

COMBINED CLINICAL AND STATISTICAL REVIEW

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Clinical Reviewer Names	Aliza Thompson (Hyponatremia Efficacy and Integrated Summary of Safety) Shari Targum (Heart Failure Efficacy)
Statistical Reviewer Name	Steven Bai (Statistical Reviewer)
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Established Name	Tolvaptan
(Proposed) Trade Name	Samska TM
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Applicant	Otsuka Pharmaceutical
Priority Designation	S
Formulation	Oral
Dosing Regimen	30 mg/day (Heart Failure) 15-60 mg/day (Hyponatremia)
Indications	(1) Treatment of Worsening Heart Failure (2) Treatment of Hyponatremia (Euvolemic and Hypervolemic)
Intended Population	Adults

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List of Abbreviations and Definition of Terms

Δ	Change
ACE	Angiotensin converting enzyme
ACEI	Angiotensin converting enzyme inhibitor
AE	Adverse event
AICD	Automatic implantable cardioverter/defibrillator
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ARB	Angiotensin-receptor blocker
AUC	Area under the curve
AVP	Arginine vasopressin
BPH	Benign prostatic hypertrophy
BNP	Brain natriuretic peptide
BP	Blood pressure
BUN	Blood urea nitrogen
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CEC	Clinical events committee
CHF	Congestive heart failure
CI	Cardiac Index
CMH	Cochran-Mantel-Haenszel
COPD	Chronic obstructive pulmonary disease
Cr	Creatinine
CRF	Case report form
CSR	Clinical study report
CV	Cardiovascular
CVA	Cerebrovascular accident
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DM	Diabetes mellitus
DMEP	Division of Metabolism and Endocrinology Products
DVT	Deep Vein Thrombosis
ECG, EKG	Electrocardiogram
EF	Ejection fraction
EOT	End of treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
HF	Heart failure
HR	Heart rate
ICH	International Conference on Harmonisation
IND	Investigational New Drug Application
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
ITT	Intent-to-treat
IV	Intravenous
JVD	Jugular venous distension

KCCQ	Kansas City Cardiomyopathy Questionnaire
KVO	Keep vein open
LOCF	Last observation carried forward
LVEDV	Left ventricular end-diastolic volume
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
NA	Not applicable
NDA	New Drug Application
NSAID	Non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
OC	Observed cases
PAP	Pulmonary artery pressure
PCI	Percutaneous coronary intervention
PCWP	Pulmonary capillary wedge pressure
PD	Pharmacodynamic
PE	Pulmonary Embolism
PK	Pharmacokinetic
PM	Pacemaker
PO	By mouth
PRO	Patient-reported outcome
PTCA	Percutaneous transluminal coronary angioplasty
PVR	Pulmonary vascular resistance
QD	Once daily
QOL	Quality of life
RAP	Right atrial pressure
RVG	Radionuclide ventriculogram
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SEALD	Study Endpoints and Label Development
SIADH	Syndrome of inappropriate antidiuretic hormone secretion
SVR	Systemic vascular resistance
TEAE*	Treatment-emergent adverse event*
TIA	Transient ischemic attack
ULN	Upper limit of normal
US	United States
VF	Ventricular fibrillation
VMAC	Vasodilatation in the Management of Acute CHF
VT	Ventricular tachycardia

Note: The following terms are used interchangeably in this review: “Tolvaptan” and “OPC-41061,” “congestive heart failure” and “heart failure,” “body weight” and “weight,” and “subject” and “patient.”

*This term is defined and discussed in Section 7.3.

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

An approvable action is recommended for euvoletic hyponatremia. A non-approval action is recommended for hypovolemic hypervolemic hyponatremia. b(4)

1.2 Risk Benefit Assessment

The following discussion focuses on the two proposed indications for tolvaptan: (1) as a treatment for euvoletic and hypervolemic hyponatremia, and (2) as a treatment for worsening heart failure.

1.2.1 Hyponatremia

1.2.1.1 Efficacy

Tolvaptan's clinical development program for hyponatremia sought to establish the product's efficacy in raising serum sodium. The co-primary endpoints in the phase 3 hyponatremia trials were the AUC of the change from baseline in serum sodium up to days 4 and 30 following study drug initiation. Secondary endpoints largely addressed alternative ways of defining this change and tolvaptan's efficacy in raising serum sodium in sub-populations with greater or lesser degrees of hyponatremia. The results of these analyses are convincing that tolvaptan can raise serum sodium. The p-value for the primary endpoint was highly significant ($p < .0001$) in both phase 3 trials and secondary analyses in which changes in serum sodium were defined in other ways, supported the primary efficacy analysis and suggested that this finding was robust. But while these trials successfully establish tolvaptan's efficacy in raising serum sodium, the clinical significance of this rise in the studied population (subjects with a serum sodium < 135 mEq/L) is unclear.

Of the 15 listed secondary endpoints in the phase 3 hyponatremia trials, only one, the Short Form (SF)-12, addressed a possible clinical benefit to treatment beyond a change in a laboratory value. At day 30, a statistically significant improvement in the Mental Component Summary Score (MCSS) was seen in one of the phase 3 trials (156-02-235), while statistical significance was not reached in the other (156-03-238). Several concerns are raised by this instrument. These include statistical concerns due to the lack of a prespecified analysis plan and method for adjusting for multiplicity. In addition, it cannot be excluded that knowledge of changes in serum sodium may have biased a subject's response to questionnaire items ("my sodium is better therefore I am better"). The most critical issue, however, surrounds the validity of this instrument in the enrolled population. In a Study Endpoint Review, the Study Endpoints and Label Development Team deemed the SF-12 MCSS to be an inadequate measure of function and health related quality of life in the targeted population and recommended that it not be used to support efficacy claims. Thus the clinical significance of a change in serum sodium in this broadly defined population remains uncertain. That being said, in this reviewer's opinion, a change in serum sodium is a reasonable surrogate for clinical benefit in those with more severe hyponatremia.

Severe hyponatremia can cause morbidity and mortality and clinical benefit is likely to be incurred from interventions that raise serum sodium. Few subjects in tolvaptan's phase 3 studies had markedly low serum sodium levels, as these trials largely excluded symptomatic patients and those with "asymptomatic severe hyponatremia" that was "likely to require saline intervention." Nonetheless, analyses suggest that tolvaptan's

ability to raise serum sodium levels was preserved in study subjects with the lowest baseline serum sodium levels. In this reviewer's opinion, tolvaptan is likely to raise serum sodium levels in patients with severe hyponatremia, a subpopulation of hyponatremic subjects in whom a change in serum sodium is expected to predict a clinically meaningful endpoint. A critical question that remains is how to define this level of "severe hyponatremia."

Historically, FDA has accepted a change in serum sodium as a surrogate endpoint. Conivaptan was approved for the treatment of euvolemic and hypervolemic hyponatremia by the Division of Metabolism and Endocrinology Products (DMEP) based on a change in serum sodium in subjects with a baseline serum sodium 115-130 mEq/L (in a double-blind, placebo-controlled trial cited on conivaptan's label, the mean serum sodium at entry was 123.3 mEq/L). During tolvaptan's development program, the need to enroll patients with "clinically significant hyponatremia" was repeatedly emphasized by DMEP and in defining this population, DMEP cited a serum sodium threshold of < 130 mEq/L. The basis for this cut-off is unclear and further discussion is needed on changes in serum sodium as a surrogate endpoint and the context(s) in which (and/or level of hyponatremia at which) a change in serum sodium can be expected to predict a clinically meaningful benefit. This issue will be addressed further at an Advisory Committee Meeting scheduled for late June.

1.2.1.2 Safety

Adequacy of the safety database

Although over 4,000 subjects were exposed to tolvaptan during its clinical development, the applicability of these data to the hyponatremic population at the doses proposed for use (15 to 60 mg) is uncertain. This is in part because the safety database is heavily weighted by subjects with heart failure who did not have hyponatremia and it is unclear if adverse effects observed in this population are predictive of adverse effects in subjects without heart failure or those with hyponatremia. Of the 3294 subjects with heart failure and/or hyponatremia treated in multiple-dose, placebo-controlled trials, only 607 subjects had a serum sodium <135 mEq/L, 189 subjects had a serum sodium <130 mEq/L and 52 subjects had a serum sodium < 125 mEq/L. Moreover, the vast majority of subjects had heart failure; only 97 subjects carried a diagnosis of SIADH/other while 100 subjects were reported to have hyponatremia in the setting of cirrhosis. If susceptibility to tolvaptan's adverse effects is influenced by the underlying etiology of hyponatremia (cirrhosis, heart failure and SIADH/other) and/or baseline serum sodium level, analyses of this larger dataset may not provide an accurate assessment of tolvaptan's safety in these populations of interest.

This safety database also contains limited data on tolvaptan's safety at the upper end of the proposed dosage range for hyponatremia (60 mg), a dose that appears to be useful in getting hyponatremic patients to goal. Outside of the phase 3 hyponatremia trials, in which 223 subjects were exposed to tolvaptan doses of 15 to 60 mg, approximately 332 subjects with heart failure and/or hyponatremia and fewer than 70 subjects with hyponatremia were exposed to tolvaptan doses of 60 mg or greater in multiple dose-placebo controlled trials. For chronic use, the data are even more limited; at 6 months and beyond, all placebo-controlled data in hyponatremic subjects are derived from the phase 3 heart failure trial and hence reflect exposure to a 30 mg dose. Because of these limitations of the safety database and concerning safety signals in subjects with hyponatremia in the setting of cirrhosis and heart failure (discussed below), this reviewer believes that tolvaptan should not be approved for hyponatremia at this time.

Adverse events

The goal of treating hyponatremia is to raise serum sodium levels; however, overly rapid correction can lead to 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, and, to minimize this risk, current guidelines recommend rates of correction of < 10-12 mEq/L over 24 hours. In **tolvaptan's development program**, no case of osmotic demyelination was reported and in the phase 3 hyponatremia studies, 5.3% of tolvaptan subjects had an increase in serum sodium greater than 8 mEq/L at approximately 8 hours and 1.1% had an increase greater than 12 mEq/L at approximately 21 hours post first dose. In contrast, less than 1% of placebo-treated subjects had a rise greater than 8 mEq/L at approximately 8 hours and no placebo-treated subject had a rise greater than 12 mEq/L at approximately 21 hours post first dose. That being said, few subjects with marked hyponatremia were included in the phase 3 hyponatremia trials and it is unclear if the experience in the studied population is predictive of the risk of overly rapid correction in those with more severe hyponatremia. Analyses stratifying hyponatremic subjects by degree of hyponatremia (baseline serum sodium < 130 mEq/L vs. 130-134 mEq/L), suggest a greater risk of overly rapid (based on these guidelines) correction in tolvaptan-treated subjects with a lower baseline serum sodium. Because few subjects with marked hyponatremia were enrolled in these trials, the risk of overly rapid serum sodium correction in this key population remains poorly characterized. **In this reviewer's opinion**, if tolvaptan were approved for the treatment of hyponatremia, patients should be hospitalized for initiation and the label should advise clinicians of the need for frequent serum sodium measurements.

The hyponatremia safety dataset (N=607) was heavily weighted by heart failure subjects with hyponatremia enrolled in heart failure trials, and, as a result, safety analyses of this dataset to some extent mirrored those described below for the heart failure indication. A slightly greater incidence of cardiac arrest, dehydration, ventricular arrhythmia (ventricular fibrillation) was observed in tolvaptan-treated subjects. In addition, sepsis, ascites and respiratory failure were also reported at a slightly greater incidence in the tolvaptan arm. In all cases the absolute difference between treatment arms was less than 1.5%, though the relative difference was greater. To address possible unique risks, analyses were also stratified by underlying disease etiology (heart failure, cirrhosis and SIADH/other), and the discussion that follows addresses the safety findings in these subpopulations.

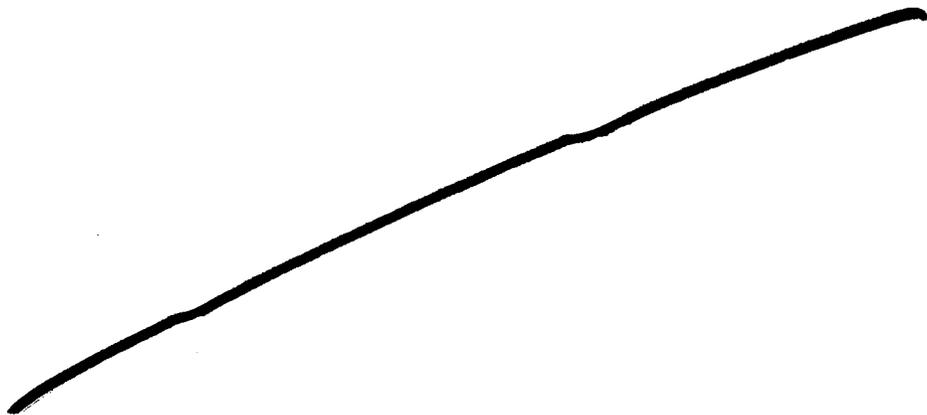
Hyponatremic subjects with heart failure: 410 subjects with both heart failure and hyponatremia were enrolled in multiple-dose, placebo-controlled trials. The majority of these subjects were enrolled in trials conducted for **tolvaptan's proposed heart failure** indication (as a treatment for worsening heart failure) and received a fixed 30 mg dose and not the proposed 15 to 60 mg dose-titration. The phase 3 heart failure trial enrolled the greatest number of subjects with both heart failure and hyponatremia and is the only placebo-controlled trial in which heart failure subjects with hyponatremia were exposed to tolvaptan for greater than 6 months. Of the 2,063 heart failure subjects treated with tolvaptan in the phase 3 heart failure trial, 242 subjects had both heart failure and hyponatremia. Among all subjects enrolled in this trial, mortality was not greater in tolvaptan (N=2063) compared to placebo (N=2055) treated subjects with heart failure; however in the subgroup of subjects with both heart failure and hyponatremia, slightly greater mortality was observed in the tolvaptan (N=242) than the placebo (N=232) treatment arm. In this subgroup of subjects with both heart failure and hyponatremia, treatment-emergent fatalities were reported in 42.1% of tolvaptan and 38.4% of placebo-treated subjects. These results suggest that tolvaptan does not cause a dramatic increase in mortality in patients with both heart failure and hyponatremia; however, they do not exclude a small increase in mortality. **In this reviewer's opinion**, this potential risk outweighs the somewhat uncertain benefit of raising serum sodium with tolvaptan in patients with heart failure and hyponatremia.

Hyponatremic subjects with cirrhosis: Approximately 100 hyponatremic cirrhotics were studied in multiple-dose placebo-controlled trials; the majority of these subjects were enrolled in the phase 3 hyponatremia trials. Death rates were similar in tolvaptan and placebo-treated cirrhotics with hyponatremia. Analyses of adverse events, however, revealed a greater incidence of gastrointestinal (GI) bleeding in tolvaptan than placebo-treated cirrhotics with hyponatremia. In the phase 3 hyponatremia trials, in which subjects were exposed to 30 days of tolvaptan, GI bleeding was reported in 6 (9.5%) hyponatremic cirrhotics in the tolvaptan treatment arm and 1 (1.8%) hyponatremic cirrhotic in the placebo treatment arm. Pooling GI bleeding events with adverse event reports of hematomas and ecchymoses (another possible sign of impaired coagulation) magnified the difference in incidence between treatment arms. In the phase 3 hyponatremia trials, adverse event reports of GI bleeding, hematomas and/or ecchymoses were reported in 11 out of 63 (17.5%) hyponatremic cirrhotics treated with tolvaptan and only 1 out of 57 (1.8%) hyponatremic cirrhotics treated with placebo. The V2 receptor plays a role in von Willebrand factor release and hence a biologically plausible mechanism for this adverse effect in a population at high risk for bleeding can be hypothesized. That being said, the number of study subjects with hyponatremia and cirrhosis was small, as were the number of bleeding events reported. Nonetheless these data raise the question of an increased risk of bleeding in cirrhotics with hyponatremia treated with tolvaptan. In this reviewer's opinion, the safety database of cirrhotics with hyponatremia is insufficient to establish tolvaptan's safety at the doses proposed for use in cirrhotics with hyponatremia. Additional studies are needed to establish tolvaptan's safety in this population. Moreover, given the potential clinical importance of this safety signal, this reviewer believes that prior to approval, additional efficacy studies would need to establish tolvaptan's efficacy in hyponatremic subjects with cirrhosis via a clinically meaningful endpoint (an endpoint measuring how a patient feels, functions or survives) and not via a surrogate.

Hyponatremic subjects with SIADH/other: In contrast to the experience in subjects with hypervolemic hyponatremia, no unique concerning safety signals were identified in subjects with SIADH/other. Deaths, serious adverse events and severe adverse events all occurred at a numerically lower incidence in tolvaptan than placebo-treated subjects with SIADH/other. The safety data in subjects with SIADH/other do not suggest significant risks in this subgroup, however, few subjects with SIADH/other were studied; in multiple-dose, placebo-controlled trials, 97 subjects with SIADH/other were treated with tolvaptan. While the safety database containing all subjects with hyponatremia is larger, it is heavily weighted by heart failure subjects and subjects receiving a dose of 30 mg (less than the proposed upper end of the dosage range). It is unclear if the experience in subjects with heart failure and hyponatremia is predictive of risk in subjects with SIADH/other at the doses proposed for use. Moreover, this experience does not provide reassurance of safety; analyses do not exclude a small increase in mortality in tolvaptan-treated subjects with both heart failure and hyponatremia. In this reviewer's opinion, the safety database is too small to establish safety in this subpopulation at the doses proposed for use. Additional studies are needed to establish tolvaptan's safety in subjects with SIADH prior to approval for use in patients with euvolemic hyponatremia.

1.2.2 Heart Failure

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 Safety

Tolvaptan's clinical development program was heavily weighted by subjects with heart failure. In multiple-dose, placebo controlled trials, 3184 subjects with heart failure were treated with tolvaptan; 1372 subjects were exposed to tolvaptan for greater than 6 months and 817 for more than 1 year. The vast majority of these subjects (N=2063) were enrolled in the phase 3 heart failure trial and received 30 mg of tolvaptan, the dosage proposed for the heart failure indication.

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In analyses of this safety dataset, mortality and serious treatment emergent adverse events were not markedly different between the tolvaptan and placebo study arms. Serious adverse events occurring at a slightly greater

incidence in tolvaptan-treated heart failure subjects included ventricular arrhythmias, cardiac arrest, syncope, dehydration and cardiac shock. Analyses of adjudicated events from the phase 3 heart failure trial similarly showed a slightly greater incidence of hospitalizations for cardiac arrhythmias and a greater incidence of sudden cardiac death. In addition to these findings, the incidence of pulmonary embolism and strokes/ischemic events was also slightly greater in tolvaptan-treated subjects in the phase 3 heart failure trials. Taken separately, however, none of these AEs occurred at an incidence greater than 1.0% that observed in the placebo arm. These are not unexpected adverse events in this population and the clinical significance of these findings remains unclear. On the hand, they may represent real risks associated with tolvaptan; on the other hand they may be a statistical artifact- a hazard of conducting innumerable analyses.

Given tolvaptan's mechanism of action, hypernatremia is of concern, particularly in patients with worsening heart failure, a population in which hyponatremia is not a requirement for therapy. In the phase 3 HF trial, adverse events of hypernatremia were reported in 1.7% of tolvaptan and 0.5% of placebo-treated subjects. Although adverse events of hypernatremia were relatively uncommon in the phase 3 heart failure study, analyses of laboratory values suggest a high incidence of hypernatremia. 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 adverse event reports.

1.3 Recommendations for Postmarketing Risk Management Activities

Approval is not recommended at this time and hence no Postmarketing Risk Management Activities are recommended.

1.4 Recommendations for other Postmarketing Study Commitments

Approval is not recommended at this time and hence no other Postmarketing Study Commitments are recommended.

2 Introduction and Regulatory Background

2.1 Product Information

Samska® (Tolvaptan) is an orally administered selective vasopressin V₂- receptor antagonist developed for the treatment of worsening congestive heart failure and treatment of euvolemic and hypervolemic hyponatremia. **Tolvaptan (chemical name: (±)-4'-[(7-chloro-2,3,4,5-tetrahydro-5-hydroxy-1*H*-1-benzazepin-1-yl) carbonyl]-*o*-toluim-toluidide; chemical formula: C₂₆H₂₅ClN₂O₃)** is a member of a new chemical and pharmacologic class of **drugs known as “vaptans” or aquaretics. These drugs lower urine osmolality by blocking the vasopressin V₂-receptor located on the basolateral aspect of collecting duct cells of the renal tubule. Antagonism of the V₂ receptor prevents the insertion of aquaporins (water channels) into the luminal membrane of collecting duct cells. In so doing, V₂ receptor antagonists induce a water diuresis (aquaresis) and raise serum osmolality and sodium concentrations.**

To date, conivaptan is the only member of this class approved for use in the United States. Conivaptan is an intravenous drug and has been approved for use for up to 4 days for the treatment of hypervolemic and euvolemic hyponatremia in hospitalized patients. Another member of this class, mozavaptan, is approved for use in Japan. To date, no members of this class have been approved in the United States for the treatment of worsening heart failure. To date, no member of this class has been approved for chronic use in the treatment of hyponatremia.

Tolvaptan’s proposed indications are for the (1) short-term improvement of signs and symptoms of worsening heart failure beyond that achieved with standard care and (2) treatment of hypervolemic and euvolemic hyponatremia and prevention of worsening hyponatremia. Tolvaptan is formulated in 15 and 30 mg tablets. For the indication of worsening heart failure, 30 mg tolvaptan is to be taken by mouth once a day. For the indication of hypervolemic and euvolemic hyponatremia, 15mg tolvaptan is to be taken by mouth once a day with dose titration by 15 mg every 24 hours to a maximum dose of 60 mg once a day as needed for effect.

2.2 Tables of Currently Available Treatments for Proposed Indications

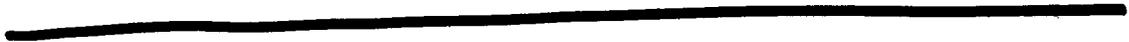
2.2.1 Hyponatremia

Serum osmolality and serum sodium are tightly regulated by the hormone vasopressin and hyponatremia can **develop when vasopressin’s release is** stimulated via a non-osmotically mediated mechanism. In subjects with hypervolemic hyponatremia due to cirrhosis or heart failure, vasopressin release is baroreceptor mediated- a compensatory response to inadequate blood pressure and/or volume (effective extracellular fluid volume depletion). In contrast, in patients with SIADH, a physiologic stimulus for release (osmotic or baroreceptor) is often lacking; SIADH can be due to a reset osmostat (in which patients release vasopressin at a serum sodium level lower than normal) or unregulated secretion/ectopic secretion, in which secretion is independent of plasma osmolality.

The treatment of hyponatremia is determined by the etiology of hyponatremia, its severity and duration. Treatment of asymptomatic non-hypovolemic hyponatremia generally consists of fluid restriction, and, diuretics combined with salt supplementation (in subjects with euvolemic hyponatremia). In severe cases of euvolemic hyponatremia, there are also case reports of demeclocycline, lithium or urea use (off-label indications). In

patients with severe symptomatic non-hypovolemic hyponatremia, the goal of therapy is to raise serum sodium more rapidly than in patients who are asymptomatic and/or have more chronic disease and hypertonic saline or saline and diuretics can be administered. In hospitalized patients, conivaptan can also be administered as a short term therapy for euvolemic and hypervolemic hyponatremia. Table 2.2.2-1 below provides an overview of currently available therapies for hyponatremia and a brief discussion of their limitations.

Table 2.2.1-1 Treatment of hyponatremia			
Treatment	Proposed Mechanism of Action	Administration	Limitations
Fluid Restriction	Limits free water intake	N/A	Difficult to implement, especially in cases where more severe fluid restriction needed (higher urine osmolality)
Hypertonic saline	Direct addition of concentrated salt solution to intravascular space	IV	Volume overload, risk of overly rapid correction, not a chronic therapy
Diuretics	Increases solute-free water excretion	oral or IV	Risk of volume depletion, inconsistent results
Demeclocycline	Induces nephrogenic diabetes insipidus	oral	Pseudotumor cerebri (Precaution on label), acute renal failure and nephrogenic diabetes insipidus as potential adverse reactions, among others listed on label. Literature suggests that nephrogenic diabetes insipidus typically resolves after cessation
Lithium	Induces nephrogenic diabetes insipidus	oral	Narrow therapeutic window with dose-related toxicity including tremor, mild ataxia, drowsiness, muscular weakness, diarrhea or vomiting. Chronic use associated with nephrogenic diabetes insipidus. Nephrogenic diabetes insipidus thought to typically improve after cessation, although more prolonged exposure associated with less recovery and meta-analysis (2005) reported that up to 70% failed to resolve after drug cessation
Urea	A solute load, increases solute-free water excretion	oral	There are limited case reports on the use of urea in adults and children with SIADH. According to some authors, urea is “well tolerated” without significant side effects; according to others it is “poorly tolerated”
Conivaptan	V2 receptor antagonism (also antagonizes V1a receptor)	IV	Thirst, overly rapid correction of serum sodium, hypotension/orthostatic hypotension, infusion site reaction, hypokalemia among others; according to label, safety database insufficient to establish safety in subjects with underlying heart failure; cannot be used as a chronic therapy



b(4)

1 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Withheld Track Number: Medical- 1

[Redacted]

b(4)

2.3 Availability of Proposed Active Ingredient in the United States

This product is not currently marketed in this country.

2.4 Important Safety Issues With Consideration to Related Drugs

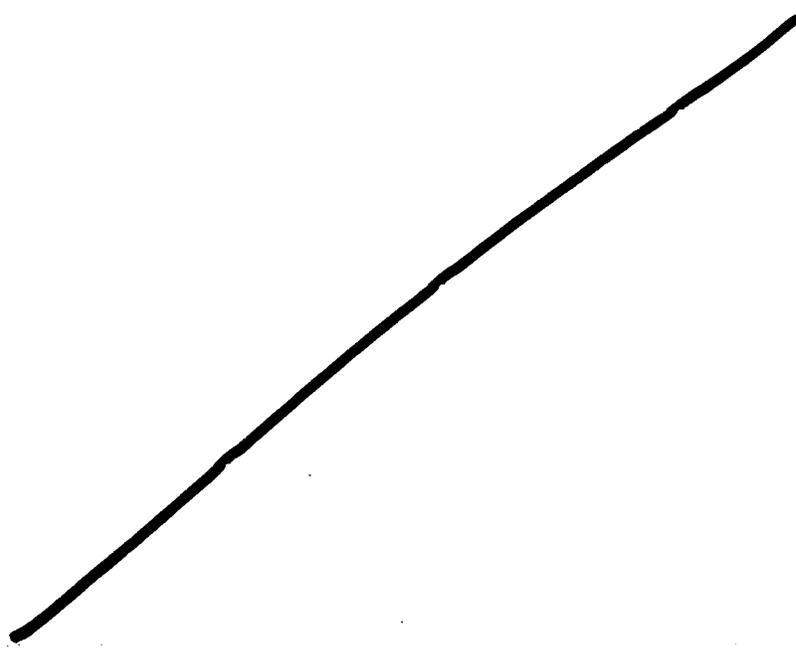
See section 7.2.6 for a discussion of TEAEs associated with conivaptan use.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Tables 2.5.1 and 2.5.2 below provide an overview of Presubmission regulatory activity related to this NDA for the heart failure and hyponatremia development programs respectively.

[Redacted]

b(4)



b(4)

Table 2.5.2 Presubmission Regulatory Activity Related to IND 54,200 (Hyponatremia Indication)		
Date	Type of Correspondence/Meeting	Comments
September 23, 1997	IND Submit Date to Division of Metabolic and Endocrine Products	
July 12, 2002	Safety Teleconference	Arranged to discuss disproportionate numbers of cardiovascular events, primarily arrhythmias seen in the treatment group in protocols 156-98-213; 156-00-220; 156-00-222. Concern was also raised at the meeting about possible QT prolongation. <i>“Dr. Parks commented that it is difficult to say that the findings are drug-related or associated with the disease, but the adverse events are concerning...”</i>

		<p><i>“Although there is still some concern, the Agency believes it is acceptable to continue the studies with appropriate monitoring.”</i></p>
November 3, 2002	EOP2	<p>With respect to dose selection for phase 3 study, Division expressed concern that data insufficient to recommend an initial dose for proposed phase 3 studies; given concern for severe AEs noted to date (including worsening HF, ventricular tachycardia and progression to hepatic failure), Dr. Orloff recommended starting with the lowest potentially effective dose.</p> <p>Division emphasized need to study subjects with serum sodium less than 130. <i>“Ideally, inclusion criteria for hyponatremia studies would be modified to include only patients with serum sodiums less than 130, which would target the likely treatment population.”</i></p> <p>Division raised concern for off-label use in Heart Failure patients and in this setting stressed need for cardiovascular safety and efficacy data before approval for use in hyponatremia.</p> <p>Sponsor informed that 30 days exposure in phase 3 studies of hyponatremia likely not sufficient for safety. Division also noted that 300 patients from phase 3 studies of hyponatremia <i>“might not be enough to adequately look at the cardiac adverse event question”</i></p>
March 7, 2003	Special Protocol Assessment Response	<p><i>“The primary message that we wish to communicate to you is that if an NDA is submitted for tolvaptan for treatment of hyponatremia, our review will focus on the following:</i></p> <ol style="list-style-type: none"> <i>1. Is the agent effective in treating clinically significant (<130mEq/L) hyponatremia?</i> <i>2. Is the agent likely to be safe for all populations who are likely to receive the drug?”</i> <p><i>“... at this time, the medical literature does not appear to support recognition of mild hyponatremia as a disease state meriting specific treatment. In order for the Division to consider an indication in this area, the benefit: risk ratio would need to be clearly positive. You would need to demonstrate some clinical improvement in the treated patients, and not just a change in a laboratory value...”</i></p> <p>With respect to the primary endpoint, it was noted that “While day 4 AUC should be the primary endpoint, day 30 AUC remains an important endpoint.”</p>
May 24, 2003	Meeting Minutes: Clarification of Division’s statistical plan recommendations made in SPA	Division recommends co-primary endpoints of serum sodium AUC days 0-4 and AUC days 0-30 to be tested in entire hyponatremia population, with utilization of a multiple-comparisons procedure such as the Hochberg procedure.
May 23, 2006	pre-NDA scheduled with DMEP then cancelled after receiving preliminary response	<p><i>“Given the limited number of hyponatremic subjects exposed to tolvaptan at six months and one year that fall significantly below ICH guidelines, it is unlikely that tolvaptan will be approved for indefinite treatment based on the current safety database. The approved duration of treatment will depend on the duration of adequate exposure in clinical trials and may be limited based on results of the safety review.”</i></p> <p>Also raised concern about ability of database to identify unique safety signals in hyponatremia subpopulations (cirrhosis, SIADH, etc).</p>
April 6, 2007	IND transferred to Division of Cardiovascular and Renal Products	
May 7, 2007	pre-NDA meeting minutes	The need for an adequate database of subjects with a serum sodium less than 130 was stressed. <i>“Dr. Temple indicated the need for data for a significant number of patients with a serum sodium level below 130, where the usefulness of treatment is not in doubt.”</i> Concern was also raised by the

		Division of Metabolism and Endocrinology Products regarding tolvaptan's limited long-term safety database for hyponatremic patients.
October 19, 2007	CardioRenal response to proposed cognitive and neurologic outcome measures in protocol 156-04-246	If approval for a specific indication such as the treatment for cognitive and/or other neurological deficits accompanying hyponatremia was sought, further discussion with the Agency would be needed. <i>"The existence of the entity (e.g., cognitive or other neurological deficits accompanying mild to moderate hyponatremia) and its operational definition must be broadly accepted by medical experts. Clinical trials should be appropriately designed to measure the effect of tolvaptan as a treatment for that entity, with suitable instruments being used for that purpose."</i>

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Overall, the quality of the submission was acceptable. In general, the submission was well organized and information could be easily located. When additional data or clarification was sought, the sponsor responded promptly.

3.2 Compliance with Good Clinical Practices

According to the sponsor (page 4, module 2.5.1), clinical trials were conducted in accordance with Good Clinical Practices and International Conference on Harmonisation Guidelines.

Requests for audits by the Division of Scientific Investigations were made for 7 sites:

- (1) Study 156-03-236- Sites 521, 152, and 787
- (2) Study 156-03-238- Sites 200 and 212
- (3) Study 156-02-235- Sites 39 and 35

These sites were selected because they demonstrated a larger tolvaptan treatment effect than that seen in the study population as a whole and because they enrolled more subjects than most other participating sites for a particular study. Findings from these sites available at the time of submission of this review are shown in the table below. At this time, the audits have not revealed violations of such potential to affect the integrity and reliability of the data submitted for this NDA.

Inspection Site (Study)	Results
39 (156-02-235)	No deficiencies were noted and DSI recommended the data from the site as acceptable

	in support of tolvaptan's NDA.
35 (156-02-235)	A failure to adhere to the protocol (failure to meet eligibility criteria, obtain laboratory values and administer drug in specified time window) and inadequate and inaccurate records (source documents did not document eligibility criteria, failure to use the most recent informed consent document) were uncovered. A voluntary action was indicated however DSI did not consider the violations of such potential significance to affect the integrity and reliability of the data for tolvaptan's NDA.
(156-03-236)	A failure to report to the IRB all unanticipated problems involving risks to human subjects was uncovered- the IRB was not notified of the death of a study subject until 6 weeks later. A voluntary action was indicated and DSI recommended the data from the site as acceptable in support of tolvaptan's NDA.

3.3 Financial Disclosures

Forms certifying financial interests and arrangements with clinical investigators were submitted by the sponsor. According to the sponsor, as of September 10, 2007, 863 statements from 946 investigators had been received and 5 of these investigators had disclosable information. An additional 4,593 statements had been received from 4,719 sub-investigators, 1 of whom had disclosable information. The sponsor describes reasonable efforts to try to collect information from the remaining investigators and sub-investigators. Forms pertaining to the disclosable financial interests of the 6 investigators were submitted and in all cases, the study was blinded and no investigator enrolled a significant proportion of the trial population (individually or collectively). Based on the available information, the sponsor has adequately disclosed financial arrangement with clinical investigators. These arrangements do not raise significant concerns about the integrity of the data.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The FDA chemistry review has not yet been finalized. The findings discussed in this section are based on preliminary discussions with the FDA chemistry reviewer, Dr. Amit Mitra.

With respect to drug substance, it is possible that residual toluene sulfonic acid could form a methyl ester at the final recrystallization step when [REDACTED] Toluene sulfonic acid methyl ester is a potential genotoxic carcinogen and the sponsor has been asked to provide data on the residual level of this potential impurity in the drug substance batches. According to Dr. Mitra, the sponsor needs time (possibly a month) to developing an analytical method and a set specification for this impurity. b(4)

The drug product review is not completed at this time. According to Dr. Mitra, [REDACTED]

[REDACTED] . Though the sponsor has performed dissolution studies, the discriminatory capability of these studies is unclear and a consult has been placed to determine if a bio-waver can be granted. For further information on chemistry manufacturing and control issues, please see Dr. Mitra's review. b(4)

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

The FDA preclinical pharmacology/toxicology review has not yet been finalized. The findings discussed in this section are based on preliminary discussions with the FDA preclinical pharmacology/toxicology reviewer, Dr. Xavier Joseph. According to Dr. Joseph, as a whole the preclinical pharmacology/toxicology program was adequate and revealed no significant safety issues. According to Dr. Joseph, at this time, the application is approvable from a preclinical pharmacology/toxicology perspective. For further information on preclinical pharmacology/toxicology findings, please see Dr. Joseph's review. Preclinical Pharmacology/Toxicology findings are also discussed further in Sections 7.2 and 7.6.

4.4 Clinical Pharmacology

The FDA clinical pharmacology review has not yet been finalized. The findings discussed in this section are based on preliminary discussions with the FDA clinical pharmacology reviewer, Dr. Peter Hinderling and review of the sponsor's submission. In addition to the findings discussed below, Dr. Hinderling noted that additional studies exploring the dosing interval (QD vs. BID) and dose range (particularly at the high end) would have been informative. Moreover, earlier measurements of serum sodium following drug withdrawal (e.g. in the day and days immediately following drug withdrawal) would have also provided greater insight into the time course over which serum sodium falls after drug withdrawal. Nonetheless, according to Dr. Hinderling, this application is approvable from a clinical pharmacology perspective. For further information on tolvaptan's clinical pharmacology, please see the review by Dr. Hinderling, and by pharmacometrics.

4.4.1 Mechanism of Action

Tolvaptan is a selective vasopressin V2- receptor antagonist. The V2 receptor is found on the basolateral aspect of collecting duct cells of the renal tubule. Antagonism of the V2 receptor prevents the insertion of aquaporins (water channels) into the apical membrane of collecting duct cells. In so doing, V2 receptor antagonists are thought to increase the excretion of water without increasing electrolyte excretion.

4.4.2 Pharmacodynamics

In general, tolvaptan administration increased urine volume and serum sodium concentration and osmolality, decreased body weight and urine osmolality and caused a negative fluid balance in clinical studies.

4.4.3 Pharmacokinetics

- Following oral administration within the proposed dose range, peak plasma levels of tolvaptan is observed at approximately 2-4 hours. Oral bioavailability of the 30 mg tablet is > 40% and food does not cause a clinically significant change in plasma concentrations.
- Tolvaptan is extensively metabolized in the liver by cytochrome P450 isoenzyme, CYP3A4. In mass balance studies, less than 1% of tolvaptan was excreted unchanged in the urine.
- Although tolvaptan does not significantly induce or inhibit cytochrome P450 isoenzymes, it is a substrate and inhibitor of MDR1 transport.
- Fourteen metabolites have been identified to date. In vitro studies suggest that these metabolites have little to no antagonist activity at the V2 receptor at the doses proposed for clinical use.
- Plasma elimination of tolvaptan follows first order kinetics. The terminal elimination half life is approximately 7-11 hours.
- At the doses proposed for clinical use, approximately 98% of tolvaptan is protein bound.
- Drug interaction studies tested the affect of ketoconazole, rifampin, grapefruit juice, furosemide, HCTZ and lovastatin on tolvaptan pharmacokinetics. In these studies, potentially clinically significant drug interactions were noted between tolvaptan and ketoconazole and rifampin. Administration of ketoconazole 200 mg was associated with an approximately 3.5 to 5.4-fold increase in tolvaptan exposure (C_{max} and AUC_∞, respectively) while rifampin administration decreased tolvaptan exposure to approximately 10 to 20 % (C_{max} 0.17 and AUC_t 0.13 for ratio of rifampin + tolvaptan: tolvaptan).

Reviewer's comment: As discussed in Section 2.5, the dose of ketoconazole used in the interaction study with tolvaptan (200 mg instead of 400 mg) was too low. Moreover, in the phase 3 heart failure study, one death was observed in a patient with markedly elevated tolvaptan levels in the setting of clarithromycin coadministration. Tolvaptan's role in this death could not be excluded. Coadministration of tolvaptan with potent CYP3A4 inhibitors should be contraindicated.

Coadministration with rifampin causes a clinically significant reduction in tolvaptan levels and hence may markedly diminish tolvaptan's efficacy in raising serum sodium levels. Though it is difficult to make exact dose adjustment recommendation, the label should inform the clinician that efficacy may be markedly reduced in this setting.

- Drug interaction studies tested the affect of tolvaptan on lovastatin, amiodarone, warfarin, digoxin, furosemide and HCTZ pharmacokinetics. Clinical studies indicated a potentially clinically significant effect of tolvaptan on digoxin pharmacokinetics. Tolvaptan caused a 1.3 and 1.2 fold increase in C_{max} and AUC_τ, **however tolvaptan's effects on digoxin's renal clearance was more marked (59% reduction)**, suggesting a potentially greater effect on digoxin pharmacokinetics than indicated by C_{max} and AUC data.

Reviewer's comment: Digoxin is a MDR1 substrate and tolvaptan is a substrate and an inhibitor of this transporter. Measurements of digoxin renal clearance suggest that tolvaptan has a greater effect on digoxin pharmacokinetics than indicated by the reported AUC and C_{max} measurements. Digoxin has a narrow therapeutic window and the label should alert clinicians to the possibility of increases in digoxin levels in patients on tolvaptan.

- The effects of hepatic impairment and heart failure on tolvaptan pharmacokinetics were studied. In subjects with hepatic impairment, single dose administration resulted in an approximately 2-fold increase in tolvaptan levels. A similar rise was seen in heart failure patients.
- No formal studies were conducted in subjects with renal impairment. According to Dr. Hinderling, population PK analyses showed no significant effect of renal impairment on tolvaptan clearance.
- Age and gender do not significantly alter **the drug's pharmacokinetic profile**.

5 Sources of Clinical Data

Data from trials conducted by the sponsor or designee and submitted under NDA 22-275 were reviewed. Two consults were placed with the Study Endpoint and Label Development Team: (1) to evaluate the validity of the **sponsor's method for evaluating patient assessed dyspnea** status and of the Kansas City cardiomyopathy questionnaire, and (2) to evaluate the validity of the SF-12 in subjects with hyponatremia. A consult was also placed with the Interdisciplinary Review Team for QT Studies. Requests for audits by the Division of Scientific Investigations were also made.

5.1 Tables of Clinical Studies

In addition to the studies described below, data from studies conducted for other indications were reviewed in the safety assessment. By indication these studies are:

- (1) ADPKD: 156-04-249, 156-04-248, 156-04-001, 156-04-250, 156-05-002
- (2) Extracellular fluid volume expansion: 156-03-001, 156-06-002

Table 5.1-1 Mass Balance, Bioavailability and Food Effect

Protocol Number	Design	Number Enrolled	Comments
156-05-254	Open-label, sequential study	14	Bioavailability (30 mg oral tolvaptan)
156-97-202	Open-label, single-dose study	12	Mass Balance
156-05-256	Open-label, randomized, crossover study	14	Effect of high fat meal on tolvaptan PK
156-00-002*	Open-label, crossover study	16	Effect of Japanese meal on tolvaptan PK in healthy Japanese subjects

* This study was preformed in Japan and a synopsis is provided.

Table 5.1-2 Healthy Subjects- Safety, Tolerability, PK, PD and Dose Finding

Protocol Number	Design	Number Enrolled	Comments
156-95-302	Single dose, dose-ranging	30	Tolvaptan (capsule): 5, 10, 15, 30 or 60 mg

156-98-210	Single dose, randomized, double-blind, placebo-controlled, dose-ranging, cross-over	40	Tolvaptan (15 mg tablets): 60, 90, 120, 180, or 240 mg
156-01-229	Single dose, randomized, double-blind, placebo-controlled, dose-ranging	59	Tolvaptan (60 mg tablets): 180, 240, 300, 360, 420 or 480 mg
156-00-001*	Single dose, randomized, single-blind, placebo controlled, dose-ranging	56	Tolvaptan: 15, 30, 45, 60, 90, or 120 mg
156-95-305	Randomized, double-blind, placebo-controlled	24	Tolvaptan: 30 or 60 mg; 28 days dosing
156-00-003*	Randomized, double-blind, placebo-controlled	18	Tolvaptan: 30 or 60 mg ; 7 days dosing
156-05-001*	Randomized, single-blind, placebo-controlled	18	Tolvaptan: 90 or 120 mg; through 7 days
156-94-001*	Randomized, single-blind, placebo-controlled dose-ranging	25	Tolvaptan (jet milled powder): 1, 3, 10, 30, 60, 100; single dose x 2

* These studies were performed in Japan and a synopsis is provided.

Table 5.1-3 Interaction Studies

Protocol Number	Design	Comments
156-01-233	Drug interaction	Lovastatin and tolvaptan
156-96-205	Drug interaction	Furosemide, HCTZ and tolvaptan
156-98-201	Drug interaction	Ketoconazole and tolvaptan
156-01-225	Drug interaction	Warfarin and tolvaptan
156-01-226	Drug interaction	Amiodarone and tolvaptan
156-01-234	Drug interaction	Digoxin and tolvaptan
156-03-239	Drug interaction	Rifampin and tolvaptan
156-03-240	Drug interaction	Grapefruit juice and tolvaptan
156-98-202	Demographic effects	Age and gender
156-03-242	Demographic effects	Fasting and non-fasting state in male subjects of Caucasian and Japanese descent
156-01-224	Population PK study	Included subjects from 3 hyponatremia and 5 heart failure trials

Table 5.1-4 Disease States- Dose-ranging/titration, Efficacy, Safety and PK

Protocol Number	Design	Number Enrolled	Comments
156-01-231	Randomized, double-blind	40	Comparison of 15 mg BID and 30 mg QD in HF patients
156-97-251	Dose-ranging, randomized, double-blind, placebo-controlled	55	HF patients administered tolvaptan: 10, 15, 30, 60, 90 or 120 mg for 13 days
156-97-252	Dose ranging, randomized, double-blind, placebo-controlled	254	HF patients administered tolvaptan 30, 45, or 60 mg
156-96-203	Dose ranging, randomized, double-blind, placebo-controlled	45	Hyponatremia secondary to liver disease administered tolvaptan: 5, 10, 15, 30 or 60 mg; 13 days
156-96-201	Dose ranging, randomized, double-blind, placebo-controlled	9	Hyponatremia secondary to HF administered tolvaptan: 5, 10, 15 or 30 mg ; terminated early
156-97-204	Dose titration, randomized, open-label, placebo-controlled	28	Hospitalized patients with hyponatremia administered tolvaptan: 10, 15, 30, 45 or 60 mg; terminated early
156-98-213	Dose ranging, randomized, double-blind, placebo-controlled	319	Hospitalized patients with worsening HF administered tolvaptan: 30, 60, 90 mg

Table 5.1-5 Hyponatremia Indication- Efficacy Trials*

Protocol Number	Design and Type of Control	Number of Subjects	Indication (population)	Treatment Duration	Comment
156-02-235	Randomized, double-blinded, placebo-controlled	205	Hyponatremia (SIADH/other, cirrhosis, heart failure)	30 days	Phase 3 efficacy study
156-03-238	Randomized, double-blinded, placebo-controlled	243	Hyponatremia (SIADH/other, cirrhosis, heart failure)	30 days	Phase 3 efficacy study
156-03-236	Randomized, double-blind, placebo-controlled	474 (subgroup with hyponatremia)	Heart Failure	Minimum of 60 days	Supportive for efficacy (phase 3 heart failure efficacy, subgroup with hyponatremia)
156-96-203	Randomized, double-blind, placebo-controlled, dose-ranging	45	Hyponatremia (cirrhosis)	13 days	Supportive for efficacy
156-03-244	Ongoing, open label, uncontrolled, extension of trials 156-02-235 and 156-03-238	111	Hyponatremia (SIADH/other, cirrhosis, heart failure)	Up to 214 weeks	Supportive for efficacy (a long-term safety study)

Studies 156-96-201 and 156-97-204 are not included as efficacy studies. These phase 2 trials were terminated early (after 5 and 6 subjects completed the trial in the tolvaptan-arm, respectively) and emphasis in this review is given to their safety findings.

Table 5.1-6 Heart Failure Indication- Efficacy Trials

Protocol Number	Design and Type of Control	Number of Subjects	Treatment Duration	Primary Endpoint	Population; tolvaptan doses
156-03-236	Randomized, double-blind, placebo-controlled	4133	Minimum of 60 days (median 8 months)	Long-term: time to all-cause mortality; time to CV mortality or HF hospitalization. Short-term: composite of change in weight and global clinical status at Day 7/discharge	Hospitalized patients with worsening HF; tolvaptan 30 mg QD
156-98-213	Randomized, double-blind, placebo-controlled, dose ranging	319	Up to 61 days	Change in weight at 24 hours post-first dose; worsening HF (overall and outpatient);	Hospitalized patients with worsening HF ; tolvaptan: 30, 60, 90 mg QD
156-04-247	Randomized, double-blind, placebo-controlled, single dose	181	1 day	Peak change in PCWP 3-8 hours post-dose	Class III-IV HF, PCWP \geq 18 mm Hg; tolvaptan 15, 30, 60 mg
156-00-220	Randomized, double-blind, placebo-controlled, dose-ranging	330	6 months	Clinical status at 6 months	Class II-IV HF with \geq 1 HF hospitalization/IV therapy within yr; Administered furosemide and tolvaptan :15, 30 or 60 mg
156-01-232	Randomized, double-blind,	240	54 weeks	LV EDV	Class II-III HF; Tolvaptan 30 mg

	placebo-controlled				
156-00-222	Randomized, double-blind, placebo-controlled	80	7 days	Change in weight	Class II-III HF; Tolvaptan 30 mg, furosemide 80 mg, tolvaptan + furosemide or placebo
156-97-251	Dose ranging, randomized, double-blind, placebo-controlled	55	13 days	Change in weight from Day 1 to 3	Class I-III HF and volume expansion; Tolvaptan: 10, 15, 30, 60, 90 or 120 mg
156-97-252	Randomized, double-blind, placebo-controlled, dose-ranging	249	25 days	Change in weight at Day 14	Class I-III HF and volume expansion; furosemide and tolvaptan: 30, 45 or 60 mg

5.2 Review Strategy

A detailed review of the pivotal efficacy trials (large, randomized, double-blind, placebo-controlled phase 3 trials) was first performed. Supportive efficacy studies were then reviewed. Emphasis then shifted to safety-clinical safety data was analyzed as an aggregate and within the context of the individual studies. As part of this safety review, the meeting minutes of the tolvaptan data safety and monitoring committee, were reviewed and further attention was given to safety concerns raised by the committee. The conivaptan and nesiritide labels and FDA clinical reviews were also referenced.

5.3 Discussion of Individual Studies

Please see Section 9.4.

6 Review of Efficacy

6.1 Hyponatremia Indication

The proposed indication is the treatment of euvolemic and hypervolemic hyponatremia and prevention of worsening hyponatremia in adults.

6.1.1 Methods

Two phase 3 studies evaluated tolvaptan's efficacy in the treatment of hyponatremia. These studies, studies 156-02-235 and 156-03-238, provide the bulk of efficacy data for this indication and are the focus of this section. Additional supportive data is provided by other studies conducted as part of the hyponatremia program

(studies 156-03-244, 156-96-203) as well as studies conducted as part of the heart failure program that enrolled subjects with hyponatremia (studies 156-03-236, 156-97-251, 156-97-252, 156-98-213, 156-00-220, 156-01-232).

General Discussion of Endpoints

The primary efficacy endpoint in tolvaptan's phase 3 hyponatremia trials was a change in serum sodium in subjects with hyponatremia. Severe hyponatremia, especially if it develops rapidly, can be associated with significant morbidity and mortality. Confusion, seizures, coma and death have been described, while more subtle non-specific manifestations including lethargy, nausea and headache are thought to arise in patients with more mild disease. While clinical benefit is likely to be incurred from treatments that raise serum sodium levels in patients with severe or symptomatic disease, the clinical benefit of raising serum sodium levels in patients with more mild and/or asymptomatic disease is not well established. Moreover, the serum sodium threshold at which patients are at risk of harm if left untreated remains unclear and likely varies from patient to patient, based in part, on the acuity of the fall.

Changes in serum sodium have been used as a surrogate endpoint by FDA. Conivaptan was approved for the treatment of euvolemic and hypervolemic hyponatremia by the Division of Metabolism and Endocrinology Products (DMEP) based on a change in serum sodium in subjects with a baseline serum sodium 115-130 mEq/L (in a double-blind, placebo-controlled trial **sited on conivaptan's label**, the mean serum sodium at entry was 123.3 mEq/L). DMEP also accepted changes in serum sodium as a primary efficacy endpoint in subjects with **"clinically significant hyponatremia" in tolvaptan's phase 3 hyponatremia trials**. Furthermore, in defining this population, DMEP chose a serum sodium threshold of < 130 mEq/L. However for the reasons outlined above, the basis for this threshold is unclear and the validity of this endpoint as a surrogate for clinical benefit in subjects with mild, largely asymptomatic hyponatremia has not been shown.

Study Design

The two phase 3 hyponatremia studies were similar with respect to design. Both were randomized, double-blind, placebo-controlled trials in subjects with hyponatremia, defined by a serum sodium less than 135 mEq/L. While study 156-02-235 was conducted only in the United States, study 156-03-238 was conducted in and outside the United States. Only subjects with non-hypovolemic hyponatremia were enrolled- this included patients with hyponatremia due to heart failure, cirrhosis, SIADH and "other" etiologies. **For analysis purposes, patients were further stratified as having "mild" hyponatremia (serum sodium 130-134 mEq/L) or "severe" hyponatremia (serum sodium <130 mEq/L).** Enrolled patients were treated for 30 days and then followed for 7 days after discontinuation of the study medication. Both protocols called for dose-titration; patients were started at a dose of 15 mg/day and could be titrated up to 60 mg as needed, based on serum sodium concentrations (see Figure below).

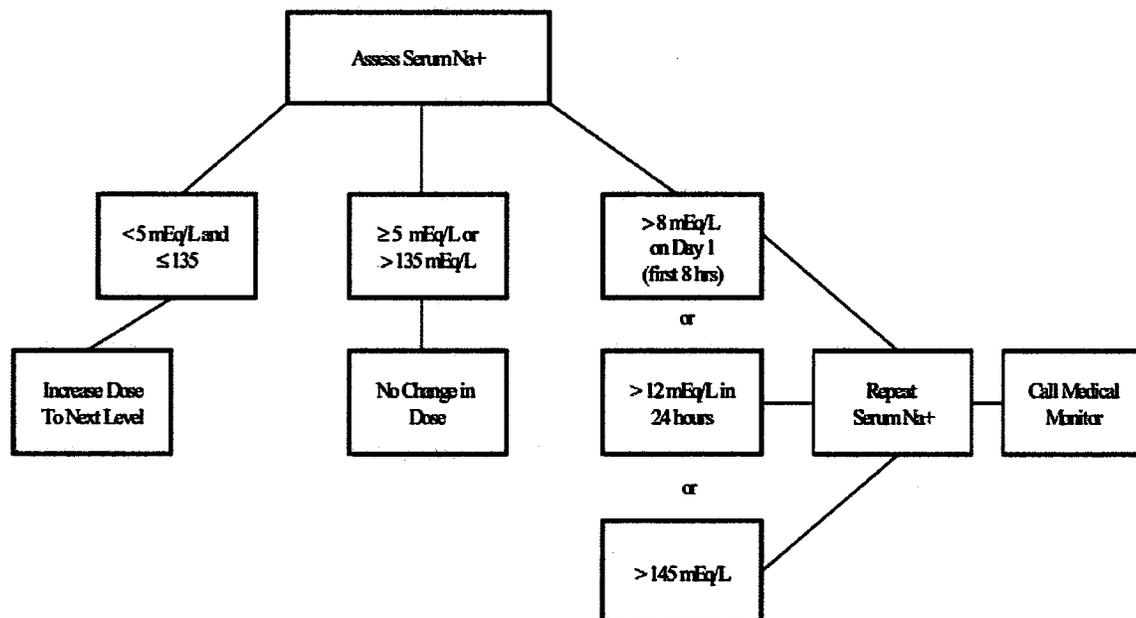


Figure 6.1.1-1 Sponsor’s Figure of algorithm used for dose-titration based on serum sodium level. Subjects’ serum sodium levels were to be compared with the previous measurement taken 24 hours prior.

Primary Efficacy Endpoints and Pre-specified Statistical Analyses

The co-primary endpoints for these studies were the average daily AUC of the change from baseline in serum sodium up to Days 4 and/or 30. These endpoints were to be tested in the entire hyponatremia population, with **“utilization of a multiple-comparisons procedure such as the Hochberg procedure” (recommended for study 156-02-235 in May 2003 by the Division of Metabolic and Endocrinology Products)**. According to the SPA submitted for study 156-02-235, all randomized patients with a baseline and at least one follow-up baseline measurement were to be used in efficacy analyses for outcomes measured as a change in a variable. The sponsor also specified an ANCOVA model with would include treatment, baseline serum sodium level and baseline stratification (disease severity and etiology) for their primary efficacy analysis. Baseline measurements were defined as the last measurement taken prior to first dosing of study medication. For missing data between 2 observations, the trapezoidal rule was to be used. For missing data following the last observation, the AUC was to be normalized to the average daily AUC (AUC divided by the number of days under observation). LOCF was to be used for other missing data. Of note, discussions with the Agency surrounding the SPA focused on the statistical analysis of the primary endpoints and no method for adjusting for multiple-comparisons in the analysis of secondary endpoints was pre-specified.

6.1.2 Demographics

A total of 448 patients with euvolemic and hypovolemic hyponatremia were randomized in the phase 3 hyponatremia studies; 223 subjects to placebo and 225 to tolvaptan. As shown in Table 6.1.2-1, approximately 51% of subjects had a baseline serum sodium <130 mEq/L. Approximately 42% of subjects had an underlying diagnosis of SIADH/other, 30% had HF and 28% of subjects had cirrhosis. Approximately 13 % of subjects were fluid restricted at baseline.

Characteristics	Trial 156-02-235		Trial 156-03-238	
	Tolvaptan (N=102)	Placebo (N=103)	Tolvaptan (N=123)	Placebo (N=120)
Mean Age in years (range)	60 (18-86)	60 (35-90)	62 (27-92)	63 (28-100)
Male	50.9%	60.2%	61.0%	60.8%
Mean Height in cm (range)	167 (142-188)	170 (144-196)	168 (142-198)	167 (138-188)
Mean Weight in kg (range)	78 (45-162)	75 (37-153)	73 (34-146)	75 (36-149)
Race				
Caucasian	69.6%	73.8%	95.9%	90.8%
Hispanic	12.7%	16.5%	2.4%	5.0%
Black	12.7%	8.7%	0.8%	2.5%
Asian	2.9%	0.0%	0.0%	0.8%
Other	2.0%	1.0%	0.8%	0.8%
Smokers	23.5%	33%	29.3%	23.3%
Baseline serum sodium < 130 mEq/L	52.0%	50.5%	48%	48.3%
Diseases†				
SIADH	26.5%	24.3%	20.3%	27.5%
HF	37.3%	35.0%	30.1%	30.8%
Liver Cirrhosis	24.5%	20.4%	30.9%	30.0%
Other	17.6%	27.2%	21.1%	20.0%
Hypervolemic Hyponatremia	40.2%	33%	47.2%	50 %
Fluid Restriction at Baseline	17.5% (17/97)	18.3% (17/93)	6.7% (8/119)	12.2% (14/115)

Source: Sponsor's tables 8.1-2 (page 108), 8.3-1 (page 114) and 8.2-1 (page 111) in CSRs 156-02-235 and 156-03-238 and Table 3.2 page 471 ISE

† Subjects could have more than one disease listed.

6.1.3 Patient Disposition

Discontinuations were common during treatment. Table 6.1.3 below provides an overview of subjects who discontinued and their reasons for discontinuation grouped by severity of hyponatremia. Rates of discontinuation due to adverse experiences appear similar in the placebo and tolvaptan treated arm. TEAEs were the leading cause of study discontinuation in both treatment arms, followed by withdrawal of consent. No single TEAE leading to discontinuation occurred at an incidence > 1% in the tolvaptan treatment arm.

Subjects	156-02-235		156-03-238		Pooled	
	Tolvaptan	Placebo	Tolvaptan	Placebo	Tolvaptan	Placebo
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
All Randomized Subjects	102	103	123	120	225	223
Randomized Subjects Dataset*	97	93	119	115	216	208
ITT Dataset*†	95	89	118	114	213	203
Discontinued:	22 (22.7)	31 (33.3)	30 (25.2)	30 (26.1)	52 (24.1)	61 (29.3)
Adverse experience	8 (8.2)	14 (15.1)	18 (15.1)	10 (8.7)	26 (12.0)	24 (11.5)
Withdrew consent	9 (9.3)	7 (7.5)	4 (3.4)	11 (9.6)	13 (6.0)	18 (8.7)
Protocol deviation	0 (0.0)	1 (1.1)	4 (3.4)	1 (0.9)	4 (1.9)	2 (1.0)
Met withdrawal criteria	1 (1.0)	0 (0.0)	2 (1.7)	1 (0.9)	3 (1.4)	1 (0.5)
Withdrawn by investigator	2 (2.1)	4 (4.3)	1 (0.8)	6 (5.2)	3 (1.4)	10 (4.8)
Lost to follow up	2 (2.1)	5 (5.4)	1 (0.8)	1 (0.9)	3 (1.4)	6 (2.9)

Source Table 5.1-1 ISE page 122

*Excludes subjects from sites 004,006 and 237

† Includes subjects with a baseline and post-baseline efficacy evaluation

Reviewer's comment: Discontinuation rates were high. Overall, more patients discontinued treatment in the placebo arm, particularly in the subgroup with more severe hyponatremia.

6.1.4 Analysis of Primary Endpoint(s)

The co-primary endpoint for the phase 3 hyponatremia trials was the average daily AUC of the change from baseline in serum sodium up to days 4 and/or 30. As shown in Table 6.1.4-1 below, the results were highly statistically significant at days 4 and 30 using an ANCOVA model adjusting for baseline covariates including hyponatremia origin, severity and baseline serum sodium.

156-02-235						
Visits Up to:	Treatment Group	N	LS Mean	P-value	Estimated Treatment Effect	95% CI
Day 4	Tolvaptan	95	3.64	<0.0001	3.40	2.74, 4.07
	Placebo	89	0.23			
Day 30	Tolvaptan	95	6.23	<0.0001	4.59	3.66, 5.53

		Placebo	89	1.64		
156-02-238						
Visits Up to:	Treatment Group	N	LS Mean	P-value	Estimated Treatment Effect	95% CI
Day 4	Tolvaptan	118	4.37	<0.0001	4.00	3.32, 4.68
	Placebo	114	0.37			
Day 30	Tolvaptan	118	6.29	<0.0001	4.54	3.62, 5.47
	Placebo	114	1.75			

[Source: Statistical Reviewer’s results, which confirm sponsor’s results]

Reviewer’s comments: While missing data at day 4 was minimal (more than 90% of subjects had Day 4 measurements), approximately 24 and 29% of tolvaptan and placebo-treated subjects, respectively, did not complete the trial. However given the magnitude of the treatment effect/level of statistical significance, it is unlikely that the difference in treatment arms would be lost at Day 30.

6.1.5 Analysis of Secondary Endpoints(s)

Fifteen secondary endpoints were explored in the phase 3 hyponatremia trials. For the most part, these **secondary efficacy endpoints addressed tolvaptan’s efficacy** in the subgroup of subjects with a serum sodium < 130 mEq/L, and **alternative ways of quantifying tolvaptan’s efficacy** in raising serum sodium levels. Secondary endpoints also included changes in fluid balance and body weight in hypervolemic subjects, the need for fluid restriction, treatment failures (defined as the need for saline infusion) and changes in the 12-item Short-form Health Survey. A list of secondary efficacy endpoints is shown in the table below. Discussions with the Agency focused on the statistical analysis of the primary endpoints and no method for adjusting for multiple-comparisons in the analysis of secondary endpoints was pre-specified.

List of Secondary Endpoint in Phase 3 hyponatremia trials

- (1) Average daily AUC of change from baseline in serum sodium level up to Day 4 within double blind on therapy period, for patients with severe hyponatremia (serum sodium < 130 mEq/L at baseline).* ‡
- (2) Average daily AUC of change from baseline in serum sodium level up to Day30 within double blind on therapy period, for patients with severe hyponatremia (serum sodium < 130 mEq/L at baseline).* ‡
- (3) Percentage of patients with normalized serum sodium at Day 4. †
- (4) Percentage of patients with normalized serum sodium at Day 30. †
- (5) Time to first normalization in serum sodium. †
- (6) Change from baseline in serum sodium at Day 4. ‡
- (7) Change from baseline in serum sodium at Day 30. †
- (8) Percentage of patients requiring fluid restriction at any time during the study. †
- (9) Urine output at Day 1. †
- (10) Change from baseline in body weight at Day 1 for hypervolemic patients. †
- (11) Fluid balance at Day 1 for hypervolemic patients. †
- (12) Change from baseline in the SF-12 (health survey) Physical Component Summary (PCS) and Mental Component Summary (MCS) scales (trial 156-02-235 Week 1 and Day 30, trial 156-03-238 Week 2 and Day 30). †
- (13) Categorical change in serum sodium at Day 4 and Day 30 for patient with baseline serum sodium < 130 mEq/L.‡
- (14) Categorical change in serum sodium at Day 4 and Day 30 for patient with baseline serum sodium ≥130 mEq/L. ‡
- (15) Percentage of patients who are designated as treatment failure due to the need for saline infusion, with or without fluid restriction. ‡

*Listed as and endpoint under “Subgroup analyses” in the SPA for trial 156-02-235.

† Listed as an endpoint under “Secondary Efficacy Analyses” in the SPA for trial 156-02-235

‡ Added as a secondary endpoint in Protocol Amendment 1 to study 156-02-235, made approximately 2 months after trial initiation.

Table 6.1.5-1 below shows the average daily AUC up to Day 4 and Day 30 of the mean change from baseline in serum sodium concentration in the subset of patients with a serum sodium <130 mEq/L at baseline. A numerically greater increase in the average daily AUC up to Day 4 and Day 30 was observed in tolvaptan compared to placebo subjects (analyses confirmed by FDA).

Study	Visits Up to:	Treatment Group	N	Mean	Estimated Treatment Effect
	156-02-235	Day 4	Tolvaptan	51	
Placebo			47	0.76	
Day 30		Tolvaptan	51	8.24	5.70
		Placebo	47	2.54	
Study 156-02-238	Visits Up to:	Treatment Group	N	Mean	Estimated Treatment Effect
	Day 4	Tolvaptan	59	5.06	
		Placebo	58	0.71	
	Day 30	Tolvaptan	59	7.60	4.88
Placebo		58	2.72		

[Source: Statistical Reviewer's Results]

*Analysis excludes subjects from sites 004, 006 and 237

Table 6.1.5-3 below shows the results of analyses of other secondary endpoints addressing changes in serum sodium. According to these analyses, the percentage of subjects with a normalized serum sodium at Day 4 and Day 30 appears to be numerically greater in tolvaptan than placebo treated subjects. The mean change in serum sodium at Day 4 and Day 30 also appears to be numerically greater in tolvaptan than placebo subjects.

Table 6.1.5-3 Analysis of Serum Sodium Level at Day 4 and 30				
	Tolvaptan		Placebo	
Percent of subjects with normalized serum sodium (>135)				
	N	n (%)	N	n (%)
156-02-235				
Day 4	95	38 (40.0)	89	12 (13.4)
Day 30	95	50 (52.6)	89	22 (24.7)
156-03-238				
Day 4	118	65 (55)	114	12(11)
Day 30	118	69 (58)	114	28(25)
Change from baseline in serum sodium at Day 4 and at Day 30				
	N	Mean	N	Mean
156-02-235				
Day 4	95	5.33	89	0.91
Day 30	95	7.15	89	2.26
156-03-238				
Day 4	118	5.92	114	0.76
Day 30	118	6.58	114	2.58

[Source: Statistical Reviewer's results]

Finally, as shown in the sponsor's figure below for trial 156-02-235, the time to normalization of serum sodium also appears to be numerically shorter in tolvaptan treated subjects. The Kaplan-Meyer Curve for trial 156-03-238, not shown, appeared similar.

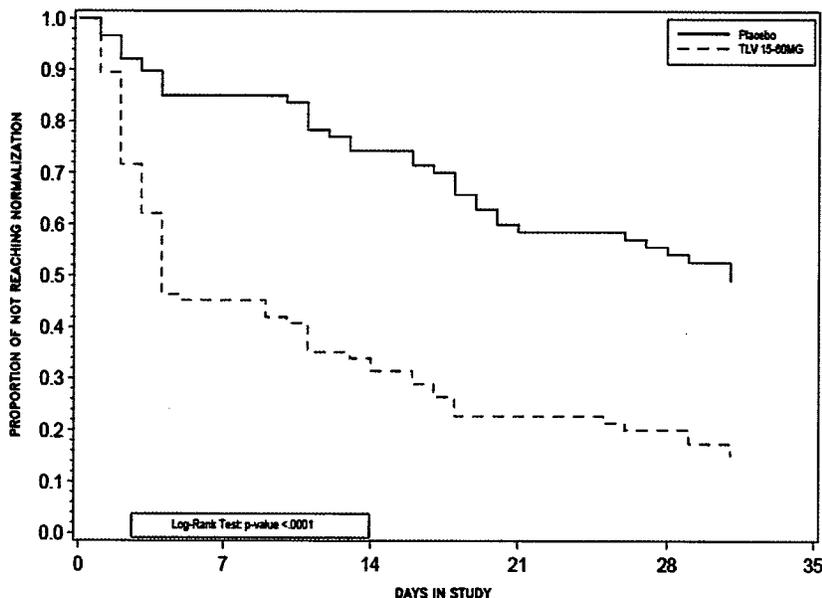


Figure 6.1.5-1. Sponsor’s Kaplan Meier Curve of Time to First Normalization in Serum Sodium Concentration in Phase 3 Hyponatremia Trial 156-02-235; Intent-to-treat Dataset (OC)
 [Source: Sponsor’s Figure 5.5.3-1 page 149 ISE]

Reviewer’s comment: The results of these secondary analyses suggest that the primary efficacy endpoint analysis is robust.

Of the secondary endpoints listed, the Short Form (SF)-12, used in the phase 3 hyponatremia trials, is the only endpoint to explore a possible clinical benefit to treatment with tolvaptan beyond a change in serum sodium levels. According to the sponsor’s analyses, at day 30, a statistically significant improvement in the Mental Component Summary Score (MCSS) was seen in trial 156-02-235, while statistical significance was not reached in study 156-03-238 based on LOCF and OC analyses. FDA analyses of changes in the MCSS in these trials produced similar p-values. In the sponsor’s analyses of the pooled data from these trials, a statistically significant difference between treatment arms for the MCSS score was also observed (p=0.004 and 0.01, respectively for OC and LOCF analyses). In contrast, no greater improvement in the Physical Component Summary (PCS) was reported with tolvaptan treatment. In a Study Endpoint Review, Dr. Ann Marie Trentacosti concluded that the SF-12 PCS and MCSS were not adequate measures of function and health related quality of life in the targeted population and recommended that they not be used to support efficacy claims (please see her review for further discussion).

Table 6.1.5.3.1. Change from baseline in SF-12 Health Survey: OC and LOCF Analyses							
SF12	Analysis	Mean Baseline (SD)		Mean Change from Baseline at Day 30 (N)		Treatment Effect	P-value†
		Tolvaptan	Placebo	Tolvaptan	Placebo		
Study 156-03-235							
Physical Component	LOCF	34.03 (10.6)	34.40 (11.1)	0.55 (N=83)	0.19 (N=71)	0.29	0.85

	OC	34.03 (10.6)	34.40 (11.1)	0.35 (N=71)	0.81 (N=58)	-0.21	0.88
Mental Component	LOCF	42.34 (11.7)	45.4 (11.8)	6.40 (N=83)	1.08 (N=71)	3.92	.02
	OC	42.34 (11.6)	45.4 (11.8)	8.04 (N=71)	0.88 (N=58)	5.26	0.004
Study 156-03-238							
Physical Component	LOCF	33.93 (10.68)	33.89 (10.86)	1.65 (N=101)	0.35 (N=103)	1.47	0.24
	OC	33.93 (10.63)	33.89 (10.82)	2.69 (N=86)	1.2 (N=85)	1.22	0.37
Mental Component	LOCF	44.69 (11.99)	45.14 (11.91)	4.45 (N=101)	2.00 (N=103)	2.20	0.15
	OC	44.69 (11.99)	45.14 (11.91)	4.87 (N=86)	2.39 (85)	2.40	0.12

[Source: Statistical Reviewer's results]

‡ P values for ANCOVA model with factors of treatment, baseline disease origin and severity and baseline score as covariates.]

Reviewer's comments: Several concerns are raised by this instrument. These include concerns about its validity as a measure of function or health related quality of life and statistical concerns raised by the lack of a prespecified analysis plan and method for adjusting for multiplicity. Moreover, it cannot be excluded that knowledge of changes in serum sodium may have biased a subject's response to questionnaire items ("my sodium is better therefore I am better"). Given these concerns, little weight is placed on the reported findings.

Other secondary endpoints, including urine output, and changes in body weight and fluid balance in hypervolemic subjects, were also explored. As shown in the table below, changes in urine output and fluid balance appear to be numerically greater in tolvaptan-treated subjects.

Table 6.1.5-3 Analyses of Urine Output, Weight, and Fluid Balance Endpoints				
	Tolvaptan		Placebo	
	N	Mean	N	Mean
156-02-235				
Urine Output	86	3222	77	2071
Change in Weight (kg) for Hypervolemic Patients	39	-1.52	26	-0.54
Change in Fluid Balance For Hypervolemic Patients	30	-1915	21	-416
156-03-238				
Urine Output	111	3214	100	1904
Change in Weight (kg) for Hypervolemic Patients	54	-0.76	57	-0.70
Change in Fluid Balance For Hypervolemic Patients	49	-1421	46	-222

[Source: Sponsor's Study Reports]

The percentage of subjects requiring fluid restriction during the study was also explored as a secondary endpoint. As shown in the tables below, fluid restriction was not more common in tolvaptan than placebo treated subjects with a baseline serum sodium <130 mEq/L.

Table 6.1.5-4 Percentage of Subjects on Fluid Restriction in the Phase 3 Hyponatremia Trials				
	Tolvaptan		Placebo	
Subjects on fluid restriction at baseline				
	N	n (%)	N	n (%)
156-02-235	97	17 (17.5)	93	17 (18.3)
156-03-238	119	8 (6.7)	115	14 (12.2)
No fluid restriction at baseline and fluid restriction initiated during treatment (excluding study day 30)				
156-02-235	96	9 (9.4)	91	16 (17.6)
156-03-238	119	8 (6.7)	115	16 (13.9)
No fluid restriction at baseline and fluid restriction initiated during treatment (excluding study day 30) OR subject with fluid restriction at baseline that was maintained during double-blind trial period				
156-02-235	96	19 (19.8)	91	29 (31.9)
156-03-238	119	11 (9.2)	115	22 (19.1)

[Source= Sponsor's Table 5.7.1.4.6-1]

Excludes subjects from sites 004, 006, 237

Table 6.1.5-5 Percentage of Subjects with baseline serum sodium < 130 mEq/L on Fluid Restriction in the Phase 3 Hyponatremia Trials				
	Tolvaptan		Placebo	
No fluid restriction at baseline and fluid restriction initiated during treatment (excluding study day 30)				
156-02-235	51	7 (13.7)	48	13 (27.1)
156-03-238	59	6 (10.2)	58	13 (22.4)
No fluid restriction at baseline and fluid restriction initiated during treatment (excluding study day 30) OR subject with fluid restriction at baseline that was maintained during double-blind trial period				
156-02-235	51	15 (29.4)	48	20 (41.7)
156-03-238	59	6 (10.2)	58	18 (31.0)

[Source= Sponsor's Table 5.7.1.4.6-1]

Excludes subjects from sites 004, 006, 237

Reviewer's comment: Fluid restriction is a standard treatment for euvolemic and hypervolemic hypernatremia, and is not associated with significant toxicity. Nonetheless, the majority of study subjects were not fluid restricted.

6.1.6 Other Endpoints

Exploratory Efficacy Analyses Addressing Possible Clinical Benefits

To further explore a possible clinical benefit of raising serum sodium, the sponsor conducted exploratory efficacy analyses looked at changes in physician assessed hyponatremia symptoms/signs, the neurological examination and the hyponatremia disease-specific survey. It is important to note that the content validity of these tests for assessing treatment benefit in this population is unclear and, because multiple statistical analyses were performed, the likelihood of a false positive association is high. A description of these test and their results

are provided in the table below. As shown, for the most part, these analyses failed to uncover significant differences between the 2 study arms.

Table 6.1.6-1. Exploratory Efficacy Analyses Addressing Possible Clinical Benefits	
Neurological Examination	<p>Description: Following the baseline measurement, neurologic assessments were made at 2 to up to 5 additional time points during the course of the study. Neurologic assessments included: the level of consciousness, ophthalmic examination, facial motor, dysarthria, reflexes, muscle strength, muscle tone, ataxia, tremor, and stance, gait, and coordination.</p> <p>Results: According to the sponsor, in analyses of the ITT dataset for Trial 156-02-235, reflexes in the right and left achilles were statistically significantly improved at week 1. According to the sponsor, statistically significant improvements were seen in the ITT dataset for trial 156-03-238, the ataxia right finger-to-nose test at Day 37 and stance with eyes closed at Week 2.</p>
Hyponatremia Disease-specific Survey	<p>Description: The hyponatremia disease-specific survey, a 12-item questionnaire developed internally by the sponsor's project medical director, was conducted in trail 156-03-238. Subjects were asked to rate themselves on general health, thinking ability (including concentrating, calculating, language and memory activities), strength/coordination (including endurance, strength, gross coordination and fine coordination activities), self perception, thirst sensation and overall assessment of activity, symptoms and emotional well-being. The investigator was similarly asked to rate how the study treatment affected the subject's activity, symptoms and emotional well-being. Following the baseline assessment, the survey was completed at 3 time points during the course of the study. The sponsor acknowledges that this survey has not yet been validated.</p> <p>Results: According to the sponsor, in the ITT Dataset, statistically significant improvements in memory activities were observed for tolvaptan compared with placebo subjects at Week 2. The physician assessment did not reach statistical significance for the ITT dataset.</p>
Physician assessed disease specific survey	<p>Description: According to the sponsor, post-hoc analyses of physician-assessed symptoms/signs were also conducted.</p> <p>Results: The sponsor writes that, "With the exception of sporadic improvements in dyspnea, orthopnea and JVP for subjects with heart failure, the only symptom consistently improved and maintained over a period of time was fatigue."</p>

Reviewer's comment: These are exploratory analyses and as such, their interpretation is limited. Nonetheless, the results of these analyses do not provide strong supportive evidence of a significant clinical benefit to raising serum sodium/treatment with tolvaptan in the studied population.

Prevention of worsening hyponatremia

The sponsor's proposed label includes the prevention of worsening hyponatremia as an indication for tolvaptan. **Only one of the sponsor's secondary efficacy endpoints** addressed this issue. According to the sponsor, 11/110 (10%) tolvaptan-treated subjects and 46/105 (43.8%) placebo-treated subjects in the phase 3 hyponatremia trials with a baseline serum sodium < 130 mEq/L had a decrease in serum sodium of at least 3 mEq/L at any post-baseline time point. Additional analyses were conducted to further explore this possible effect. Table 6.1.6-2 shows the incidence of worsening hyponatremia (defined as a decrease in the AUC at days 4 and 30) in all subjects. The incidence of worsening hyponatremia appeared lower in tolvaptan than placebo treated subjects at Day 4 and Day 30. This was true for all subjects and those with a baseline serum sodium < 130 mEq/L.

Table 6.1.6-2. Incidence of worsening hyponatremia (defined by a decrease in the average daily AUC up to days 4 or 30 by more than 2 meq/L)

	Pooled Data			
	Day 4		Day 30	
	Tolvaptan	Placebo	Tolvaptan	Placebo
All Subjects	2/222 (1%)	30/218 (14%)	2/222 (1%)	36/218 (16.5%)
Baseline serum Na < 130 mEq/L	0/112 (0%)	12/108 (11%)	0/112 (0%)	14/108 (13%)
Baseline serum Na < 125 mEq/L	0/26 (0%)	1/33 (3%)	0/26 (0%)	1/33 (3%)
Baseline serum Na < 120 mEq/L	0/5 (0%)	0/9 (0%)	0/5 (0%)	0/9 (0%)

Reviewer's comments: Though not addressed as a primary endpoint, the data suggest that tolvaptan may be effective in preventing further drops in serum sodium levels.

6.1.7 Subpopulations

As shown in the Table 6.1.7-1 below, tolvaptan's efficacy in raising serum sodium levels up to days 4 and 30 was preserved across major demographic subgroups (age, sex and race), etiologies of hyponatremia (cirrhosis, HF, SIADH) and severity of hyponatremia (<130 and between 130 and 134).

Table 6.1.7-1 Subpopulation analyses of the AUC of the mean change from baseline in serum sodium concentration up to Day 4 and Day 30 in the phase 3 hyponatremia trials (pooled data)

Populations	Pooled Data			
	Day 4		Day 30	
	Tolvaptan (N)	Placebo (N)	Tolvaptan (N)	Placebo (N)
Restricted ITT	4.01 (213)	0.35 (203)	6.21 (213)	1.77 (203)
Hyponatremia Group				
<130 mEq/L	4.83 (110)	0.73 (105)	7.90 (110)	2.64 (105)
130-134 mEq/L	3.14 (103)	-0.06 (98)	4.40 (103)	0.83 (98)
Etiology				
Cirrhosis	3.50 (63)	0.42 (54)	4.18 (63)	1.46 (54)
HF	3.52 (65)	0.51 (61)	6.58 (65)	2.38 (61)
SIADH/Other	4.76 (85)	0.19 (88)	7.42 (85)	1.53 (88)
Hyponatremia				
Euvolemic	4.37 (117)	0.15 (117)	6.90 (117)	1.82 (117)
Hypervolemic	3.53 (94)	0.62 (86)	5.36 (94)	1.69 (86)
Sex				
Male	3.89 (123)	0.19 (124)	5.69 (123)	1.59 (124)
Female	4.17 (90)	0.60 (79)	6.92 (90)	2.04 (79)
Age				
<65	4.16 (130)	0.31 (114)	5.74 (130)	1.28 (89)
>=65	3.77 (130)	0.39 (114)	6.93 (130)	2.39 (89)
Race				
Caucasian	4.17 (180)	0.33 (171)	6.34 (180)	1.72 (171)
Non-Caucasian	3.15 (33)	0.43 (32)	5.47 (33)	2.01 (32)

[Source: Statistical Reviewer's Analysis]

Reviewer's comment: Very few non-Caucasian subjects were enrolled in the phase 3 trials, nonetheless, the results suggest efficacy in this general subgroup as well.

Table 6.1.7-2 below shows the effect of tolvaptan on serum sodium levels at Day 4 and Day 30 by baseline serum sodium level. The results show that tolvaptan's ability to raise serum sodium levels was preserved at the lowest levels of serum sodium tested. Pharmacometric analyses confirmed these findings.

Population		Mean Change				Median Change			
		At Day 4		At Day 30		At Day 4		At Day 30	
		Tolvaptan	Placebo	Tolvaptan	Placebo	Tolvaptan	Placebo	Tolvaptan	Placebo
Baseline serum sodium	130-135	3.1	<0.1	4.4	0.9	3.2	0.1	4.7	1.2
	125-129	4.5	0.6	7.2	2.0	4.6	0.7	7.5	2.0
	120-124	5.5	1.0	10.1	3.7	4.8	1.0	9.2	2.9
	<120	6.5	1.1	9.6	4.2	5.2	1.3	6.3	1.8

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Two dose-ranging studies were conducted in hyponatremic subjects. The clinical development program also included, one phase 2 and two phase 3 dose titration studies, however data from such studies are difficult to interpret given the inability to separate dose and time effects. Of these studies, one dose titration trial (156-97-204) and one dose ranging study (156-96-201) was terminated early (according to the sponsor because of declining enrollment) and hence only limited information can be obtained from these studies. For a more detailed discussion of these trials, please see the review by the assigned FDA clinical pharmacology reviewer and the appendix of this review. Table 6.1.8 below provides an overview of these trials.

Because overly rapid correction of serum sodium is associated with significantly morbidity and mortality, the goal of dosing is to raise serum sodium but not at an overly rapid rate. In trial 156-96-203, a dose-ranging study in cirrhotics and in trial 156-96-201, a dose-ranging study in heart failure subjects with hyponatremia (terminated early), tolvaptan 5mg did not produce a significant effect on serum sodium and the greatest effect on serum sodium appeared to occur at 60 mg, the highest dose tested. In trial 156-07-204, in which tolvaptan was initiated at 10 mg and then titrated to 60 mg as needed, the mean effect of 10 mg on serum sodium at 4 and 23 hours post treatment was small (mean change of 1.6 and 2.6 mEq/L, respectively). In the phase 3 hyponatremia trials, tolvaptan was initiated at 15 mg. At this dose, 5.1 % of subjects experienced an overly rapid rate of correction at 8 hours and 1.1% of subjects experienced a rise in serum sodium > 12 mEq/L at 12 hours.

Protocol Number	Design	Number Enrolled	Comments
156-96-203	Dose ranging, randomized, double-blind, placebo-controlled	45	Hyponatremia secondary to liver disease administered tolvaptan: 5, 10, 15, 30 or 60 mg; 13 days
156-96-201	Dose ranging, randomized, double-blind, placebo-controlled	9	Hyponatremia secondary to HF administered tolvaptan: 5, 10, 15 or 30 mg ; terminated early
156-97-204	Dose titration, randomized,	28	Hospitalized patients with hyponatremia administered

	open-label, placebo-controlled		tolvaptan: 10mg titrated to, 15, 30, 45 and 60 mg; terminated early
156-02-235	Dose-titration, randomized, double-blinded, placebo-controlled phase3 study	205	Hyponatremia secondary to SIADH/other, cirrhosis, HF administered 15 mg titrated to 30 and 60 mg; 30 days
156-03-238	Dose-titration, randomized, double-blinded, placebo-controlled phase3 study	243	Hyponatremia secondary to SIADH/other, cirrhosis, HF administered 15 mg titrated to 30 and 60 mg; 30 days

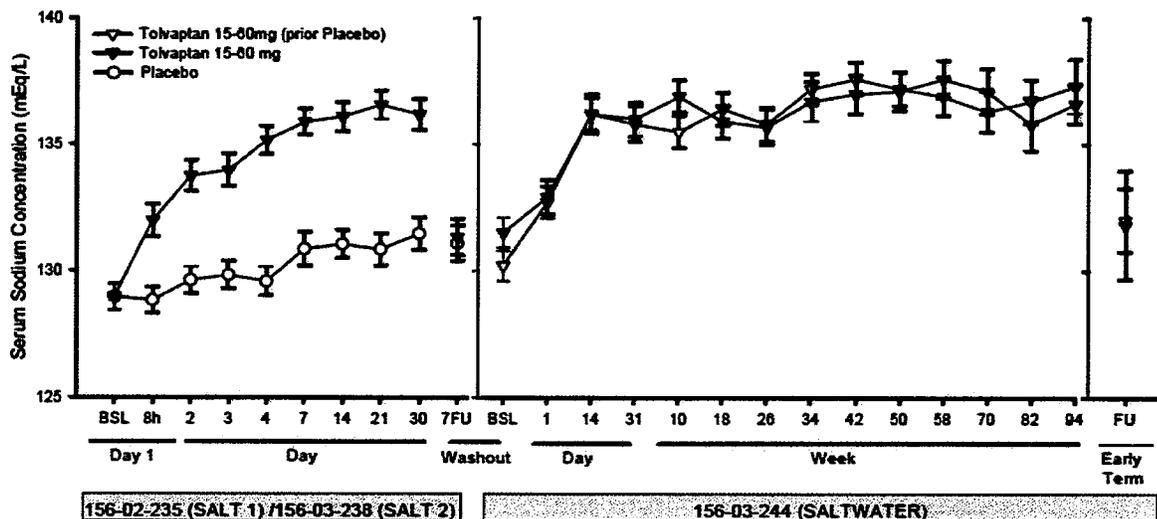
Reviewer's comments: The selected dose for initiation must weigh the benefits of correction with the potential risks of overly rapid correction. The selected dose for initiation seems appropriate.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of efficacy was addressed in the phase 3 hyponatremia studies, in which a follow up serum sodium measurement was made 7 days after discontinuing study medication. As shown in Table 6.1.9-1 below, following study medication withdrawal, serum sodium levels fell in tolvaptan-treated subjects. This fall also occurred in the subgroup of subjects with a baseline serum sodium concentration < 130 mEq/L and was not seen in placebo-treated subjects. In hyponatremic subjects with a serum sodium \geq 130 mEq/L at baseline, serum sodium levels fell to approximately baseline/placebo levels. In patients with a serum sodium < 130 mEq/L at baseline, serum sodium levels similarly fell to approximately placebo levels. However, in both placebo and tolvaptan treated subjects with a baseline serum sodium < 130 mEq/L, day 7 post treatment levels were improved from baseline.

Subjects (by baseline sodium)	Study 156-02-235		Study 156-03-238	
	Tolvaptan (n=72)	Placebo (n=60)	Tolvaptan (n=88)	Placebo (n=79)
<i>Na</i> \geq 130				
Baseline	132.2	132.2	132.1	132.5
Mean Day 30	136.1	134.1	138.3	133.9
Mean Day 7 post	132.0	133.7	133.9	133.4
<i>Na</i> < 130				
Baseline	125.1	126.0	126.6	126.0
Mean Day 30	135.0	129.3	135.4	131.1
Mean Day 7 post	131.8	130.8	131.2	131.8

In the open-label extension study, trial 156-03-244, subjects previously treated with placebo or tolvaptan were treated chronically with **tolvaptan**. As shown in the sponsor's figure below (Figure 6.1.9), following reintroduction of study medication to tolvaptan-treated subjects, serum sodium levels rose again.



Source: ISE Figure 7.4.1-1 (OC dataset)

Figure 6.1.9-1 Sponsor's figure: Mean serum sodium concentration over time in the phase 3 hyponatremia studies (156-02-235 and 156-03-238) and the open-label extension study (156-03-244)

Reviewer's comments: These data suggest persistence of drug effect and loss of drug effect by 7 days with discontinuation of therapy. The rise from baseline to post-Day 7 serum sodium levels in placebo and tolvaptan-treated subjects patients with a baseline serum sodium < 130 mEq/L suggests that the natural history of the condition is to improve, or that other therapies implemented in the placebo arm were effective.

6.1.10 Additional Efficacy Issues/Analyses

As noted above, additional supportive data is provided by other studies conducted as part of the hyponatremia program as well as studies conducted as part of the heart failure program that enrolled subjects with hyponatremia.

In trials 156-03-244 and 156-96-203 conducted as part of the hyponatremia development program, tolvaptan use was associated with a mean increase in plasma sodium concentration. This was shown in the uncontrolled open label phase 3 hyponatremia trial, in which an increase from baseline in serum sodium levels was seen following study drug initiation. This was also observed in the dose ranging study in cirrhotics in which the mean increase in plasma serum sodium was numerically greater in tolvaptan than placebo-treated subjects.

Six heart failure trials included subjects with hyponatremia. With respect to these heart failure trials, it must be kept in mind that changes in serum sodium were not the primary objective of treatment and serum sodium was measured at multiple time points without any clearly prespecified statistical plan for analyzing this endpoint and/or addressing multiplicity. Hence these findings should be viewed only as providing either corroborative or **contradictory evidence of tolvaptan's efficacy in raising** serum sodium. In general those studies enrolling a greater number of hyponatremic subjects (Trials 156-03-237, 156-98-213 and 156-97-252) showed a numerically greater mean change in serum sodium in tolvaptan than placebo treated subjects and a greater proportion of tolvaptan than placebo-treated subjects with normalization of serum sodium. In the three studies

with smaller sample sizes (156-97-251, 156-00-220 and 156-01-232 all had 21 subjects or less with hyponatremia), these differences between treatment arms were not clearly seen.

Reviewer's comments: Viewed as a whole, these studies support tolvaptan's efficacy in raising serum sodium, as established by the phase 3 studies.

6.2 Worsening Heart Failure Indication

6.2.1 Methods

A single, large phase 3 outcome study (156-03-236, or the EVEREST trial) with its two embedded short-term studies (trials A and B), was used to support of the sponsor's proposed indication. Study 156-03-236 randomized 4133 subjects with NYHA class III-IV CHF who were hospitalized with worsening heart failure and had evidence of volume overload (at least two of the following: JVD, $\geq 1+$ pitting edema, or dyspnea); patients received placebo or a fixed dose of tolvaptan 30 mg QD. The two primary endpoints of the overall study were time to all-cause mortality and time to the first occurrence of CV mortality or HF hospitalization; the study was event-driven, designed to terminate after a prespecified number of deaths (1065) and minimum subject follow-up of 60 days. Trials A/B were identical short-term (one week) trials embedded within study 156-03-236; the primary endpoint of trials A and B was a composite of the change from baseline in weight at Inpatient Day 7 (or discharge, if earlier) and the change from baseline in patient-assessed global clinical status at Inpatient Day 7 (or discharge, if earlier).

The submission also included seven randomized, double-blind, parallel-group phase 2 studies in subjects with heart failure. Of these studies, only 156-98-213 was conducted in subjects hospitalized with worsening heart failure. In several of these studies (e.g., 156-98-213, 156-00-220, 156-97-251, 156-97-252), the primary endpoint was based (entirely or among several endpoints) on weight.

Study 156-98-213 was a "proof of concept" study evaluating the effects of placebo or tolvaptan 30, 60 and 90 mg QD on acute and chronic outcomes (weight change 24 hours post-first dose and a worsening heart failure composite, respectively) in 319 subjects hospitalized with worsening heart failure; no statistical adjustment was made for the three primary endpoints or any of the secondary endpoints.

Study 156-04-247 evaluated the effect of a single oral dose of placebo or tolvaptan 15, 30 or 60 mg on hemodynamics (via invasive monitoring) in subjects with heart failure and elevated PCWP; the primary endpoint was the peak change from baseline in PCWP 3-8 hours postdose.

Studies 156-97-251 and 156-97-252 were dose-ranging trials in subjects with heart failure; the primary endpoint in both trials was a change from baseline in body weight. Study 156-00-222 was a 7-day study assessing the effect of tolvaptan 30 mg QD, furosemide 80 mg QD, tolvaptan 30 mg + furosemide 80 mg QD or placebo on the change in weight.

Study 156-00-220 evaluated the effect of three tolvaptan doses (15, 30, 60 mg) or placebo on clinical status (as defined in the study) at six months in subjects with chronic heart failure; the primary endpoint was not significantly different from placebo.

Study 156-01-232 evaluated the effect of tolvaptan 30 mg or placebo QD for 1 year on LV end-diastolic volume in subjects with CHF; in this study, no primary or secondary endpoint was significantly different from placebo.

Study	Number of sites	Design	Treatment groups	Total N	Treatment duration	Mean age (range) (years)	Gender (%) Race (%)
156-97-251	10	R, DB, P, sequential, dose-ranging	Placebo, tolvaptan 10, 15, 30, 60, 90, 120 mg QD	45	13 days	64 (44-86)	62% M, 38% F; 82% White, 16% Black, 2% Other
156-97-252	30	R, DB, P, dose-ranging	Placebo, tolvaptan 30, 45, 60 mg QD	254	25 days	67 (29-94)	64% M, 36% F; 74% White, 24% Black, 2% Hisp, <1% Asian.
156-98-213	46	R, DB, P	Placebo, tolvaptan 30, 60, 90 mg QD	319	Up to 61 days	62 (18-89)	70% M, 30% F; 49% White, 23% Black, 26% Hisp, <1% Asian, 2% Other
156-00-220	67	R, DB, P	Placebo, tolvaptan 15, 30, 60 mg QD	330	Up to 169 days	65 (28-92)	68% M, 32% F; 80% White, 11% Black, 8% Hisp, <1% Asian, 1% Other
156-00-222	18	R, DB, P	Placebo, Tolvaptan 30 mg QD, Furosemide 80 mg QD, tolvaptan 30 mg + furosemide 80 mg QD	83	7 days	59 (24-82)	81% M, 19% F; 59% White, 28% Black, 12% Hisp, 1% Other
156-01-232	38	R, DB, P	Placebo, tolvaptan 30 mg QD	240	54 weeks	64 (29-87)	82% M, 18% F; 87% White, 9% Black, 3% Hisp, 1% Other
156-03-236	432	R, DB, P, long-term outcome + 2 short-term acute studies	Placebo, tolvaptan 30 mg QD	4133	60 days-32 months	66 (18-94)	74% M, 26% F; 85% White, 8% Black, 5% Hisp, <1% Asian, 2% Other
156-04-247	48	R, DB, P, single-dose	Placebo, tolvaptan 15, 30, 60 mg	181	One day	60 (26-89)	80%M, 20%F; 71% White, 23% Black, 4% Hisp, 1% Asian, 1% Other

R=randomized, DB=double-blind, P=placebo-controlled, M=male, F=female, Hisp=Hispanic

6.2.2 Demographics

The heart failure phase 2/3 study population was mostly Caucasian and male; the mean age was mostly in the 60-70 year range. In the two studies of subjects hospitalized with worsening heart failure (156-03-236 and 156-98-213), the mean age was 60-66 years.

The baseline characteristics for the study population hospitalized with worsening heart failure (156-03-236 and 156-98-213) included mean ejection fraction 24-28% (SD 7-8); about 65% of subjects had treated hypertension, 26-35% with treated hypercholesterolemia, and 29-42% with valvular disease. Of this population, 35-43% in study 213 and 48-52% in study 236 and a history of myocardial infarction. Both studies enrolled subjects with NYHA class III-IV symptoms.

In studies 236 and 213, a majority of subjects had frequent or continuous dyspnea (90% in 236; 68% in 213). Fatigue was not assessed in study 213; in study 236, about 84% had frequent or continuous fatigue. For a detailed discussion of baseline characteristics, the reader is referred to the individual study reviews.

6.2.3 Patient Disposition

Patient disposition for study 156-03-236 is shown below. Most subjects completed the short-term study where the primary endpoint was measured at Inpatient Day 7 or discharge, if earlier. The most common reasons for discontinuation were adverse event, withdrawal of consent, and death (which was a primary endpoint in the long-term outcome trial).

	Trial A		Trial B		Long-term Outcome Trial	
	Tolvaptan 30 mg (N = 1018)	Placebo (N = 1030)	Tolvaptan 30 mg (N = 1054)	Placebo (N = 1031)	Tolvaptan 30 mg (N = 2072)	Placebo (N = 2061)
Randomized	1018	1030	1054	1031	2072	2061
Treated	1015	1027	1048	1028	2063	2055
Completed	986	1008	1029	1006	1231	1235
Discontinued, n (%)	32 (3.1)	22 (2.1)	25 (2.4)	25 (2.4)	841 (40.6)	826 (40.1)
Lost to follow up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	15 (0.7)	20 (1.0)
Adverse event	10 (1.0)	3 (0.3)	2 (0.2)	1 (0.1)	137 (6.6)	115 (5.6)
Subject met withdrawal criteria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)	7 (0.3)
Investigator withdrew subject	1 (0.1)	2 (0.2)	1 (0.1)	0 (0.0)	81 (3.9)	74 (3.6)
Subject withdrew consent	13 (1.3)	10 (1.0)	13 (1.2)	13 (1.3)	226 (10.9)	220 (10.7)
Protocol deviation/violation	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	3 (0.1)	4 (0.2)
Death	8 (0.8)	6 (0.6)	9 (0.9)	11 (1.1)	376 (18.1)	385 (18.7)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Analyzed for efficacy	1018	1030	1054	1031	2072	2061



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7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

Table 7.1 provides an overview of the trials that comprised the datasets used for the primary safety analyses. Analyses focused on the following populations:

- (1) all HF and hyponatremia subjects enrolled in placebo-controlled phase 2/3 multiple dose trials (referred to as **“all subjects with HF and/or hyponatremia” dataset**)
- (2) all heart failure subjects from multiple-dose trials
- (3) all heart failure subjects from multiple-dose placebo-controlled trials

- (3) all hyponatremia subjects from placebo-controlled, multiple-dose trials (referred to as “all hyponatremia subjects” dataset)
- (4) subjects enrolled in the phase 3 heart failure trial
- (5) subjects enrolled in the phase 3 hyponatremia trials
- (6) subjects enrolled in the open label long-term extension study of the phase 3 hyponatremia trials
- (7) subjects with worsening heart failure enrolled in the phase 2 heart failure
- (8) subjects with stable heart failure enrolled in phase 2 heart failure studies
- (9) subjects enrolled in trials for other indications(edema: 156-03-001 and 156-03-002; ADPKD: 156-04-250 and 156-05-002)

Table 7.1 Trials comprising datasets used for primary safety analyses.

Multiple-dose placebo controlled trials			Phase 3 trials		Open label long-term extension study
All heart failure and hyponatremia	All heart failure subjects*	All hyponatremia subjects	Heart Failure	Hyponatremia	Hyponatremia subjects
156-96-201 156-96-203 156-97-204 156-97-251 156-97-252 156-98-213 156-00-220 156-00-222 156-01-232 156-02-235 156-03-001 156-03-236 156-03-238	Worsening HF: 156-03-236 156-98-213 Stable HF 156-97-251 156-97-252 156-00-220 156-00-222 156-01-232 156-02-235 156-01-232 Terminated Early 156-96-201 156-97-204 Phase 3 hyponatremia trials 156-02-235 156-03-238	156-96-201 156-96-203 156-97-204 156-97-251 156-97-252 156-98-213 156-00-220 156-00-222 156-01-232 156-02-235 156-03-236 156-03-238	156-03-236	156-02-235 156-03-238	156-03-244

The sponsor’s analyses of all multiple dose trials in subjects with heart failure includes these trials and also trial 156-01-231 (a trial that was not placebo-controlled).

7.1.2 Adequacy of Data

According to the sponsor, as of October 2007, 4423 subjects have been exposed to any dose of tolvaptan in clinical trials. 3294 subjects with a baseline diagnosis of heart failure and/or hyponatremia have been treated with tolvaptan in placebo-controlled phase 2/3 multiple-dose trials. The majority of studied subjects had heart failure (3147 tolvaptan and 2571 placebo in multiple-dose, controlled trials), while a minority of the studied subjects had hyponatremia (607 tolvaptan and 518 placebo subjects). Over 90% of subjects (4048) received tolvaptan doses of 15 to 60 mg. Over 80% of heart failure subjects in multiple-dose, placebo-controlled trials received tolvaptan doses of 30 mg. Outside of the phase 3 hyponatremia trials, in which 223 subjects were exposed to tolvaptan doses of 15 to 60 mg, approximately 332 subjects with HF and/or hyponatremia and fewer than 70 subjects with hyponatremia in multiple dose placebo-controlled trials were exposed to tolvaptan doses of 60 mg or greater.

Reviewer’s comments: *Because few subjects in the safety database received doses at the upper end of the proposed dosage range for hyponatremia (60 mg), use of this large safety database to characterize tolvaptan’s safety at the proposed doses/dose-titration for hyponatremia is somewhat limited.*

7.1.3 Pooling Data across Studies to Estimate and Compare Incidence

For analyses purposes, data were pooled across studies. A description of these pooled datasets is given in section 7.1 (Clinical Studies Used to Evaluate Safety).

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

3294 tolvaptan-treated subjects and 2738 placebo-treated subjects were studied in multiple-dose, placebo-controlled trials and had the characteristics of the patients targeted for treatment with tolvaptan (HF and/or hyponatremia). A broad overview of the demographic breakdown of subjects by indication, etiology and severity of hyponatremia, and volume status is provided in Table 7.2.1-1 below.

Table 7.2.1-1. Demographic Breakdown of Heart Failure and Hyponatremia Subjects Enrolled in Multiple-Dose Placebo-Controlled Trials		
Population	Tolvaptan	Placebo
Heart failure and hyponatremia subjects	3294	2738
Heart failure subjects	3147	2571
Hyponatremia subjects	607	518
Hyponatremia subjects by etiology hyponatremia		
SIADH/other	97 (16%)	99 (19.1%)
Cirrhosis	100 (16.5%)	83 (16%)
HF	410 (67.5%)	336 (64.9%)
Hyponatremia subjects by volume status		
Euvolemia	131 (21.6%)	129 (24.9%)
Hypervolemia	476 (78.4%)	389 (75.1%)
Hyponatremia subjects by severity		
Na \geq 130 and Na<135 mEq/L	418 (68.9%)	340 (65.6%)
Na<130 mEq/L	189 (31.1%)	178 (34.4%)
Na<125 mEq/L	52 (8.6%)	55 (10.6%)
Na<120 mEq/L	7 (1.2%)	13 (2.5%)
Na<115mEq/L	1 (0.2%)	0 (0%)

Reviewer’s comment: *The vast majority of subjects in the safety database had heart failure and did not have hyponatremia. Very few subjects enrolled in multiple-dose, placebo-controlled trials had a serum sodium < 125 mEq/L*

Table 7.2.1-2 below provides a more detailed overview of dosage and the demographic and baseline characteristics of subjects with HF studied in multiple-dose placebo-controlled trials. The mean age of HF subjects was 65.3 years, over 70% of subjects were male and over 70% were Caucasian.

Table 7.2.1-2. Demographic and Baseline Characteristics of All Heart Failure Subjects From Multiple-dose Trials

Parameter	Characteristic	Tolvaptan		
		30 mg (N = 2527)	Any Tolvaptan Oral Dose (N = 3147)	Placebo (N = 2571)
Age	Mean (SD), years	65.4 (12.0)	65.3 (12.2)	65.1 (12.3)
	Median	67	66	66
	Range	22-94	18-94	18-93
	< 65 years, n (%)	1105 (43.7)	1383 (43.9)	1138 (44.3)
	≥ 65 years, n (%)	1422 (56.3)	1764 (56.1)	1433 (55.7)
Gender	Male, n (%)	1845 (73.0)	2252 (71.6)	1931 (75.1)
	Female, n (%)	682 (27.0)	895 (28.4)	640 (24.9)
Race	Caucasian, n (%)	2053 (81.2)	2444 (77.7)	2135 (83.0)
	Black, n (%)	242 (9.6)	341 (10.8)	216 (8.4)
	Hispanic, n (%)	151 (6.0)	215 (6.8)	135 (5.3)
	Asian, n (%)	37 (1.5)	99 (3.1)	38 (1.5)
	Other, n (%)	43 (1.7)	47 (1.5)	47 (1.8)
	Not available, n (%)	1 (0.0)	1 (0.0)	0 (0.0)

Source: Sponsor's Table 2.7.4.1.3.2-1 page 41 Summary of Clinical Safety

Reviewer's comments: The vast majority of subjects in the safety database was enrolled in a single trial (156-03-236) and received 30 mg of tolvaptan.

Table 7.2.1-3 provides additional information on dosage, demographic and baseline characteristics of subjects with hyponatremia studied in multiple-dose placebo-controlled trials. One-hundred and eighty-nine subjects, approximately 30%, had a serum sodium less than 130 meq/L and more than 60% of subjects had heart failure as the reported origin of hyponatremia. The vast majority of subjects were Caucasian, the mean age was 62.3 years, and approximately 30% of subjects were female. Outside of the phase 3 hyponatremia trials, approximately 66 hyponatremic subjects were exposed to doses of 60 mg or greater while approximately 82% of hyponatremic subjects (313) received a dose of tolvaptan ≤ 30 mg.

Table 7.2.1-3. Demographic and Baseline Characteristics of All Hyponatremia Subjects From Multiple-dose, Placebo-controlled Hyponatremia and Heart Failure Trials

Parameter	Characteristic	Tolvaptan			Placebo (N = 518)
		30 mg (N = 275)	15 - 60 mg (N = 223)	Any Dose (N = 607)	
Age (years)	Mean (SD)	63.3 (13.7)	61.5 (14.6)	62.3 (14.1)	62.8 (13.9)
	Range	22 - 89	18 - 92	18 - 93	18 - 100
	< 65 years	136 (49.5)	135 (60.5)	332 (54.7)	276 (53.3)
	≥ 65 years	139 (50.5)	88 (39.5)	275 (45.3)	242 (46.7)
Gender	Male, n (%)	229 (83.3)	126 (56.5)	422 (69.5)	363 (70.1)
	Female, n (%)	46 (16.7)	97 (43.5)	185 (30.5)	155 (29.9)
Race	Caucasian, n (%)	237 (86.2)	188 (84.3)	498 (82.0)	427 (82.4)

	Hispanic, n (%)	13 (4.7)	15 (6.7)	51 (8.4)	44.(8.5)
	Black, n (%)	19 (6.9)	14 (6.3)	46 (7.6)	37 (7.1)
	Asian, n (%)	0 (0.0)	3 (1.3)	3 (0.5)	3 (0.6)
	Other, n (%)	6 (2.2)	3 (1.3)	9 (1.5)	7 (1.4)
Baseline serum sodium	130-134 mEq/L, n (%)	228 (82.9)	111 (49.8)	418 (68.9)	340 (65.6)
	< 130 mEq/L, n (%)	47 (17.1)	112 (50.2)	189 (31.1)	178 (34.4)
Hyponatremia	Cirrhosis, n (%)	12 (4.4)	63 (28.3)	100 (16.5)	83 (16.0)
Origin	CHF, n (%)	262 (95.3)	70 (31.4)	410 (67.5)	336 (64.9)
	SIADH/other, n (%)	1 (0.4)	90 (40.4)	97 (16.0)	99 (19.1)
Volume	Euvolemic	1 (0.4)	124 (55.6)	131 (21.6)	129 (24.9)
Status	Hypervolemic	274 (99.6)	99 (44.4)	476 (78.4)	389 (75.1)

Source: Sponsor's Table 2.7.4.1.3.4-1 page 46 Summary of Clinical Safety

Reviewer's comments: The safety experience for the indication of hyponatremia is derived largely from subjects with hyponatremia in the setting of heart failure and/or a serum sodium \geq 130 mEq/L. Moreover, the safety experience is heavily weighted by subjects receiving a set dose of 30 mg.

Data on duration of exposure are presented in Table 7.2.1-4. In multiple-dose, placebo-controlled trials of subjects with HF and/or hyponatremia, 3181 subjects were exposed to tolvaptan at doses of 15-60 mg for up to 30 days. 1372 subjects were exposed for greater than 6 months and 817 for more than 1 year. An additional 113 subjects with exposures outside this dose range were enrolled in multiple-dose placebo-controlled trials; however, with the exception of four of these subjects, all had exposures of 60 or fewer days. Of note, data on chronic exposure are derived largely from the phase 3 HF trial. Of subjects receiving any oral dose for more than 30 days, more than 75% were enrolled in the phase 3 HF trial and of subjects receiving more than 6 months of tolvaptan, more than 90% were enrolled in this trial.

Exposure (Days)	Tolvaptan 15-60 mg (N=3181)		Placebo/Other (N=2738)	
	By Period of Greatest Exposure†	Cumulative Exposure‡	By Period of Greatest Exposure†	Cumulative Exposure‡
1-30	808 (25.4%)	3181 (100%)	562 (20.5%)	2738 (100%)
31-60	288 (9.1%)	2373 (74.6%)	237 (8.7%)	2176 (79.5%)
61-90	124 (3.9%)	2085 (65.5%)	112 (4.1%)	1939 (70.8%)
91-180	589 (18.5%)	1961 (61.6%)	427 (15.6%)	1827 (66.7%)
181-360	555 (17.4%)	1372 (43.1%)	602 (22.0%)	1400 (51.1%)
361-720	745 (23.4%)	817 (25.7%)	704 (25.7%)	798 (29.1%)
>720	72 (2.3%)	72 (2.3%)	94 (3.4%)	94 (3.4%)

†Period of Greatest Exposure: subjects are counted once in the category representing their greatest period of exposure

‡Cumulative Exposure: subjects are counted in each category for which they had exposure

Reviewer's comments: The safety database contains data on long-term exposure to tolvaptan, however the database is heavily weighted by HF subjects enrolled in the phase 3 HF trial.

In contrast to HF, the data on the long term safety of exposure to tolvaptan in hyponatremia subjects are more limited. In multiple-dose, placebo-controlled trials of subjects with hyponatremia, 607 subjects were exposed to tolvaptan at any oral dose for up to 30 days, 132 subjects were exposed for greater than 6 months and 69 for more than 1 year. The extent of exposure of hyponatremic subjects, as a group and by baseline serum sodium level, is shown below. Beyond 30 days of treatment, placebo-controlled safety data are derived exclusively from hyponatremic subjects with HF enrolled in HF trials. At 6 months and beyond, all data are derived from the phase 3 HF trial and hence reflect exposure to a 30 mg dose. Of the 189 subjects with a serum sodium < 130 mEq/L, 72 subjects were exposed for greater than 30 days, 21 subjects were exposed for more than 6 months and 13 subjects for more than 1 year.

Table 7.2.1-5. Exposure of All Hyponatremia Subjects from Placebo-Controlled, Multiple-dose Hyponatremia and Heart Failure Trials by Baseline Serum Sodium

Exposure	Tolvaptan (N=607) n (%)		Placebo (N=518) n (%)	
	Period of Greatest Exposure	Cumulative Exposure	Period of Greatest Exposure	Cumulative Exposure
1 to 30	296 (48.8)	607 (100.0)	253 (48.8)	518 (100.0)
31 to 60	112 (18.5)	311 (51.2)	90 (17.4)	265 (51.2)
61 to 90	12 (2.0)	199 (32.8)	15 (2.9)	175 (33.8)
91 to 180	55 (9.1)	187 (30.8)	35 (6.8)	160 (30.9)
181 to 360	63 (10.4)	132 (21.7)	56 (10.8)	125 (24.1)
361 to 720	63 (10.4)	69 (11.4)	59 (11.4)	69 (13.3)
> 720	6 (1.0)	6 (1.0)	10 (1.9)	10 (1.9)

Source: Source: Sponsor's Table 2.7.4.1.2.4-1 page 36 Summary of Clinical Safety

†Period of Greatest Exposure: subjects are counted once in the category representing their greatest period of exposure

‡Cumulative Exposure: subjects are counted in each category for which they had exposure

Table 7.2.1-6. Exposure of All Hyponatremia Subjects from Placebo-Controlled, Multiple-dose Hyponatremia and Heart Failure Trials by Baseline Serum Sodium

Days of Exposure	Any Tolvaptan				Placebo			
	Baseline Serum Sodium				Baseline Serum Sodium			
	130 to 134 mEq/L (N = 418) n (%)		< 130 mEq/L (N = 189) n (%)		130 to 134 mEq/L (N = 340) n (%)		< 130 mEq/L (N = 178) n (%)	
	Period†	Cumulative‡	Period†	Cumulative‡	Period†	Cumulative‡	Period†	Cumulative‡
1 to 30	179 (42.8)	418 (100.0)	117 (61.9)	189 (100.0)	145 (42.6)	340 (100.0)	108 (60.7)	178 (100.0)
31 to 60	69 (16.5)	239 (57.2)	43 (22.8)	72 (38.1)	53 (15.6)	195 (57.4)	37 (20.8)	70 (39.3)
61 to 90	12 (12.9)	170 (40.7)	0 (0.0)	29 (15.3)	11 (3.2)	142 (41.8)	4 (2.2)	33 (18.5)
91 to 180	47 (11.2)	158 (37.8)	8 (4.2)	29 (15.3)	28 (8.2)	131 (38.5)	7 (3.9)	29 (16.3)
181 to 360	55 (13.2)	111 (26.6)	8 (4.2)	21 (11.1)	47 (13.8)	103 (30.3)	9 (5.1)	22 (12.4)

361 to 720	51 (12.2)	56 (13.4)	12 (6.3)	13 (6.9)	48 (14.1)	56 (16.5)	11 (6.2)	13 (7.3)
> 720	5 (1.2)	5 (1.2)	1 (0.5)	1 (0.5)	8 (2.4)	8 (2.4)	2 (1.1)	2 (1.1)

Source: **Source: Sponsor's Table 2.7.4.1.2.4-1 page 36 Summary of Clinical Safety**

†**Period: subjects are counted once in the category representing their greatest period of exposure**

‡**Cumulative: subjects are counted in each category for which they had exposure**

Reviewer's comments: The long-term placebo-controlled safety database for subjects with a serum sodium level < 130 meq/L is very small and is derived exclusively from subjects with hyponatremia in the setting of heart failure. Beyond 30 days, there are no placebo-controlled data on subjects with hyponatremia due to SIADH/other and cirrhosis. At 6 months and beyond, all data are based on hyponatremic subjects enrolled in the phase 3 HF trial receiving a set dose of 30mg.

An extension study of the phase 2/3 studies in patients with hyponatremia (156-03-244) provides long-term uncontrolled safety data, and is the only source of long-term safety data available on subjects with hyponatremia due to etiologies other than heart failure. The duration of exposure to tolvaptan (in days) is given in Table 7.2.1-7. An overview of this exposure by etiology, degree of underlying hyponatremia and volume status at baseline is shown in Table 7.2.1-8 below.

Days of Exposure	Tolvaptan (N=111) n (%)	
	Period†	Cumulative‡
1-30	7 (6.3)	111 (100.0)
31-60	6 (5.4)	104 (93.7)
61-90	4 (3.6)	98 (88.3)
91-180	7 (6.3)	94 (84.7)
181-360	7 (6.3)	94 (84.7)
361-720	33 (29.7)	80 (72.1)
>720	47 (42.3)	47 (42.3)

†**Period: subjects are counted once in the category representing their greatest period of exposure**

‡**Cumulative: subjects are counted in each category for which they had exposure**

Baseline Characteristics		Subjects with Given Duration of Exposure		
		1-30 Days	At least 91 Days	At least 361 Days
Hyponatremia Origin	HF	33	26	18
	Cirrhosis	20	15	10
	SIADH/other	58	53	52
Volume Status	Euvolemia	68	59	57
	Hypervolemia	43	35	23
Hyponatremia Severity	Na 130-134	59	48	40
	Na 125-129	28	26	25
	Na<125	7	5	4

Reviewer's comment: *There is limited long-term experience using tolvaptan in subjects with hyponatremia due to SIADH and cirrhosis. Moreover, there are very little long-term uncontrolled and placebo-controlled data on subjects with a serum sodium level < 130 mEq/L.*

7.2.2 Explorations for Dose Response

Explorations for Dose Response are discussed under Efficacy. Data on drug exposure are presented above.

7.2.3 Special Animal and/or In Vitro Testing

According to the sponsor, anaphylaxis was not observed in guinea pigs sensitized to tolvaptan in an antigenicity study. According to the sponsor, acute dermal and ocular irritation studies in rabbits revealed no significant corrosive effects. According to the sponsor, an immunotoxicity study in rats showed no significant effect of tolvaptan on the humoral immune response to sheep red blood cells.

7.2.4 Routine Clinical Testing

Routine clinical testing of study subjects appears to be adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

Drug metabolism and excretion are discussed in Section 4.4. Drug-drug interactions are discussed in Section 4.4 and Section 7.5.5. Please see the clinical pharmacology review for a more in depth review of pharmacology data.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Conivaptan, a V1a and V2 receptor antagonist, is currently approved for the treatment of euvolemic and hypervolemic hyponatremia. While approved for use in subjects with hypervolemic hyponatremia, the label also carries the following precaution: ***“The number of heart failure patients with hypervolemic hyponatremia who have been treated with intravenous VAPRISOL is too small to establish safety in patients with underlying congestive heart failure. Under Indications and Usage, it is also written that “VAPRISOL should only be used for the treatment of hyponatremia in patients with underlying heart failure when the expected clinical benefit of raising serum sodium outweighs the increased risk of adverse events for heart failure patients.”***

With respect to adverse events, the conivaptan label carries a precaution on overly rapid rates of serum sodium correction, defined as > 12 mEq/L/24 hours. In controlled clinical trials, approximately 9% of conivaptan-treated subjects experienced such a rapid rate of correction. Adverse reactions listed on the conivaptan label occurring in ≥ 5% of patients or healthy volunteers and exceeding placebo are shown in Table 7.2.6-1 below. In addition, pollakiuria, polyuria, hypoglycemia, hyperglycemia and dehydration were seen with conivaptan, but at rates < 5 %. Dry mouth, oral candidiasis and hematuria were also seen in ≤2% of patients treated with conivaptan. As discussed in the safety sections that follow, thirst, dry mouth, polyuria/pollakiuria, gastrointestinal disorders, dehydration, hyperglycemia and overly rapid rates of serum sodium correction were

also observed at a greater incidence in tolvaptan than placebo-treated subjects in tolvaptan's development program.

Table 7.2.6-1. Adverse reactions listed on the Conivaptan Label Occurring in $\geq 5\%$ of Patients or Healthy Volunteers and at an Incidence Greater than that Observed in Placebo Subjects

Term	Placebo (N=69) N (%)	20 mg (N=37) N (%)	40 mg (N=315) N (%)
Blood and lymphatic system disorders			
Anemia NOS	2 (3%)	2 (5%)	18 (6%)
Cardiac disorders			
Atrial fibrillation	0 (0%)	2 (5%)	7 (2%)
Gastrointestinal disorders			
Constipation	2 (3%)	3 (8%)	20 (6%)
Diarrhea NOS	0 (0%)	0 (0%)	23 (7%)
Nausea	3 (4%)	1 (3%)	17 (5%)
Vomiting NOS	0 (0%)	2 (5%)	23 (7%)
General disorders and administration site conditions			
Edema peripheral	1 (1%)	1 (3%)	24 (8%)
Infusion site erythema	0 (0%)	0 (0%)	18 (6%)
Infusion site pain	1 (1%)	0 (0%)	16 (5%)
Infusion site phlebitis	1 (1%)	19 (51%)	102 (32%)
Infusion site reaction	0 (0%)	8 (22%)	61 (19%)
Pyrexia	0 (0%)	4 (11%)	15 (5%)
Thirst	1 (1%)	1 (3%)	19 (6%)
Infections and infestations			
Pneumonia NOS	0 (0%)	2 (5%)	7 (2%)
Urinary tract infection NOS	2 (3%)	2 (5%)	14 (4%)
Injury, poisoning and procedural complications			
Post-procedural diarrhea	0 (0%)	2 (5%)	0 (0%)
Investigations			
Electrocardiogram ST segment depression	0 (0%)	2 (5%)	0 (0%)
Metabolism and nutrition disorders			
Hypokalemia	2 (3%)	8 (22%)	30 (10%)
Hypomagnesemia	0 (0%)	2 (5%)	6 (2%)
Hyponatremia	1 (1%)	3 (8%)	20 (6%)
Nervous system disorders			
Headache	2 (3%)	3 (8%)	32 (10%)
Psychiatric disorders			
Confusional state	2 (3%)	0 (0%)	16 (5%)
Insomnia	0 (0%)	2 (5%)	12 (4%)
Respiratory, thoracic and mediastinal disorders			
Pharyngolaryngeal pain	3 (4%)	2 (5%)	3 (1%)
Skin and subcutaneous tissue disorders			
Pruritus	0 (0%)	2 (5%)	2 (1%)
Vascular disorders			
Hypertension NOS	0 (0%)	3 (8%)	20 (6%)
Hypotension NOS	2 (3%)	3 (8%)	16 (5%)
Orthostatic hypotension	0 (0%)	5 (14%)	18 (6%)

Adapted from MedDRA version 6.0

Reviewer's comment: Tolvaptan's greater selectivity for the V2 receptor may explain some of the differences in the AE profiles of these agents.

7.3 Major Safety Results

The phase 3 HF trial contributed the greatest number of patient-years of exposure to the safety database, and as a result, the safety findings discussed throughout this Review of Safety are heavily weighted by subjects participating in the phase 3 HF trial. Two aspects of the design of this study impact the safety analyses. Because mortality was a primary outcome of the phase 3 HF trial, data on mortality were collected, at times, for long after a subject discontinued from treatment. In addition, subjects enrolled in this trial were allowed to go on and off treatment during the course of the trial.

The analyses that follow focus on treatment-emergent adverse events (TEAEs). For trials other than the phase 3 HF trial, this includes any adverse event occurring after the initiation of study drug. In addition, the sponsor also **defined TEAE's as those starting prior to first dose and continuing after first dose** that were reported as serious, study drug related, or resulting in death, discontinuation, interruption, or reduction of study drug. For the phase 3 HF trial, the sponsor altered this definition by excluding adverse events beginning more than 7 days after the end of the treatment period (defined as the later of the study drug end date, or the date when the decision was made to permanently withdraw study drug).

In conducting safety analyses of the phase 3 HF trial, **other definitions of "treatment-emergent" were explored. Analyses were conducted defining "treatment-emergent" as events occurring while subjects were receiving study drug or as events within 7 days of receiving study drug.** In general, these analyses appeared to produce **similar results as those obtained using the sponsor's definition, and hence the sponsor's definition of "treatment-emergent" was adopted.** There was one notable exception where changing the definition of "treatment-emergent" appeared to affect the results. This was the case for "treatment emergent" deaths in subjects with hyponatremia. Hence mortality data is displayed using various definitions of "treatment-emergent."

7.3.1 Deaths

As of the 120-day safety update, deaths were reported in 651/3536 (18.4%) tolvaptan-treated subjects and 620/2800 (22.1%) placebo-treated subjects in any trial with tolvaptan. In the all HF subjects population, mortality was not greater in the tolvaptan treatment arm (see Table 7.3.1-1 below). In the all hyponatremia subjects population, the incidence of **"all" deaths was similar in the two** treatment arms. However, in analyses of treatment-emergent fatalities in hyponatremic subjects, mortality was slightly greater in tolvaptan than placebo-treated subjects. No deaths were reported in trials of healthy volunteers, subjects with ADPKD, or in subjects in hepatic edema trials.

Population	All		Treatment Emergent†	
	Tolvaptan	Placebo	Tolvaptan	Placebo
Subjects in any trial with Tolvaptan	18.4% (651/3536)	22.1% (620/2800)	16.6% (588/3536)	19.5% (547/2800)
All Heart Failure Subjects	19.1% (632/3311)	23.2% (611/2633)	17.1% (572/3311)	20.4% (538/2633)
All Hyponatremia Subjects	25.7% (170/662)	25.5% (132/518)	24.6% (163/662)	22.8% (118/518)

Source: Sponsor email correspondence dated 2.29.2008 and Figure 6-1 ISS (revised version) submitted as an Amendment on 2.1.2008. This table includes an additional 3 tolvaptan deaths that were reported in the 12- day safety update.

†* For the phase 3 HF trial, this includes AEs starting during the treatment period with an outcome of fatal. The treatment period was defined as starting after the subject took the first dose of medication and ended seven days after the latter of (1) study drug end date or (2) date when decision was made to permanently withdraw drug.

Reviewer’s comment: Subjects with heart failure and hyponatremia have a high background mortality rate. Including deaths that occur long after tolvaptan has been stopped may make it more difficult to detect a small adverse drug effect on mortality.

In analyses of placebo-controlled trials in subjects with hyponatremia, treatment-emergent deaths were also observed at a slightly greater incidence in tolvaptan than placebo-treated subjects (23.7% and 22.8% respectively). This difference between treatment arms was driven entirely by subjects with heart failure and hyponatremia. Table 7.3.1-2 further explores the relationship between tolvaptan and mortality in subjects with HF and hyponatremia. As shown in the table, this difference in mortality between treatment arms is largely driven by subjects enrolled in the phase 3 HF trial. Pooled data from other studies did not contradict this result.

Population		Tolvaptan	Placebo
All Heart Failure subjects with hyponatremia*		29.3% (125/427)	28.1% (99/353)
Hyponatremia subjects in phase 3 heart failure trial	All Deaths †	50.4% (122/242)	48.7% (113/232)
	As an outcome of an AE‡	47.5% (115/242)	42.7% (99/232)
	Treatment Emergent *	42.1% (102/242)	38.4% (89/232)
Phase 2 Heart Failure Trials		13.2% (12/91)	10.0% (4/40)
Heart Failure subjects in controlled hyponatremia trials		11.5% (10/87)	6/79 (7.6%)

Source: Sponsor email correspondence dated 2.29.2008 and Figure 6-1 ISS (revised version) submitted as an Amendment on 2.1.2008

†For the phase 3 HF trial, this includes deaths collected as an outcome for the intent-to-treat efficacy analysis and occurring after discontinuation and not reported as an outcome of an adverse event.

‡ For the phase 3 HF trial, this includes deaths reported as an outcome of an AE, regardless of treatment status at the time of death

* For the phase 3 HF trial, this includes AEs starting during the treatment period with an outcome of fatal. The treatment period was defined as starting after the subject took the first dose of medication and ended seven days after the latter of (1) study drug end date or (2) date when decision was made to permanently withdraw drug.

To further explore the association between tolvaptan and mortality in heart failure subjects with hyponatremia, analyses were conducted to determine the dose-dependence of this relationship. As shown in Table 7.3.1-3, few subjects were exposed to doses outside of the 15 to 60 mg dose range, making the results difficult to interpret. Adjusting for subject exposure at each dose, there may be a dose-dependence to the association.

	Tolvaptan Dose (mg)							
	≤15	30	45	60	90	120	15-60	Placebo
	N=20	N=269	N=5	N=47	N=10	N=3	N=73	N=353
Treatment-emergent fatalities	0 %	38.3% (103)	0%	21.3% (10)	20.0% (2)	0%	13.7% (10)	28.1% (99)
Treatment-emergent fatalities by patient days of exposure*	0	.17	0	0.48	0.74	0	0.55	0.16

*Number of deaths divided by patient days of exposure to drug x 100

Additional analyses focused on the incidence of mortality in tolvaptan and placebo-treated subjects across 3 grades of hyponatremia (baseline serum sodium < 125 mEq/L, 125-129 mEq/L and 130-134 mEq/L). As shown in Table 7.3.1-4, the incidence of treatment emergent deaths was similar in tolvaptan and placebo-treated subjects with a serum sodium < 130 mEq/L, however the number of subjects with a serum sodium < 130 mEq/L was small.

Baseline Serum Sodium	All		Treatment Emergent	
	Tolvaptan	Placebo	Tolvaptan	Placebo
130-134	44.6% (91/204)	37.6% (67/178)	39.7% (81/204)	33.0% (58/178)
125-129	66.7% (16/24)	63.2% (24/38)	58.3% (14/24)	60.5% (23/38)
<125	57.1% (8/14)	50% (8/16)	50% (7/14)	50% (8/16)

Reviewer's comment: The number of subjects with HF and hyponatremia is small, making the mortality data difficult to interpret. Nonetheless, the slightly greater incidence of death in tolvaptan than placebo-treated subjects with HF and hyponatremia is of concern. Adverse events and fatalities in this subgroup are discussed further in Section 7.5.4.3.

Mortality data by region (U.S. vs. all sites) are shown in Table 7.3.1-5. In the phase 3 heart failure trial, slightly greater mortality was observed in tolvaptan as compared to placebo-treated subjects enrolled at U.S. study sites; however analyses focused on the larger HF and hyponatremia population did not reproduce this finding.

Population	U.S. Sites		All Sites	
	Tolvaptan	Placebo	Tolvaptan	Placebo
Phase 3 Heart Failure Trial	26.6% (149/561)	24.7% (141/570)	22% (453/2063)	22.7% (466/2055)
All Heart Failure and Hyponatremia Subjects in multiple- dose, placebo-controlled trials	13.0% (199/1531)	16.0% (178/1114)	15.9% (523/3294)	18.7% (511/2758)
All Heart Failure Subjects in multiple-dose, placebo-controlled trials	13.9% (194/1401)	17.0% (171/101)	17.1% (516/3014)	19.6% (500/2541)
Phase 3 Hyponatremia Trials	5.5% (8/146)	7.1% (10/141)	6.3% (14/223)	5.9% (13/220)

*Includes treatment-emergent deaths in trial 156-03-236

Reviewer's comment: The significance of this finding is unclear.

7.3.2 Serious Adverse Events

The discussion that follows focuses on treatment-emergent adverse events (TEAEs) occurring in multiple-dose placebo-controlled trials. See section 7.1.1 for a description of the various datasets.

Serious TEAEs (including fatal events) occurred in 47.2% (1555/3294) of tolvaptan and 51.1% (1400/2738) of placebo-treated subjects with HF and/or hyponatremia. Table 7.3.2-1 below shows serious TEAEs occurring at an incidence greater than 1% and at a greater incidence in tolvaptan than placebo-treated subjects. Of note, a disproportionate number of subjects in **tolvaptan’s clinical development program** had HF and/or participated in the phase 3 HF trial. As a result, there is significant overlap between the all HF and hyponatremia subjects, all HF and phase 3 HF trial datasets. Given this overlap, it is perhaps not surprising that results of analyses conducted in these datasets largely mirror each other with respect to TEAEs.

As shown in Table 7.3.2-1, a slightly greater incidence of cardiac arrest, ventricular tachycardia, cardiogenic shock, and syncope was observed in tolvaptan-treated subjects in the all HF and hyponatremia subjects, all HF subjects and phase 3 HF trial datasets. For each of these AEs, the absolute difference in incidence between tolvaptan and placebo subjects was small (< 1.0%). However these events occurred infrequently and the relative increase in incidence of these events was more appreciable. These TEAEs are discussed further in the sections that follow.

In the phase 3 HF trial, cardiac failure and cardiac failure congestive, common in both treatment arms, also occurred at a slightly greater incidence in tolvaptan than placebo-treated subjects. The adjudicated dataset for the phase 3 HF trial was used to further explore this issue. In the adjudicated dataset, the incidence of death due to heart failure was not different in the two treatment arms (10.8% in both) while a slightly greater incidence of adjudicated hospitalizations for HF was observed in tolvaptan than placebo subjects (30.3% and 29.5%, respectively). This difference represented a small relative increase in the incidence of HF hospitalizations and its significance, if any, is unclear.

Table 7.3.2-1 also provides an overview of serious treatment emergent adverse events occurring in subjects with hyponatremia. Of note, the dataset of all subjects with hyponatremia is heavily weighted by HF subjects with hyponatremia enrolled in HF trials. As a result, safety analyses of this dataset also mirror to some extent those described above for the HF indication. Again, a slightly greater incidence of cardiac arrest and cardiac failure is observed and the incidence of ventricular fibrillation, another ventricular arrhythmia, is also greater in tolvaptan than placebo-treated subjects in the all hyponatremia subjects dataset. While TEAEs of cardiac failure were reported at a slightly greater incidence in tolvaptan treated subjects, analyses of adjudicated heart failure deaths and hospitalizations in this subpopulation revealed no clear difference in incidence between treatment arms. Serious TEAEs in hyponatremic subjects are discussed further in Section 7.5.4

Of the datasets shown below, only the phase 3 hyponatremia trials dataset is comprised of an appreciable proportion of non-HF subjects. In the phase 3 hyponatremia trials, a slightly greater incidence of cardiac failure, dehydration, encephalopathy, and ascites is observed in tolvaptan-treated subjects. For each of these serious TEAEs, the difference in incidence between the two study arms is due to differences in event rates of 3 or less. Compared to the HF datasets, the phase 3 hyponatremia trial dataset is much smaller and small differences in event rates have a more marked effect on AE incidence. Dehydration is discussed further in this section while the other AEs are addressed in Section 7.5.4.

Table 7.3.2-1. Serious Treatment Emergent Adverse Events Occurring at an Incidence Greater than 1% in Tolvaptan-Treated Subjects and at an Incidence Greater than in the Placebo Arm*		
	Tolvaptan	Placebo
All Heart Failure and Hyponatremia Subjects from Multiple-Dose Placebo-Controlled Trials (occurring at an incidence at least 0.2% greater in tolvaptan than placebo-treated subjects)		

AE	N=3294	N=2738
Cardiac Arrest	1.5% (50)	0.9% (26)
Ventricular Tachycardia	2.2% (71)	1.8% (49)
Cardiogenic Shock	1.1% (35)	0.9% (25)
Chest Pain	1.7% (57)	1.4% (38)
Sepsis	1.0% (32)	0.8% (23)
Dehydration	1.2% (41)	1.0% (27)
Syncope	1.2% (38)	1.0% (27)
Phase 3 Heart Failure Trial (occurring at an incidence at least 0.4% greater in tolvaptan than placebo-treated subjects)		
AE	N=2063	N=2055
Cardiac Failure	22.2%	21.4%
Cardiac Failure congestive	14.0%	13.5%
Ventricular Tachycardia	2.7%	2.1%
Cardiac Arrest	2.0%	1.2%
Cardiogenic Shock	1.6%	1.2%
Pneumonia	3.5%	3.1%
Syncope	1.6%	1.1%
All Hyponatremia Subjects from Multiple-Dose Placebo-Controlled Heart Failure and Hyponatremia Trials (occurring at an incidence at least 0.4% greater in tolvaptan than placebo-treated subjects)†		
AE	N=607	N=518
Cardiac Arrest	14 (2.3%)	5 (1.0%)
Ventricular Fibrillation	8 (1.3%)	2 (0.4%)
Cardiac Failure Chronic	6 (1.0%)	3 (0.6%)
Ascites	7 (1.2%)	2 (0.4%)
Sepsis	10 (1.6%)	5 (1.0%)
Dehydration	11 (1.8%)	4 (0.8%)
Respiratory Failure	8 (1.3%)	4 (0.8%)
Phase 3 Hyponatremia Trials (occurring at an incidence at least 0.4% greater in tolvaptan than placebo-treated subjects)		
AE	N=223	N=220
Cardiac Failure congestive	9 (4.0%)	7 (3.2%)
Cardiac Failure	5 (2.2%)	2 (0.9%)
Abdominal Pain	3 (1.3%)	0 (0%)
Ascites	3 (1.3%)	1 (0.5%)
Dehydration	4 (1.8%)	1 (0.5%)
Encephalopathy	3 (1.3%)	0 (0%)
Respiratory Failure	3 (1.3%)	1 (0.5%)

*The pooled dataset containing all subjects with HF and hyponatremia is derived disproportionately from HF studies (over 90%). To a large extent, serious TEAEs were similar in the all HF and hyponatremia subjects and all HF subjects datasets and hence are not shown or discussed separately.

Arrhythmias, cardiac arrest and sudden death

Cardiac arrest and serious ventricular arrhythmias were observed at a greater incidence in the tolvaptan than placebo-treatment arm in datasets heavily weighted by HF subjects. Because these AEs could be thought of as belonging to a common disease pathway (ventricular arrhythmia leading to cardiac arrest and sudden cardiac death), the incidence of cardiac arrest, ventricular arrhythmias and sudden cardiac death was determined as a

group using the AE dataset. The incidence of sudden cardiac death and arrhythmias was also explored using the adjudicated dataset from the phase 3 HF study. As shown in the table below, the difference in incidence of these AEs between treatment arms was small, though pooling terms appeared to magnify the difference between the study arms. It is important to note that in the adjudicated database, the incidence of sudden cardiac death was much higher than in the AE database. This difference between the datasets highlights the limitations of the diagnoses made, terms used by the primary investigator and/or translation of these terms by the sponsor. A possible association between tolvaptan use, ventricular arrhythmias and cardiac arrest is further explored below.

Table 7.3.2-2. Incidence of serious ventricular arrhythmias, cardiac arrest, syncope and/ or sudden cardiac death ‡			
Serious Adverse Event		Tolvaptan	Placebo
		Phase 3 Heart Failure trial	
Adjudicated	Arrhythmia leading to hospitalization	4.8% (98)	4.0% (82)
	Sudden Cardiac Death	6.5% (135)	6.2% (128)
AE database	Serious Ventricular Arrhythmia* , cardiac arrest† , or sudden cardiac death	8.1% (167)	7.1% (146)
	Serious Ventricular Arrhythmia	3.8% (78)	3.2% (65)
	Sudden Cardiac Death	2.1% (44)	2.0% (42)
All Heart Failure Subjects from other multiple-dose Placebo Controlled Trials		N=951	N=464
AE database	Serious Ventricular Arrhythmia* , cardiac arrest† , or sudden cardiac death	3.5% (33)	3.2% (15)
	Serious Ventricular Arrhythmia	2.2% (21)	1.7% (8)
	Sudden Cardiac Death	0.2% (2)	0.4% (2)

‡Subjects with multiple AEs (e.g. cardiac arrest and ventricular arrhythmia) were counted only once within each AE grouping

*Terms pooled: ventricular arrhythmia, ventricular fibrillation, ventricular flutter, ventricular tachyarrhythmia and ventricular tachycardia

†Terms pooled: Cardiac Arrest and Cardio-Respiratory Arrest.

Ventricular Tachycardia and Ventricular Arrhythmias

In pooled data from multiple-dose placebo-controlled trials, serious ventricular tachycardias were observed in 2.2% of tolvaptan-treated subjects and 1.8% of placebo-treated subjects. As shown in Table 7.3.2-3, a slightly greater incidence of serious ventricular tachycardias and serious ventricular arrhythmias was observed across heart failure trials. This association was not noted in the phase 3 hyponatremia trials.

Table 7.3.2-3. Treatment Emergent Serious Ventricular Tachycardias and Arrhythmias				
Population	Serious Ventricular Tachycardias		Serious Ventricular Arrhythmias*	
	Tolvaptan	Placebo	Tolvaptan	Placebo
All heart failure and hyponatremia subjects in multiple-dose place-controlled trials	2.2% (71)	1.8% (49)	3.0% (99)	2.7% (73)
Placebo-controlled heart failure trials	Phase 3 heart failure study	2.7% (55)	2.1% (44)	3.8% (78)
	Phase 2 trials in subjects with worsening heart failure	2.5% (6)	1.3% (1)	3.8% (9)
	Multiple-dose phase 2 trials in subjects with stable heart failure	1.5% (10)	0.7% (2)	1.7% (11)

Source: Sponsor's Table 7.2.2-1, 8.2.4.4-2, 8.3.4.3-1, 8.4.4.3-1 ISS

*Terms pooled: ventricular arrhythmia, ventricular fibrillation, ventricular flutter, ventricular tachyarrhythmia and ventricular tachycardia

To further investigate an association between ventricular tachycardia/arrhythmias and tolvaptan use, analyses were conducted to examine the dose dependence of this relationship. As shown in Table 7.3.2-4 below, the number of events occurring in subjects at doses other than 30 mg is small, making the data difficult to interpret.

Population	Tolvaptan Dose (mg)									Placebo
	<15	15	30	45	60	90	120	15-60	Any dose	
All Heart Failure Subjects	0	4.2% (5/119)	5.6% (142/2527)	1.1% (1/91)	6.0% (14/235)	7.3% (6/82)	0 (0/7)	2.7% (2/75)	5.4% (170/3147)	5.1% (132/2571)
All Hyponatremia Subjects	0	0	6.2% (17/275)	0 (0/5)	7.5% (4/53)	10% (1/10)	0 (0/3)	0.9% (2/223)	4.0% (24/607)	3.9% (20/518)

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

Cardiac Arrest

In pooled data from multiple-dose placebo-controlled trials, cardiac arrest was seen in 1.5% of tolvaptan and 0.9% of placebo-treated subjects. As cardiac arrest and cardio-respiratory arrest are similar events/overlapping categories, these terms were pooled. As shown in Table 7.3.2-5, this difference in incidence between the 2 treatment arms was lost and/or diminished when these terms were pooled. Additional analyses revealed no clear dose-dependence in the relationship with cardiac arrest, however the number of events was small.

Population	Cardiac Arrest		Cardiac or Cardio-Respiratory Arrest	
	Tolvaptan	Placebo	Tolvaptan	Placebo
Multiple-dose place-controlled trials	1.5% (50)	1.0% (28)	2.0% (67)	2.0% (54)
Phase 3 heart failure trial	2.0% (42)	1.3% (26)	2.7% (55)	2.3% (47)
Heart failure subjects in trials other than the phase 3 heart failure trial	0.7% (7)	0.4% (2)	1.2 % (11)	1.3% (6)

Dehydration, hypotension and hypovolemia

In pooled data from multiple-dose placebo-controlled trials, AEs of serious dehydration were reported in 1.2% and 1.0% of tolvaptan and placebo-treated subjects, respectively. To further explore an association between tolvaptan use and hypotension/and or hypovolemia, additional related terms were pooled. Table 7.3.2-6 shows the incidence of treatment emergent AEs suggestive of hypotension and/or hypovolemia in the tolvaptan and placebo arms of the all subjects dataset, phase 3 heart failure trial, and dataset of all other heart failure subjects (excluding the phase 3 trials). Serious hypotension and/or hypovolemia were more common in tolvaptan than placebo-treated subjects in the phase 3 heart failure trial. This association was not seen however in analysis of data from heart failure subjects in other trials.

Table 7.3.2-6 Treatment Emergent Adverse Events of Hypotension and/or Hypovolemia*

Trials	Tolvaptan	Placebo
All Heart Failure and Hyponatremia Subjects in Multiple-dose Placebo-Controlled Trials		
	N=3294	N=2716
Serious	4.2% (138)	3.5% (96)
Severe	3.4% (113)	3.1% (83)
All	20.1% (663)	20.0% (542)
Phase 3 heart failure trial		
	N=2063	N=2055
Serious	5.7% (117)	3.9% (81)
Severe	4.4% (90)	3.7% (75)
All	21.3% (439)	20.7% (425)
Heart Failure subjects from multiple-dose placebo-controlled trials other than the phase 3 HF trial		
	N=951	N=464
Serious	1.8% (17)	2.6% (12)
Severe	2.0% (19)	1.5% (7)
All	19.4% (184)	20.5% (95)

*Pooled terms include: 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

To further explore a possible association between tolvaptan use and treatment emergent AEs of hypotension and/or hypovolemia, the dose dependence of this relationship was analyzed. As shown in Table 7.3.2-7, no clear dose dependence is seen. Similarly, in analyses of vital signs data, no clear or consistent decrease in blood pressure was observed during routine vital signs measurements.

AE Severity	Tolvaptan Dose (mg)									Placebo
	<15	15	30	45	60	90	120	15-60	Any dose	
All AEs	25.0% (6)	20.3% (26)	20.7% (513)	20.7% (19)	19.3% (47)	20.7% (17)	28.6% (2)	14.8% (33)	20.1% (663)	20.0% (542)
Serious AEs	4.2% (1)	1.6% (2)	5.0% (124)	1.1% (1)	1.2% (3)	1.2% (1)	0	2.7% (6)	4.2% (138)	3.5% (96)

Reviewer's comment: *This association between tolvaptan and hypotension and/or hypovolemia is not consistent across trials and analyses do not reveal a dose-dependence. In contrast, conivaptan appears to be associated with hypotension. This may be explained in part by tolvaptan's greater selectivity for the V2 receptor.*

7.3.3 Dropouts and/or Discontinuations

The incidence of discontinuations was similar in tolvaptan and placebo-treated subjects (34.5 and 35.9%, respectively) in multiple-dose, placebo controlled trials. As shown in Table 7.3.3-1, discontinuations due to AEs were more common in tolvaptan-treated subjects while discontinuations due to subject withdrawal of consent occurred at a greater incidence in the placebo arm.

Table 7.3.3-1. Discontinuations in tolvaptan and placebo subjects in multiple-dose, placebo-controlled

Trials*		
Reason for discontinuation	Tolvaptan (N=3294)	Placebo/Other (N=2738)
Adverse experience	9.5% (313)	7.2% (196)
Subject withdrew consent	8.2% (269)	9.4% (257)
Investigator withdrew subject	2.5% (81)	2.9% (80)
Lost to follow up	1% (33)	1.1% (29)
Subject met withdrawal criteria	0.8% (26)	0.5% (15)
Protocol violation	0.5% (15)	0.1% (4)
Protocol deviation	0.2% (7)	0.2% (6)

* Reasons reported by 4 or fewer subjects as a cause for discontinuation are not shown.

Table 7.3.3-2 shows discontinuations due to AEs in the phase 3 HF trial. According to the sponsor, in the phase 3 HF trial, 6.5% of tolvaptan-treated subjects (135/2063) and 5.5% of placebo-treated subjects (114/2055) **discontinued treatment due to an AE**. Of AE's leading to discontinuation, only thirst, dry mouth, hyperkalemia and cardiac failure were reported in tolvaptan-treated subjects at an incidence $\geq 0.2\%$ that seen in the placebo arm. Three tolvaptan-treated subjects (0.3%) discontinued treatment due to hypernatremia. In the phase 3 hyponatremia trials, 10.3% (23/223) and 11.8% (26/220) of tolvaptan and placebo-treated subjects, respectively, discontinued trial medication due to an AE. No single AE leading to discontinuation occurred at an incidence $> 1\%$ in the tolvaptan treatment arm.

Table 7.3.3-2. Discontinuations in the phase 3 heart failure trial occurring at an incidence in tolvaptan-treated subjects at least 0.2% greater than that observed in the placebo arm		
Phase 3 Heart Failure Trial- occurring at least 0.2% greater incidence in tolvaptan treated subjects		
AE	Tolvaptan (N=2063)	Placebo (N=2055)
Cardiac Failure	1.0% (20)	0.8% (16)
Thirst	0.3% (7)	0
Dry Mouth	0.2% (4)	0
Hyperkalemia	0.2% (4)	0

Source: Sponsor's Table 8.2.4.6-2 (page 444) ISS

Table 7.3.3-3 explores the incidence of discontinuations due to an adverse experience by tolvaptan dose. The number of subjects at some exposure levels is small and differences in study design and study population make the data difficult to interpret. Nonetheless, the data suggest a possible dose-dependence, with increased discontinuations due to AEs occurring at doses of ≥ 60 mg.

Table 7.3.3-3. Dose dependence of discontinuations due to Adverse Events in multiple-dose placebo-controlled trials									
Population	Tolvaptan Dose (mg)							Any Dose	Placebo
	<15	15	30	45	60	>60	15-60		
All Heart Failure and Hyponatremia	20.8% (5/24)	10.2% (13/128)	7.7% (192/2495)	9.8% (9/92)	20.6% (50/243)	19.1% (17/89)	12.1% (27/223)	9.5% (313/3294)	7.1% (194/2716)
All Hyponatremia	22.7% (5/22)	6.3% (1/16)	7.3% (20/275)	20.0% (1/5)	35.8% (19/53)	31% (4/13)	12.1% (27/223)	12.7% (77/607)	10.1% (52/517)
All Heart Failure	9.1% (1/11)	13.3% (12/90)	7.7% (189/2453)	4.8% (3/62)	20.0% (47/235)	19.1% (17/89)	17.6% (13/74)	9.4% (282/3014)	6.6% (169/2519)