (89.8)
Analyzed for primary endpoints <sup>e</sup>	95 (93.1)	89 (86.4)	184 (89.8)

Note: Subjects from Centers 004 and 006 were excluded from efficacy and primary endpoint analyses due to GCP violations.

<sup>a</sup>Subjects who were evaluated at the last scheduled visit during the treatment period (Day 30) were defined as study completers.

*Reviewer's comment: More subjects discontinued in the placebo arm, especially in the subgroup with severe hyponatremia. Of those who discontinued, more subjects in the placebo arm discontinued due to an adverse experience, withdrew consent or were lost to follow. The greater number of adverse experiences in the placebo-treated arm is unexpected and may be explained by a greater disease burden/presence of co-morbidities at baseline (see demographic data below).*

Demographics

For many characteristics, baseline demographic data were similar in the tolvaptan and placebo arms (see Review of Efficacy for hyponatremia, Section 6.1). Table 9.4.1.1-2. below highlights key demographic data and diseases/conditions where a more marked disparity in incidence in the two treatment arms was noted.

**Table 9.4.1.1-2. Baseline diseases or conditions where a more marked disparity in incidence was noted in trial 156-02-235**

Tolvaptan (N=102)      Placebo (N=103)

Mean Ejection Fraction	37%	27%
Previous Angina	19.6%	28.2%
Previous MI	19.6%	25.2 %
Previous CABG	12.7%	18.4%
Severe COPD	8.8%	17.5%
PVD	9.8%	15.5%
Arrhythmias	39.2%	33%
Family History of Heart Disease	52%	43.7%

*Reviewer's comment: The placebo arm may have been sicker at baseline than the tolvaptan-arm.*

#### Efficacy Analyses

Data from 2 study sites were excluded from the primary and secondary efficacy analyses due to irregularities noted during site inspections (Center 004 and 006). These data were included in the demographic, baseline and safety analyses. Please see the Review of Efficacy for hyponatremia (Section 6) for a discussion of the results of this study.

#### Safety

Safety is discussed under the Review of Safety (Section 7).

*Reviewer's comments: Tolvaptan appears to be effective in raising serum sodium levels. Sensitivity analyses (re-defining the primary endpoint) suggest that the results are robust.*

#### 9.4.1.2 Study 156-03-238

Title: International, Multicenter, Randomized, Double-blind, Placebo-controlled, Efficacy and Safety Study of the Effects of Titrated Oral Tolvaptan Tablets in **Patients With Hyponatremia "SALT 2 TRIAL"** (Sodium Assessment With Increasing Levels of Tolvaptan in Hyponatremia 2)

Duration of Study: Initiation: November 20, 2003; Completion: July 6, 2005.

#### Study Design and Objectives

Study 156-02-238 was an international, multi-center, randomized, double-blind, placebo-controlled efficacy and **safety study in patients with hyponatremia.** The study's primary objective was to demonstrate the efficacy and safety of tolvaptan for achieving and maintaining an increase in serum sodium in patients with non-hypovolemic hyponatremia due to a variety of causes. The treatment indication (as stated in the synopsis) is **given as: "Treatment of patients with non-acute hyponatremia associated with euvolemic and hypervolemic states."** With the exception of being conducted internationally, this study mirrored Study 156-2-235.

#### Study Sites and Investigators

Subjects were enrolled from 50 study centers: US, Canada, Germany, Belgium, Czech Republic, Spain, Poland, Hungary, and Italy.

#### Study Plan, Inclusion and Exclusion criteria

The study plan, inclusion and exclusion criteria mirrored that of study 156-02-235. Please see study 156-02-235 (Section 5.3.1) for further details.

#### Amendments, Post Hoc Changes and Protocol Violations

The first subject was enrolled on November 2003 and follow-up on the last subject was completed on July 2005. Amendments were made on September 12, 2003, May 7, 2004 and December 7, 2004. Administrative

changes were made on August 20, 2003 and June 3, 2004. For the most part, these amendments modified or clarified inclusion and exclusion criteria and laboratory procedures. Of those amendments made after subject enrollment began, the following changes are important to note (amendment December 7, 2004): (1) increase in the estimated sample size from 200 to 240 subjects, based on a re-estimation of the needed sample size using blinded results from the first 125 patients (2) clarification of the definition of “End of Study Date” (last date of contact or date of final contact attempt) and “End of Trial Date” (date of database lock) (3) determination that only subjects with  $\geq 2$  days of post baseline data would be considered evaluable for efficacy.

Clinically significant protocol deviations were reported in 80.2% of subjects and were comprised of the following: 172/243 (70.8%) procedural deviations, 84/243 (34.6%) dosing deviations, 9/243 (3.7%) entry criteria deviations, and 50/243 (20.6%) other. Table 5.3.2.1 below provides further details on these deviations.

**Table 9.4.1.2-1. Protocol Violations in Study 156-03-238**

Types of Protocol Violations	Frequency	Types
Procedural deviations	172/243 (70.8%)	Assessments not done Assessments not done in protocol specified timeframe
Dosing deviations	84/243 (34.6%)	Subjects dosed outside dosing interval Placebo subject did not receive study medication
Entry criteria deviations	9/243 (3.7%)	Sodium level outside specified range Blood pressure outside specified range Uncontrolled diabetes Receiving fluids faster than KVO Unable to provide informed consent Serum creatinine >3.5 Informed consent obtained after first study procedure History of drug or alcohol abuse
Other	50/243 (20.6%)	

A large number of such deviations were noted at one center (center 237) and because the data from this center were felt by the Sponsor to be unreliable, the Sponsor excluded the results from this center from the primary and secondary efficacy analyses (9 subjects).

**Study Disposition**

243 subjects were randomized: 123 subjects to tolvaptan and 120 subjects to placebo. The study was completed by 92/123 subjects in the tolvaptan group and 89/120 subjects in the placebo group. Of those with more severe hyponatremia, the study was completed by 43/59 subjects (72.9 %) in the tolvaptan group and 41/58 subjects (70.7%) in the placebo group. The disposition of study subjects is shown in the sponsor’s table.

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<b>Table 8.1-1 Subject Disposition</b>			
<b>Subjects</b>	<b>Tolvaptan N (%)</b>	<b>Placebo N (%)</b>	<b>Total N (%)</b>
Screened	--	--	304
Randomized	123 (100.0)	120 (100.0)	243 (100.0)
Treated	123 (100.0)	119 (99.2)	242 (99.6)
Completers <sup>a</sup>	92 (74.8)	89 (74.2)	181 (74.5)
Discontinued:	31 (25.2)	31 (25.8)	62 (25.5)
Adverse experience	18 (14.6)	10 (8.3)	28 (11.5)
Withdrew consent	5 (4.1)	12 (10.0)	17 (7.0)
Protocol deviation	4 (3.3)	1 (0.8)	5 (2.1)
Met withdrawal criteria	2 (1.6)	1 (0.8)	3 (1.2)
Withdrawn by investigator	1 (0.8)	6 (5.0)	7 (2.9)
Lost to follow up	1 (0.8)	1 (0.8)	2 (0.8)
Intent-to-treat <sup>b</sup>	123 (100.0)	120 (100.0)	243 (100.0)
Analyzed for safety <sup>c</sup>	123 (100.0)	119 (99.2)	242 (99.6)
Analyzed for efficacy <sup>d</sup>	118 (95.9)	114 (95.0)	232 (95.5)
Analyzed for primary endpoints <sup>e</sup>	118 (95.9)	114 (95.0)	232 (95.5)

Note: Subjects from Center 237 were excluded from efficacy and primary endpoint analysis due to GCP violations.

<sup>a</sup>Subjects who were evaluated at the last scheduled visit during the treatment period (Day 30) were defined as study completers.

*Reviewer's comment: More tolvaptan-treated subjects withdrew due to an adverse experience while more placebo-treated subjects withdrew consent or were withdrawn by the investigator. This contrasts with the experience in study 156-02-238 in which more placebo-treated patients reported an adverse event.*

**Demographics and Baseline Characteristics**

As a whole, baseline demographics and characteristics were similar in both treatment groups (see Review of Efficacy for hyponatremia, Section 6). The table below highlights diseases/conditions where a more marked disparity in incidence in the two treatment arms was noted.

**Table 9.4.1.2-2. Baseline diseases or conditions where a more marked disparity in incidence was noted in trial 156-03-238**

	<b>Tolvaptan (N=123)</b>	<b>Placebo (N=120)</b>
Chronic renal insufficiency	11.4%	16.7%
Previous CAD	23.6%	31.7%
PVD	19.5%	9.2%
COPD	17.1%	11.7%

**Reviewer's comment:** *In contrast to study 156-02-235, the overall baseline disease burden appears more similar in the two study arms.*

#### Efficacy Analyses

A large number of deviations were noted at one center (center 237) and because the data from this center were felt by the Sponsor to be unreliable, the Sponsor excluded the results from this center from the primary and secondary efficacy analyses (9 subjects). Please see the Review of Efficacy for hyponatremia (Section 6.1) for a discussion of study results.

#### Safety

Safety is reviewed in Section 7 (Review of Safety).

**Reviewer's comments:** *The results of this trial are similar and supportive of the results of study 156-02-235. Tolvaptan appears to be effective in raising serum sodium levels.*

#### 9.4.1.3 Study 156-03-244

**Title:** 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”)

**Duration of Study:** Initiation: May 26, 2004; Completion: Ongoing.

#### Study Design and Objective

Study 156-03-244 is an ongoing multi-center, uncontrolled, open-label extension study of Studies 156-02-235 and 156-03-238. **The study's primary objective was to demonstrate the safety and efficacy of tolvaptan in maintaining an increased serum sodium concentration in patients with hyponatremia.**

#### Study Sites and Investigators

This study is ongoing and is being conducted at 33 centers in Europe and North America.

#### Inclusion Criteria

1. Age greater than or equal to 18 years.
2. Ability to provide informed consent or assent.
3. Prior successful participation in a tolvaptan hyponatremia trial with evidence of continued need or desire for therapy. Successful participation is defined as completion of the full course of therapy (30 days) with acceptable compliance with study drug (>70% of prescribed drug taken) and study procedures. Patients may be eligible if after PI consultation with the medical monitor they have been withdrawn from the previous study due to a perceived lack of treatment effect requiring the use of intravenous saline infusion or alternate excluded therapy.

#### Exclusion Criteria

1. A current medical condition where long-term treatment with an aquaretic agent may present an undue risk to the patient:
  - a) Women who are pregnant, breast feeding, or of childbearing potential who are not using acceptable contraceptive methods.
  - b) Conditions limiting access to water (e.g. bedridden and non-communicative)
  - c) Severely disordered thirst (e.g. psychogenic polydipsia, hydrophobia or anorexia)
  - d) Patients with urinary outflow obstruction (hydronephrosis a risk unless catheterized).

- e) Significant hypotension (SBP<90 mmHg) or pulmonary artery hypertension (fragile intravascular fluid balance)
- f) History of hypersensitivity and/or idiosyncratic reaction to benzazepine or benzazepine derivatives (such as benazepril).
- 2. Hyponatremia which is acute, reversible, artifactual or due to conditions not associated with vasopressin excess or likely to respond to aquaretic therapy:
  - a) Hyponatremia in hypovolemic states
  - b) Acute and transient hyponatremia associated with head/brain trauma or post-operative pain, acute water intoxication, polydipsia, IV fluid administration, isolated pulmonary infection.
  - c) Artifactual hyponatremia due to hyperglycemia, hyperlipidemia (where flame photometry is used), etc.
  - d) Hyponatremia in states of severe renal impairment (Creatinine >3.5 mg/dL [310 µmol/L])
- 3. Hyponatremia due to reversible medical condition or therapy:
  - a) Severe, uncontrolled hypothyroidism or uncontrolled hypoadrenalism.
  - b) Use of a medication, known to be associated with hyponatremia, which may be safely and easily substituted for another class.
- 4. Conditions associated with an independent imminent risk of morbidity and mortality.
- 5. Conditions which confound the assessment of endpoints including:
  - a) Poorly controlled diabetes mellitus (glucose >300 mg/dL [ $>16.7$  mmol/L])
  - b) Participation in clinical trials believed by the PI or Sponsor likely to confound endpoint assessment. Investigators may call the medical monitor to discuss potential inclusion if no impacts on safety or efficacy are anticipated (eg, an open-label study of and already approved medication).
  - c) History of poor compliance (e.g. current illicit drug addiction, alcohol abuse, missed appointments, etc.)
  - d) Use of AVP or its analogs for treatment of any condition outside of emergent life support.

#### Study Plan

**Figure 9.4.1.3-1 shows the sponsor's schematic of the trial design.** Subjects completing Study 156-02-235 or 156-03-238 and meeting the additional inclusion/exclusion criteria were administered tolvaptan 15 mg daily for up to 214 weeks with titration up to 60 mg daily as needed for clinical effect. Subjects were followed for an additional 7 days after the treatment period. During the study, investigators could, at their own discretion, assess the clinical need for continued therapy by interrupting treatment for up to 5 days to assess sodium levels. For subjects with a serum sodium < 130 mEq/L, fluid restriction could be initiated **at the investigator's discretion**, however investigators were advised to avoid initiation for at least the first 24 hours of drug titration.

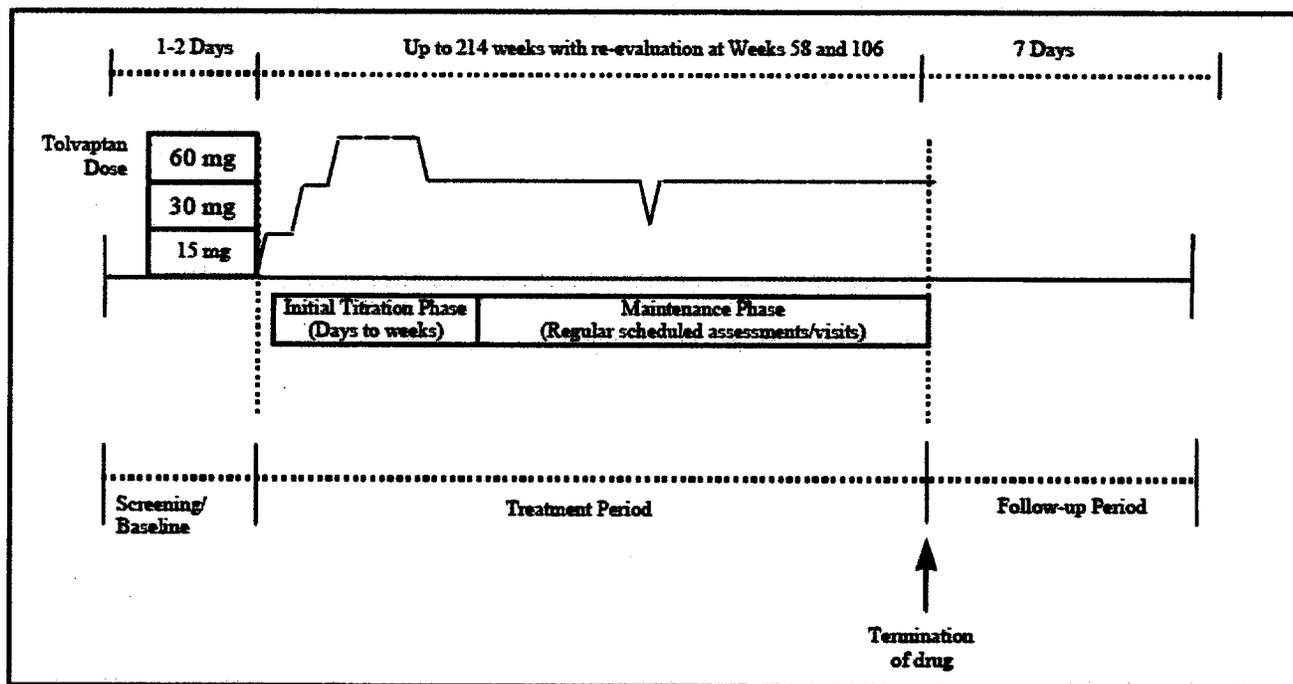


Figure 9.4.1.3-1 Sponsor's schematic of the trial design.

Statistical Analysis Plan

This was an extension of Studies 156-02-235 or 156-03-238 and as such, the study was not powered. Missing data- for outcomes defined as a change from baseline, only subjects having a baseline and at least one post-baseline visit were analyzed were included in the analysis.

Amendments, Post Hoc Changes and Protocol Violations

Amendments were made on June 27, 2005, August 2, 2005 and June 28, 2006. The sponsor's table below provides an overview of these changes.

<b>Table 9.4.1.3-1 Sponsor's Table of Protocol Amendments and Administrative Changes</b>		
Number	Date	Action
<b>Administrative Changes</b>		
1.	16 Mar 2004	Typographical errors were corrected and details were added for the coordinating principal investigator and contract research organization.
2.	01 Oct 2004	Typographical errors were corrected, entry criteria not fully explained in the original protocol were clarified, a safety oversight committee was added, details were provided for the clinical research manager, and the hyponatremia disease-specific survey was modified based on recommendations from an expert in survey design.

3.	03 Apr 2007	The mean change in serum sodium concentrations was updated, and the schedule of the safety blood samples and typographical errors were corrected. A footnote was updated in the Schedule of Assessments Table to adequately reflect the option to assess sodium concentrations between Week 58 and the start of the first study extension. Scheduled safety labs were added to the text of the Schedule of Assessments section. The protocol was updated to reflect <b>additional data from the completed phase 3 studies. The sponsor's company name and personnel were updated.</b>
<b>Amendments</b>		
1.	27 Jun 2005	The trial duration for each subject was extended from up to 14 months to 25 months and the target enrollment was decreased from 400 to 200 subjects. Evaluations were added at Weeks 70, 82, 94, and 106. The trial title was <b>changed to reflect a "multiyear" duration. In addition, the investigator agreement and signature form was deleted and replaced by an electronic form.</b>
2.	02 Aug 2005	The protocol title reverted to the original version and other typographical errors and discrepancies were corrected.
3.	28 Jun 2006	The trial duration was extended for a second time (from 25 months to 54 months). Evaluations were added at Weeks 118, 130, 142, 154, 166, 178, 190, 202, and 214. Personnel and institutions involved with the trial were updated.

Source: CSR 156-03-244

Disposition

111 subjects enrolled in this trial: 56 with prior exposure to tolvaptan and 55 with prior exposure to placebo. By October 1, 2007 over 50% of subjects had discontinued from the trial. More than 25% of these discontinuations were due to adverse events.

	<b>Tolvaptan</b>	<b>Placebo</b>	<b>Total</b>
	<b>N (%)</b>	<b>N (%)</b>	<b>N (%)</b>
Screened	58	57	115
Enrolled	56 (100.0)	55 (100.0)	111 (100.0)
Enrolled from 156-02-235	16 (28.6)	22 (40.0)	38 (34.2)
Enrolled from 156-03-238	40 (71.4)	33 (60.0)	73 (65.8)
Treatment ongoing	28 (50.0)	25 (45.5)	53 (47.7)
Discontinued	24 (42.9)	26 (47.3)	50 (45.0)
Lost to follow-up	0 (0.0)	1 (1.8)	1 (0.9)
Subject withdrew consent	4 (7.1)	4 (7.3)	8 (7.2)
Adverse experience	15 (26.8)	12 (21.8)	27 (24.3)
Subject met withdrawal criteria	2 (3.6)	2 (3.6)	4 (3.6)
Investigator withdrew subject	2 (3.6)	5 (9.1)	7 (6.3)
Sponsor discontinued study	1 (1.8)	2 (3.6)	3 (2.7)
Completed Week 58	3 (5.4)	3 (5.5)	6 (5.4)
Completed Week 106	1 (1.8)	1 (1.8)	2 (1.8)
Analyzed for efficacy	56 (100.0)	54 (98.2)	110 (99.1)
Analyzed for safety	56 (100.0)	55 (100.0)	111 (100)

**Reviewer's comments: There are a large number of discontinuations from this trial.**

Demographics and Baseline Characteristics

**Table 9.4.1.3-3 and the sponsor's table** below highlight key demographic data and baseline characteristics. The majority of subjects had SIADH, euvolemia and a baseline serum sodium  $\geq 130$  mEq/L. The mean age was 64.6 years, approximately 50% of subjects were male and over 90% were Caucasian.

<b>Baseline Characteristics</b>		<b>Enrolled (N =111)*</b>
Hyponatremia Origin	HF	33 (29.7%)
	Cirrhosis	20 (18.0%)
	SIADH/other	58 (52.3%)
Volume Status	Euvolemia	68 (61.3%)
	Hypervolemia	43 (38.7%)
Severity Hyponatremia	Na<135	94 (84.7%)
	Na<130	35 (31.5%)
	Na<125	7 (6.3%)
	Na<120	3 (2.7%)
	Na<115	3 (2.7%)

\* 17 subjects with a serum Na > 135 mEq/L were enrolled.

<b>Parameter</b>	<b>Characteristic</b>	<b>Prior Tolvaptan 15-60 mg<sup>a</sup> (N = 56)</b>	<b>Prior Placebo<sup>a</sup> (N = 55)</b>	<b>Total (N = 111)</b>
<b>Age (years)</b>	<b>Mean (SD)</b>	<b>64.9 (15.1)</b>	<b>64.4 (14.9)</b>	<b>64.6 (15.0)</b>
	<b>Range</b>	<b>27 - 92</b>	<b>31 - 89</b>	<b>27 - 92</b>
	<b>&lt; 65 years, n (%)</b>	<b>29 (51.8)</b>	<b>26 (47.3)</b>	<b>55 (49.5)</b>
	<b><math>\geq 65</math> years, n (%)</b>	<b>27 (48.2)</b>	<b>29 (52.7)</b>	<b>56 (50.5)</b>
<b>Gender</b>	<b>Male, n (%)</b>	<b>28 (50.0)</b>	<b>27 (49.1)</b>	<b>55 (49.5)</b>
	<b>Female, n (%)</b>	<b>28 (50.0)</b>	<b>28 (50.9)</b>	<b>56 (50.5)</b>
<b>Race</b>	<b>Caucasian, n (%)</b>	<b>52 (92.9)</b>	<b>52 (94.5)</b>	<b>104 (93.7)</b>
	<b>Hispanic, n (%)</b>	<b>0 (0.0)</b>	<b>1 (1.8)</b>	<b>1 (0.9)</b>
	<b>Black, n (%)</b>	<b>4 (7.1)</b>	<b>2 (3.6)</b>	<b>6 (5.4)</b>

Trial 156-03-244. Data reported in this ongoing trial up to a 01 Oct 2007 data cutoff date.

<sup>a</sup>Reflects treatment group in the parent double-blind trial.

### Efficacy

This is an open label, uncontrolled study to assess to the safety and efficacy of tolvaptan in maintaining an increased serum sodium concentration in patients with hyponatremia. Given the lack of a control group and **blinding, only limited conclusions about tolvaptan's efficacy** can be made from this study. Findings supportive of **tolvaptan's efficacy in raising serum sodium** are discussed further in Sections 6.1.9 and 6.1.10.

### Safety

This is an uncontrolled study and as such, safety data are difficult to interpret. Further discussion of safety findings to date can be found in Section 7.5.4.

#### 9.4.1.4 Study 156-96-203

**Title:** Multicenter, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging, Efficacy, Safety, and Pharmacokinetic Study of OPC-41061 in Hospitalized Patients with Hyponatremia Secondary to Liver Disease

**Duration of Study:** Initiation: May 23, 1997; Completion: April 22, 1999.

#### Study Design and Objectives

Study 156-96-203 was a multi-center, randomized, double-blind, placebo-controlled dose-ranging, efficacy, safety and PK study in patients with hyponatremia secondary to liver disease.

**The study's primary objective was to assess the safety, efficacy** (for primary analysis: change in sodium) and PK characteristics of 5 dose levels of tolvaptan: 5, 10, 15, 30, and 60 mg in patients with hyponatremia due to liver disease. For a full analysis of the PK and PD data, see the clinical pharmacology review. A review of the safety data is provided below.

#### Main Inclusion Criteria and Study Plan

Men and women 18 years of age or older meeting the following inclusion criteria were eligible for enrollment: history of liver disease for at least 30 days and Child-Pugh Score less than 10; serum sodium 125-135 meq/L; potassium 3.4-5.0 mEq/L; peripheral edema and/or ascites.

Following a 2 day baseline period, subjects were randomized to placebo or 5, 10, 15, 30, or 60 mg tolvaptan for 13 days. In addition to the termination visit, patients were evaluated at a follow-up visit 6-9 days after termination.

#### Subject Disposition

45 subjects were randomized: 5 subjects to each dose level of tolvaptan and 18 subjects to placebo. 18 subjects withdrew: 12/30 in the tolvaptan arm and 6/18 in the placebo. Tolvaptan treated patients withdrew for the following reasons:

- (1) Adverse experience- 4 patients (5 mg), 1 patient (15 mg), 2 patients (60 mg). 5 patients in the pooled placebo group withdrew for adverse experience.
- (2) Sodium exceeded protocol-specified limits- 1 patient (15 mg)
- (3) Withdrew consent - 2 patients (30 mg)
- (4) "Other reasons"- 2 patients (10mg)**

#### Efficacy

The mean change in serum sodium is shown in the sponsor's **table below**. **The 5 mg dose does not appear to be effective** in raising serum sodium. Doses of 60 mg produced the greatest rise. A more variable/less consistent rise was seen across doses of 10 to 30 mg.

**Sponsor's Table showing the mean +/- SD change from baseline in plasma sodium concentration (mEq/L) Days 1- 4: observed- case analysis.**

		OPC-41061					
Study Day	Time Post Dose	5 mg n = 6	10 mg n = 6	15 mg n = 6	30 mg n = 6	60 mg n = 6	Pooled Placebo n = 15
Baseline*		128.5 ± 5.0 (n=6)	130.5 ± 3.7 (n=6)	128.8 ± 2.9 (n=6)	127.0 ± 4.9 (n=6)	130.8 ± 2.9 (n=6)	128.7 ± 4.3 (n=15)
Day 1							
	2 h	0.0 ± 2.2 (n=6)	-0.5 ± 2.0 (n=6)	-2.5 ± 2.4 (n=6)	0.5 ± 1.6 (n=6)	-1.2 ± 2.6 (n=6)	-0.7 ± 2.2 (n=6)
	4 h	1.5 ± 1.8 (n=6)	1.8 ± 1.7 (n=6)	-1.2 ± 1.7 (n=6)	1.3 ± 1.6 (n=6)	0.5 ± 3.6 (n=6)	-0.9 ± 2.9 (n=15)
	8 h	0.0 ± 4.7 (n=6)	3.3 ± 3.1 (n=6)	1.8 ± 3.3 (n=6)	3.2 ± 1.2 (n=6)	2.0 ± 3.5 (n=6)	-1.1 ± 2.4 (n=15)
	12 h	1.2 ± 2.6 (n=6)	3.5 ± 3.5 (n=6)	3.0 ± 3.6 (n=6)	3.0 ± 2.4 (n=6)	3.0 ± 3.6 (n=6)	-0.9 ± 2.4 (n=15)
	23 h	1.5 ± 3.4 (n=6)	3.0 ± 2.4 (n=6)	2.2 ± 3.9 (n=6)	2.8 ± 2.7 (n=6)	6.0 ± 4.3 (n=6)	-0.5 ± 2.4 (n=15)
Day 2							
	2 h	1.0 (n=1)	—	3.0 (n=1)	2.3 ± 2.9 (n=3)	-0.5 ± 0.7 (n=2)	1.0 ± 1.0 (n=3)
	23 h	0.7 ± 2.9 (n=6)	3.2 ± 1.6 (n=5)	3.8 ± 3.5 (n=6)	3.3 ± 3.3 (n=6)	5.2 ± 2.6 (n=6)	0.5 ± 1.8 (n=15)
Day 3							
	2 h	1.0 (n=1)	—	4.0 (n=1)	1.7 ± 2.1 (n=5)	3.0 ± 5.7 (n=2)	-1.3 ± 2.3 (n=3)
	23 h	0.5 ± 3.4 (n=6)	4.2 ± 1.6 (n=5)	2.2 ± 4.1 (n=6)	3.7 ± 4.2 (n=6)	6.0 ± 2.5 (n=5)	0.5 ± 2.7 (n=13)
Day 4							
	2 h	—	—	-2.0 (n=1)	2.7 ± 3.8 (n=3)	2.0 (n=1)	-2.0 ± 4.2 (n=2)
	23 h	1.2 ± 4.9 (n=5)	3.2 ± 2.8 (n=5)	1.5 ± 3.2 (n=6)	4.7 ± 3.3 (n=6)	5.0 ± 1.9 (n=5)	0.2 ± 2.9 (n=13)

Source:

**Sponsor's Table (continued) showing the mean +/- SD change from baseline in plasma sodium concentration (mEq/L) Days 5 through follow-up: observed- case analysis.**

Study Day	Time Post Dose	OPC-41061					Pooled Placebo n = 15
		5 mg n = 6	10 mg n = 6	15 mg n = 6	30 mg n = 6	60 mg n = 6	
Day 5	2 h	0.2±5.5 (n=5)	2.6±2.6 (n=5)	1.7±3.7 (n=6)	3.8±5.4 (n=6)	4.2±1.5 (n=5)	-0.3±4.5 (n=12)
Day 7	Pre-dose	3.3±6.5 (n=4)	3.8±1.6 (n=5)	4.2±2.9 (n=5)	2.3±3.7 (n=6)	5.6±3.8 (n=5)	1.8±5.2 (n=12)
	2 h	---	---	---	1.5±0.7 (n=2)	---	---
Day 9	Pre-dose	0.3±4.2 (n=3)	4.8±2.3 (n=5)	2.4±6.8 (n=5)	3.2±2.7 (n=5)	4.4±4.7 (n=5)	2.0±5.6 (n=10)
	2 h	---	---	---	2.0 (n=1)	---	---
Day 11	Pre-dose	3.5±0.7 (n=2)	3.4±2.1 (n=5)	4.4±9.3 (n=5)	3.4±2.7 (n=5)	3.6±4.5 (n=5)	3.0±5.4 (n=9)
	2 h	---	---	-5.0 (n=1)	4.5±2.1 (n=2)	-1.0 (n=1)	---
Day 13	Pre-dose	4.0±4.2 (n=2)	4.5±3.4 (n=4)	4.8±9.3 (n=5)	2.2±2.7 (n=5)	5.8±2.8 (n=4)	3.3±4.7 (n=9)
	2 h	1.5±3.5 (n=2)	3.8±2.9 (n=5)	0.5±3.8 (n=4)	3.2±3.0 (n=5)	5.3±4.5 (n=4)	1.4±2.9 (n=8)
	4 h	0.5±4.9 (n=2)	1.7±2.5 (n=3)	12.5±9.2 (n=2)	2.8±2.2 (n=5)	5.8±4.6 (n=4)	3.1±5.0 (n=7)
	8 h	0.5±4.9 (n=2)	2.0±4.4 (n=3)	6.0 (n=1)	4.0±4.2 (n=5)	4.3±5.0 (n=4)	2.0±4.2 (n=7)
	12 h	1.5±3.5 (n=2)	2.3±6.7 (n=3)	3.0 (n=1)	4.0±2.9 (n=5)	4.0±7.0 (n=3)	0.5±3.0 (n=6)
	23 h	1.5±2.1 (n=2)	0.3±3.5 (n=3)	14.0±11.3 (n=2)	5.3±5.3 (n=5)	6.8±3.2 (n=4)	2.2±3.3 (n=6)
Day 14	24 h	3.3±8.3 (n=4)	3.0±1.8 (n=4)	6.2±9.5 (n=5)	2.7±1.5 (n=3)	6.8±3.2 (n=4)	3.0±3.4 (n=8)
Follow-Up Days		0.5±10.3 (n=4)	0.0±2.0 (n=3)	1.8±3.4 (n=5)	2.5±4.4 (n=4)	1.6±4.0 (n=5)	2.9±2.8 (n=11)

+ Measurement at 0700 following morning of day 0.

*Reviewer's comment: The small sample size and abundance of missing data make it difficult to determine the efficacy of doses within the 10 to 30 mg range. In cirrhotics, 5 mg doses appear ineffective while doses of 60 mg appear to reliably raise serum sodium.*

### Safety

Three deaths occurred, 2 in tolvaptan treated patients and 1 in placebo. Brief narratives of deaths in tolvaptan-treated patients are provided below. Safety results are incorporated into the Review of Safety (Section 7).

#### (1) Patient ID 002-0003

58-year-old woman with a complicated past medical history including cirrhosis with unconfirmed episode of hematemesis and history of encephalopathy and coagulopathy, history of cervical cancer complicated by radiation cystitis with hematuria, adhesions and abdominal pain attributed to adhesions, vaginal bleeding, abdominal ulceration 1x1cm, orthostatic hypotension and dizziness, systolic ejection murmur and old MI per EKG, dyspepsia, musculoskeletal stiffness, obesity, difficulty sleeping, malnutrition, anemia, leg cramps, and a

history of shortness of breath. Patient admitted 8 days after starting tolvaptan (5 mg) in setting repeated falls. Weight showed a rise from 286 to 307 lbs over last 4 days. The patient was withdrawn from the study and admitted for intractable ascites and evaluation. Day 2 of hospitalization found to be septic with staph aureus, and course was further complicated by need for dialysis. Patient died on hospital day 15.

(2) Patient ID 005-0022

37-year-old Hispanic man with past medical history including alcoholic cirrhosis complicated by ascites and synthetic dysfunction, remote history of gastrointestinal bleed (1995), abdominal pain, possible pancreatitis. Patient admitted on day 11 visit (15 mg) with complaint of cough and abdominal discomfort found to be encephalopathic. Serum sodium 120 mEq/L, amylase 220 and lipase 677, hemoglobin 7.5. Hospital course notable for EGD showing portal gastropathy with shallow duodenal ulcers and non-bleeding varices, blood transfusion, and fever with possible UTI as source. Patient discharged after 6 days at reported baseline. Patient completed study 5 days later. Admitted 6 days after completing study with peritonitis. Patient suffered cardiopulmonary arrest in ER with subsequent blood and peritoneal fluid cultures growing out Ecoli.

*Reviewer's comment: Tolvaptan's role in these deaths (if any) is unclear.*

#### 9.4.1.5 Study 156-97-204

Title: Multicenter, Randomized, Open-label, Active-Controlled, Dose-Titration, Efficacy and Safety Study of OPC-41061 in Hospitalized Patients with Hyponatremia

Duration of Study: Initiation: January 28, 1998; Last Observation: March 10, 1999. According to the sponsor, this trial was terminated early due to poor enrollment.

#### Study Design and Objectives

Study 156-97-204 was a multi-center, placebo-controlled, dose titration study in hospitalized patients with **hyponatremia**. **The study's primary objective was to demonstrate the safety and efficacy of titrated doses of tolvaptan in patients with euvolemic or hypervolemic hyponatremia. Because of the trial's premature termination, emphasis in this review is given to the safety findings.** For further discussion of the PK and PD data in this study, please see the **clinical pharmacologist's review**.

#### Main Criteria for Inclusion and Study Plan

Euvolemic or hypervolemic men and women 18 years of age or older with serum sodium < 135 meq/L were eligible for enrollment. Following a 2 day baseline period during which patients were treated with placebo and fluid restriction, subjects were randomized to fluid restriction with placebo or tolvaptan 10 mg titrated up (15, 30, 45 and 60 mg) as needed. Treatment could continue up to Day 27 with follow-up assessments planned.

#### Subject Disposition

28 subjects were randomized, 17 subjects to tolvaptan and 11 subjects to placebo. 15 subjects were treated with tolvaptan and 8 with placebo. The study was completed by 6 and 2 subjects in the tolvaptan and placebo arms respectively.

#### Demographics

Hyponatremia was attributed to HF in 8 randomized subjects in the tolvaptan arm and 6 in the placebo arm. The **etiology of hyponatremia was designated as "other" in the remaining 9 tolvaptan and 5 placebo randomized subjects.**

### Efficacy

This trial was terminated early and protocol specified efficacy analyses were not performed. At approximately 4 and 23 hours post first dose (10 mg), the mean change in serum sodium was 1.6 and 2.6 mEq/L respectively. Of the 15 subjects, 14 were titrated to a dose greater than 10 mg dose and 9 were titrated to a dose greater than 15 mg. One subject with a baseline serum sodium of 131 mEq/L became normonatremic (sodium of 136 and 137 at 4 hours and 24 hours post dose respectively). The mean increase in baseline serum sodium up to Day 5 was higher in tolvaptan-treated patients (5.2mEq/L tolvaptan, 0.8 mEq/L placebo;  $p < .02$  according to the sponsor's analysis).

**Reviewer's comment:** *It is difficult to draw conclusions about the efficacy of tolvaptan 10 mg as the study's titration design does not allow separation of dose versus time effects. The pre-mature termination of the study, the large number of drop outs (by Day 6, at least 1/3 of subjects in the tolvaptan arm had dropped-out) and the inability to perform protocol-specified analyses for efficacy also make it difficult to draw conclusions about such a titration scheme.*

### Safety

Safety results are incorporated into the Review of Safety (Section 7) and also discussed briefly below.

In one subject (PID 97204-039-0074), serum sodium rose from 129 to 137 at 4 hours post dose on treatment day 1. On treatment day 2, serum sodium was 134 mEq/L pre-dose.

Two deaths occurred in patients receiving at least one dose of study medication, 1 in a tolvaptan treated patient and 1 in placebo. A brief narrative of the death in a tolvaptan-treated patient is provided below.

#### Patient ID 032-0001

61-year-old white woman with past medical history of hypertension, pleural effusion, diabetes, retinopathy, edema, chronic dermal ulcer, cerebrovascular accident (1990) with residual left-sided weakness, right carotid endarterectomy (1997), myocardial infarction (twice in 1998) s/p coronary artery bypass graft (1998), constipation and insomnia. Patient initiated on tolvaptan in May 1998 during prolonged hospitalization that began in March 1998 when she was admitted for sternal wound debridement and pectoral major rotation flap. Hospital course was complicated by fevers, percutaneous trach in setting failed extubation, PEG, pneumothorax requiring chest tube. Patient started on tolvaptan on \_\_\_\_\_ (tolvaptan 5 mg titrated up to 60 mg), discovered on same day to be bacteremic and was treated with antibiotics. 11 days after the start of study medication, she suffered an arrest (found pulseless without respirations) and was withdrawn from the study. Patient was placed on comfort care and died 18 days later after another arrest.

b(6)

**Reviewer's comment:** *Tolvaptan's role in this death (if any) is unclear. A possible association between cardiac arrest and tolvaptan use is discussed in the Review of Safety (Section 7).*

Serious adverse events occurring in cirrhotics included a hospitalization for ascites occurring 34 days after study drug termination and an episode of severe hypoglycemia 13 days after study drug initiation (concomitant medications included insulin).

#### 9.4.1.6 Study 156-96-201

**Title:** Multicenter, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging, Efficacy, Safety and Pharmacokinetic Study of OPC-41061 in Hospitalized Patients with Hyponatremia Secondary to Congestive Heart Failure

**Duration of Study:** Initiation: December 2, 1996; Last Observation: August 30, 1997. According to the sponsor, this trial was terminated early due to poor enrollment.

**Study Design and Objectives:**

Study 156-96-201 was a multi-center, placebo-controlled, dose ranging study in hospitalized patients with **hyponatremia secondary to HF**. The study's primary objective was to demonstrate the safety, efficacy and PK of up to 4 doses of tolvaptan (5, 10, 15 and 30 mg) in patients with hyponatremia secondary to HF. Given the early termination of this study, emphasis in this review is given to the safety findings. For further discussion of the PK and PD data in this study, please see the clinical **pharmacologist's review**.

**Main Criteria for Inclusion and Study Plan:**

Men and women 18 years of age or older with NYHA class II to IV HF and a serum sodium of 118- 135 meq/L and extracellular volume expansion and sodium retention were eligible for enrollment. Following a 2-day baseline period, subjects were to be randomized to placebo or tolvaptan (5, 10, 15 or 30 mg group). Subjects were to be treated for 1 to 4 days with follow-up assessments planned.

**Subject Disposition:**

9 subjects (6 tolvaptan and 3 placebo) were randomized to the 5 mg group. The study was discontinued after completion of the 5 mg group. The study was completed by 5 and 3 subjects in the tolvaptan and placebo arms respectively. One subject in the tolvaptan arm was withdrawn. According to the sponsor, this was because the subject was lost to follow-up.

**Efficacy:**

This trial was terminated early and protocol specified efficacy analyses were not performed. The sponsor reports that at the 5 mg dose, tolvaptan did not appear to have any substantial effect on the serum sodium concentration (the primary efficacy variable).

***Reviewer's comment: Given the early termination of this study, it is difficult to draw any conclusions about tolvaptan's efficacy in raising serum sodium.***

**Safety:**

Safety results are incorporated into the Review of Safety (Section 7) and also discussed briefly below.

There were no withdrawals due to adverse events. One subject treated with tolvaptan experienced a serious adverse event (cardiac arrest due to ventricular fibrillation) 12 days after her last dose of study medication. A brief narrative of this death is provided below.

A 55 year old woman with a past medical history including ischemic dilated CM (EF approx 20%) and reported NYHA class II, CAD/angina, pericarditis, COPD/asthma, pulmonary hypertension, diabetes and HTN. On Day 0 (prior to receiving study drug), non-serious AEs of severe hypotension and mild hypoxia and hypoglycemia was reported. During drug administration, additional non-serious AEs of hypoglycemia, intermittent mild to severe lightheadedness, moderate dizziness and mild sinus tachycardia were reported. On day 5 of dosing mild fatigue and worsening dyspnea and a change in HF classification from class 2 to 3 were reported as non-serious AEs. Mild nystagmus, double vision, diminished reflexes and strength were also reported while on study drug. After stopping study drug, moderate increases in weight (day 3 post drug) were reported. A moderate upper respiratory infection was listed as an AE starting on day 6 post drug. Moderate SOB and mild pitting edema and cough at night were reported as AEs starting on day 7 post drug. Mild changes in strength, reflexes and new

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