

**Treatment of Hyponatremia: Medical Utility of Vasopressin V₂
Receptor Antagonism**

Briefing Document

**Advisory Committee Meeting of the Cardiovascular and Renal Drugs
Division of the US Food and Drug Administration**

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List of Abbreviations

ACE	Angiotensin-converting enzyme
AE	Adverse event
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AUC	Area under the concentration-time curve
AVP	Arginine vasopressin
BID	Twice daily
CHF	Congestive heart failure
CI	Confidence interval
C _{max}	Maximum plasma concentration
CMH	Cochran-Mantel-Haenszel test
CNS	Central nervous system
CV	Cardiovascular
CYP	Cytochrome P450
DB	Double-blind
DCRP	Division of Cardiovascular and Renal Products
df	Degrees of freedom
ECG	Electrocardiogram
EOT	End of treatment
ESCAPE	Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness
ET	Early termination
FDA	(United States) Food and Drug Administration
GFR	Glomerular filtration rate
HDS	Hyponatremia Disease-specific Survey
hERG	human ether-a-go-go related gene
HF	Heart failure
HR	Hazard ratio
ITT	Intent to treat
IV	Intravenous
JVP	Jugular venous pressure
KCCQ	Kansas City Cardiomyopathy Questionnaire
LOCF	Last observation carried forward
LOS	Length of hospital stay
LS	Least square
LVSD	Left ventricular systolic dysfunction
MCS	Mental Component Summary (score)
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-stage Liver Disease
MID	Minimally important difference
N, n	Number of patients
NA	Not applicable
NDA	New drug application
nDI	Nephrogenic diabetes insipidus
NYHA	New York Heart Association
OC	Observed cases
OL	Open-label
OPTIMIZE-HF	Organized Program to Initiate Life Saving Treatment in Patients Hospitalized for Heart Failure
PBO	Placebo
PC	Placebo-controlled
PCS	Physical Component Summary (score)

QD	Once a day
QTc (QTcB, QTcF)	Corrected QT interval (corrected by Bazett's formula, by Fridericia's formula)
QTcI	Individually-corrected QTc
R	Randomized
RR	Relative risk
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SF-12	Short Form-12 Health Survey
SIADH	Syndrome of inappropriate antidiuretic hormone secretion
SMQ	Standardized MedDRA query
SOC	Standard of care
TEAE	Treatment-emergent adverse event
TLV	Tolvaptan
US	United States
V ₂	Vasopressin 2 receptor

Executive Summary

This document was prepared by Otsuka Pharmaceutical Development and Commercialization, Inc., sponsor for pending tolvaptan NDA 22-275 and authorized United States agent for Otsuka Pharmaceutical Company, Ltd., Tokyo, Japan. The document is intended to provide information in preparation for the Center for Drug Evaluation and Research Cardiovascular and Renal Drugs Advisory Committee Meeting on June 25, 2008, during which the sponsor at the request of the Division of Cardiovascular and Renal Products will make presentations to discuss:

- The medical utility of correcting hyponatremia,
- The correction of serum sodium concentrations mediated by tolvaptan, an orally-administered vasopressin 2 (V₂) receptor antagonist,
- The medical impact of correcting serum sodium concentrations with tolvaptan in patients with hypervolemic and euvolemic hyponatremia as assessed by health-related patient-reported outcomes and clinical outcomes associated with patients' underlying disease, and
- The safety profile of tolvaptan.

Hyponatremia, characterized by a subnormal concentration of sodium in the blood (< 135 mEq/L), is a disease associated with risks ranging from mild neurological symptoms to significant morbidity and mortality. The correction of serum sodium associated with tolvaptan use results in the restoration of near normal mental functioning and well-being and improved symptoms associated with fluid overload.

The following table summarizes the highlights presented in this briefing document and identifies the section of the briefing package where the supporting information is located.

Highlights	Section Number(s)
Hyponatremia is associated with significant medical consequences and therefore should be treated.	2.1
Dilutional hyponatremia (increased fluid retention with decreasing serum sodium concentration) can be classified as euvolemic or hypervolemic; and is typically characterized by plasma arginine vasopressin (AVP) concentrations which are inappropriate for a given, low serum osmolality.	

Highlights	Section Number(s)
The syndrome of inappropriate antidiuretic hormone secretion (SIADH) represents any disorder where hyponatremia is associated with euvoolemia and an inappropriately high urinary sodium concentration. The pathophysiology common to SIADH, as well as to hypervolemic states such as cirrhosis and heart failure, is inappropriate antidiuresis, typically mediated through inappropriate AVP activity.	2.1
Selective V ₂ receptor antagonists inhibit the V ₂ receptor at the renal collecting ducts, thereby inducing free water excretion. Consequently, V ₂ receptor antagonists such as tolvaptan are the logical treatment to eliminate free water and thus to increase serum sodium and to improve clinical manifestations of euvolemic or hypervolemic hyponatremia.	2.1
Nonspecific neurological symptoms caused by hyponatremia may be mild initially, but may progress to alterations in consciousness, seizure and respiratory arrest. These symptoms can be reversed or prevented by correcting serum sodium concentrations, and failure to recognize and appropriately correct hyponatremia may have serious clinical consequences, including fatal outcomes. Serum sodium concentration is the most direct measure for the diagnosis of hyponatremia and by which the treatment of hyponatremia is monitored.	2.2 2.3 3.1
The decision to treat an individual patient with hyponatremia is not based on an absolute serum sodium threshold but rather is based on assessment of a combination of four criteria: <ul style="list-style-type: none"> 1) Concentration of serum sodium, 2) Rate and magnitude of serum sodium decline, 3) Presence of symptoms, and 4) Concomitant medical conditions (etiological and non-etiological). 	2.4
Currently available treatment options for hyponatremia are sub-optimal (limited efficacy and/or poor compliance), restricted to in-hospital use, and/or poorly tolerated.	2.4

Highlights	Section Number(s)
<p>Tolvaptan increases serum sodium concentrations.</p> <ul style="list-style-type: none"> Clinically meaningful and statistically significant increases in serum sodium were observed in patients regardless of the underlying disease etiology (SIADH, congestive heart failure [CHF], or cirrhosis) or baseline severity of hyponatremia (< 130 mEq/L or 130-134 mEq/L). Treatment effects were sustained by continued tolvaptan therapy but reverted upon discontinuation of tolvaptan to concentrations below 135 mEq/L. Following re-introduction of tolvaptan therapy, mean serum sodium concentrations returned to the normal range (\geq 135 mEq/L). 	3.2
<p>Tolvaptan prevents further decreases in serum sodium concentrations that could potentially lead to increasingly serious negative clinical outcomes.</p>	3.2
<p>Tolvaptan generally produces improvements in mental functioning across the various underlying diseases as assessed by patient-reported outcome measures.</p> <ul style="list-style-type: none"> Statistically and clinically significant improvements in the Mental Component Summary (MCS) Score of the Short-Form-12 Health Survey were observed at Day 30 in the overall hyponatremia population (ie, baseline serum sodium < 135 mEq/L). Improvements of MCS Score in all etiologies (SIADH, CHF, cirrhosis) contributed to this effect, equating to restoration of near normal mental functioning and well-being as compared with the general US population. Similar improvements were observed regardless of the severity of hyponatremia. Improvements in these health-related patient-reported outcomes correlated with tolvaptan-mediated improvements in serum sodium concentration. 	3.3.1

Highlights	Section Number(s)
<p>Tolvaptan generally produces improvements in clinical outcomes associated with patients' underlying disease.</p> <ul style="list-style-type: none"> Statistically significant improvements in signs and symptoms of CHF were observed short-term with tolvaptan, including body weight, fatigue and dyspnea. In cirrhosis patients, significant improvements were observed in body weight and fatigue. In a long-term CHF study with tolvaptan, the following were observed: <ul style="list-style-type: none"> Evidence of a delay in time to all-cause mortality and cardiovascular (CV) mortality/heart failure hospitalization were seen in tolvaptan patients with baseline hyponatremia <130 mEq/L. Statistically significant improvements in time to CV mortality/CV morbidity were observed in tolvaptan patients with baseline serum sodium <130 mEq/L. 	3.3.2
<p>Tolvaptan has a favorable, readily-manageable safety profile. The most common adverse events observed were consistent with the mechanism of action of tolvaptan.</p>	4

Tolvaptan is uniquely suited to address the clear unmet medical need for the correction of serum sodium and prevention of hyponatremia and its symptoms by targeting the basic underlying pathophysiological mechanism leading to hypervolemic and euvoletic hyponatremia.

1 Introduction

The Division of Cardiovascular and Renal Products (DCRP) of the United States (US) Food and Drug Administration (FDA) is convening an Advisory Committee meeting on 25 June 2008 to discuss regulatory considerations surrounding the use of tolvaptan, an orally-administered arginine vasopressin (AVP) V₂ receptor antagonist, for the treatment of hyponatremia. Pursuant to a marketing authorization application filed by Otsuka Pharmaceutical Development and Commercialization, Inc. (Otsuka) for tolvaptan tablets for the treatment of hyponatremia, the DCRP has requested a meeting for which the sponsor has prepared this briefing document addressing the following:

- Establish the medical need to treat hyponatremia and the circumstances prompting treatment initiation, as well as the consequences of inadequate treatment ([Section 2](#)),
- Establish the effects of tolvaptan on increasing sodium concentrations and clinical importance of this correction in terms of improving health-related patient-reported outcomes and clinical outcomes associated with the patients' underlying disease ([Section 3](#)), and
- Summarize the safety data of tolvaptan and demonstrate its acceptable risk-benefit profile for the treatment of hyponatremia ([Section 4](#)).

1.1 Pharmacological Class and Mode of Action

Tolvaptan (OPC-41061) is an orally-active selective AVP V₂ receptor antagonist belonging to a class of compounds called *vaptans*. The vaptans block the action of AVP in the collecting ducts and induce free water clearance in the body, an effect termed *aquaresis*. By promoting aquaresis, AVP V₂ receptor antagonists are effective in increasing serum sodium concentrations in patients with hyponatremia due to the syndrome of inappropriate antidiuretic hormone (SIADH) or due to edema-forming states such as cirrhosis and congestive heart failure (CHF).

1.2 Proposed Indication and Dosage and Administration

The proposed indication for tolvaptan is as follows:

Treatment of hypervolemic and euvoletic hyponatremia (including patients with heart failure, cirrhosis, SIADH, etc.) and for the prevention of worsening hyponatremia.

The recommended starting dose for tolvaptan in hyponatremia is 15 mg/day administered on a once-a-day (QD) schedule without regard to meals. The dose may be increased to 30 mg/day, at intervals of at least 24 hours, and to a maximum of 60 mg/day to achieve the desired concentration of serum sodium. During titration, patients should be monitored for serum sodium and volume status.

1.3 Objectives of the Briefing Package

The objectives of this briefing document are to summarize data available in the literature and from the tolvaptan development program to illustrate the following points:

- Patients with low serum sodium concentrations face a continuum of risk ranging from symptoms of mild neurocognitive and neurological impairment to coma and death. Patients with hyponatremia derive benefits from treatment with tolvaptan dependent on their overall risk. The decision to treat an individual patient is driven not by an absolute threshold of serum sodium but rather by four critical factors: the concentration of serum sodium, the rate and magnitude of the decline in serum sodium, the presence of symptoms, and concomitant medical conditions.
- Tolvaptan induces controlled and sustained increases in patients' serum sodium concentrations regardless of hyponatremia severity or underlying illness. In addition, it has been shown to prevent worsening of hyponatremia.
- In addition to affecting sodium concentrations, treatment with tolvaptan results in improvements of patients' mental functioning as based on patient-reported outcomes data.
- Clinical outcomes are improved overall in hyponatremic patients.
 - In the phase 3 hyponatremia dataset (inclusive of SIADH, CHF, and cirrhosis patients), there was a net fluid loss, as well as reductions in body weight and in the need for fluid restriction.
 - In patients with hyponatremia and CHF, there were improvements in signs and symptoms of body weight, dyspnea, and fatigue; and reduced time to cardiovascular mortality and morbidity, especially in patients with baseline serum sodium concentration of < 130 mEq/L.
 - In patients with hyponatremia and cirrhosis, there were improvements in signs and symptoms of body weight and fatigue.
- Tolvaptan demonstrates a favorable risk-benefit profile.

1.4 Regulatory History

Otsuka met with the FDA Division of Metabolic and Endocrine Products prior to and during phase 3 development and obtained concurrence that 1) serum sodium is an appropriate endpoint for hyponatremia, and 2) treatment of mild hyponatremia (130-134 mEq/L) would also require some demonstration of clinical benefit from tolvaptan studies

or the literature. The FDA Division of Cardiovascular and Renal Products is now the current review division for tolvaptan.

2 Hyponatremia

This section's goal is to describe, at the FDA's request, the historical and literature-based evidence for understanding the unmet medical need in treating hyponatremia.

- [Section 2.1](#) describes the disease state of hyponatremia and the pathophysiological basis of how a low sodium concentration might lead to functional abnormalities, symptoms, and outcomes associated with this disease.
- [Section 2.2](#) describes important clinical data and references in the literature that support a causal basis for the link of these symptoms to serum sodium concentration. Data are also presented fulfilling the postulate that correction of serum sodium improves symptoms and outcomes, while failure to correct serum sodium leads to prolonged and/or worse negative outcomes. It also describes clinical outcomes associated with the underlying disease, eg, fluid overload due to the inappropriate antidiuresis seen in hyponatremic states (ie, CHF and cirrhosis).
- [Section 2.3](#) describes the extensive body of literature that demonstrates consistent and highly significant associations of major morbidities and mortalities with hyponatremia, which is important in understanding what benefits an effective treatment might offer.
- Finally, [Section 2.4](#), [Section 2.5](#) and [Section 2.6](#) describe the general considerations which are widely recommended in determining the appropriateness of treating hyponatremia, the utility and deficiencies of currently available treatments for hyponatremia, and the potential for vasopressin V₂ receptor antagonists to address the unmet medical need in managing hyponatremia in patients in both the inpatient and outpatient settings.

2.1 Pathophysiology, Epidemiology and Unmet Medical Need

Sodium is the major extracellular electrolyte and is responsible for maintaining extracellular osmolality and trans-membrane electrical and chemical potentials. Serum sodium concentration is maintained within a narrow range (normally 135 to 145 mEq/L) to facilitate optimal cellular hydration and neuro-muscular function. Sodium concentration is normally balanced through integrated actions of the cardiovascular, renal, endocrine, gastrointestinal, and nervous systems.

Hyponatremia is a disease characterized by a subnormal concentration of sodium in the blood (serum sodium <135 mEq/L) and is manifest by a range of neurological symptoms which, left untreated, can lead to seizure, obtundation, hypoxia, and death. Hyponatremia

is rarely seen in isolation and typically is found in association with disorders, behaviors or circumstances which promote an imbalance of fluid/sodium homeostasis. Hyponatremia occurs in 7% to 8% of elderly, ambulatory patients¹ and 15 to 20% of hospitalized patients^{1,2,3,4} making it the most common serum electrolyte abnormality that physicians encounter.

While many hyponatemic patients have transient episodes which are often self-limiting or treated by management of the underlying disorder, substantial numbers of other hyponatremic patients are difficult to manage appropriately. Often, the early symptoms and consequences of hyponatremia are unrecognized. In one recent retrospective study, over 70% of patients hospitalized with symptomatic hyponatremia had previous laboratory evidence of mild hyponatremia which typically went untreated.⁵ Even when hyponatremia is recognized, therapy is often unsuitable or ineffective.⁴ Success in treating an individual's hyponatremia requires defining its root cause, understanding how the patient's clinical state may add to the risks of ineffective or inappropriate management, and knowing the proper application and limitations of current therapies.

When salt-water balance is disrupted, physiochemical sensors (baro- and osmoreceptors) located in the heart, carotid, kidney and splanchnic vessels or the central nervous system (CNS) stimulate the brain to restore osmolar homeostasis and preserve intra- and extracellular volume. One mechanism that is particularly important in the maintenance of salt-water homeostasis involves the release of the hormone AVP.

AVP is a neuropeptide produced in supraoptic and paraventricular neurons of the hypothalamus that is released into the circulation in response to increases in plasma osmolality or decreases in blood pressure. Also called antidiuretic hormone, the activity of AVP is mediated primarily by two major vasopressin receptor subtypes: V_{1a}, found on vascular smooth muscle cells and myocardium, responsible for vasopressor actions; and V₂, found on the renal collecting ducts, responsible for free water retention or antidiuresis.⁶

When challenged or stressed, the body's homeostatic mechanisms may be compromised and inappropriate antidiuresis may result in dilutional hyponatremia (increased fluid retention with decreasing serum sodium concentrations). This can produce additional adverse clinical consequences, as illustrated by the impact of low sodium concentration on neurological symptoms and morbidity and mortality in various diseases.^{7,8,9,10,11,12,13}

Classified as euvolemic or hypervolemic, dilutional hyponatremia is typically characterized by plasma AVP concentrations which are elevated or inappropriate for a given, low serum osmolality. Depletional or hypovolemic hyponatremia is contraindicated for V₂ receptor antagonists and will not be addressed further in this package.

SIADH represents any disorder where hyponatremia is associated with euvolemia and an inappropriately high urinary sodium concentration. Although fluid restriction is universally prescribed, it is only effective when urinary sodium concentration is below that of plasma sodium concentration and where compliance can be enforced (eg, in hospitalized patients). Other drugs (demeclocycline) have been employed with varying degrees of success but carry attendant risks.

Management of all hyponatremia is difficult but is particularly challenging in hypervolemic states such as cirrhosis and heart failure.^{14,15} In these conditions, arterial underfilling, due either to decreased cardiac output (in CHF) or peripheral vasodilatation (in liver cirrhosis), causes an increase in AVP release, further worsening fluid retention.^{16,17,18,19,20,21} Typical diuretics (eg, thiazide, furosemide) often deplete sodium and other electrolytes. Patient care is further complicated by excess morbidity, health care costs and mortality potentially attributable to the concurrent hyponatremia.^{10,11,12,22,23}

In conclusion, hyponatremia is the most common serum electrolyte abnormality that physicians may encounter. The symptoms of hyponatremia can often be subtle and are usually associated with impaired mental functioning. However, if left untreated, these symptoms may progress to serious sequelae such as seizure, coma, respiratory arrest, and/or death. Treatment options for hyponatremia are currently suboptimal, especially in the outpatient setting where fluid restriction is poorly effective and patients are often uncompliant. Treatment is further complicated by underlying disorders such as CHF and cirrhosis, where typical diuretics can exacerbate the hyponatremia. The literature reports that the pathophysiology common to multiple forms of dilutional hyponatremia is inappropriate antidiuresis, typically mediated through excess AVP activity. Thus, the unmet medical need in hyponatremia today is for a therapy that is directed at this underlying pathophysiology and that allows for extended treatment of hyponatremia patients in the inpatient as well as outpatient settings. Direct and specific blockade of AVP receptor stimulation has been hypothesized as the ideal therapeutic target to address the unmet medical need in hyponatremia.²⁴

2.2 Symptoms Caused by Hyponatremia

2.2.1 Neurological Symptoms

All forms of hyponatremia, dilutional and depletion, impair normal neurological function and therefore represent a disease state. Various clinical and nonclinical experiments and case studies have documented the role of sodium in maintaining extracellular osmolality and transmembrane electrical and chemical potentials. Sudden decreases in the concentration of extracellular sodium lead to influx of water into cells, often resulting in cerebral edema, irreversible neurological damage, respiratory arrest, brainstem herniation, and death if not treated quickly and appropriately.²⁵ When hyponatremia persists, osmotic adjustments can occur over hours to days through metabolic elimination of electrolytes then osmotically-active organic compounds from the cells. While these compensatory mechanisms can prevent acute brain herniation, chronic symptoms of hyponatremia may arise from electrochemical imbalances in cations that are important for nerve conduction and/or imbalances in amino acids and neurotransmitters dependent on sodium for transport. Disturbances in these physiological processes lead to symptoms and outcomes which depend on a number of factors, including rapidity of onset, severity of hyponatremia, persistence of underlying disease, and clinical context (age, gender, baseline neurological function). In many cases, morbidity and mortality associated with hyponatremia can be shown to be prevented or reversed with appropriate and timely correction of serum sodium concentration.

One of the first reports of hyponatremia associated with fatal cerebral edema in humans (then confirmed as causal in a nonclinical experiment) was reported in 1935.²⁶ The first successful treatment of presumptive cerebral edema with 5% hypertonic saline infusion was reported by the same authors 3 years later²⁷ thereby establishing a definitive link between low serum sodium and cerebral edema. Since these early reports, numerous cases of free water retention leading to critical cerebral edema have implicated a role for inappropriate antidiuresis.^{28,29,30} Some of the last clinical experiments to induce hyponatremia using AVP and water loading were conducted early in the 20th century and confirmed the causal relationship between reduction of serum sodium concentrations and adverse neurological outcomes (electroencephalograph changes, seizures, fatalities).^{31,32,33}

Inferential evidence supporting the need to identify and aggressively treat hyponatremia is illustrated in several landmark publications:

- A series of 16 children who were over-hydrated after routine surgery either died or suffered severe debilitating symptoms such as coma, paralysis, or vegetative state as a result of delayed treatment and ensuing complications.³⁴
- A series of 53 women with chronic symptomatic hyponatremia in whom delayed or inadequate therapy (fluid restriction only) resulted in persistent and/or fatal neurological outcomes than those treated promptly with intravenous (IV) saline prior to evidence of respiratory failure.³⁵
- A series of 38 patients for whom failure to treat hyponatremia at presentation to the hospital or during hospitalization was associated with a statistically significantly higher mortality rate.³⁶

Symptoms of hyponatremia can also be broad and non-specific, and do not always correlate with degree or rapidity of sodium decline.^{37,38,39} These symptoms may include headache, nausea, fatigue, dizziness, forgetfulness, vomiting, malaise, lethargy, confusion, and mental dulling or altered consciousness, and eventually progress to seizure, coma and death. Although some of the early symptoms may not be evident or attributed to hyponatremia by treating physicians (especially in elderly populations prone to cognitive decline), they represent a progression of disease, portend an increased risk of significant symptoms, and are relevant to patients in that they negatively impact day-to-day living and overall quality of life.^{3,30,34,40,41,42,43,44}

Several landmark studies have demonstrated the relationship between these nonspecific neurological complaints and hyponatremia:

- Patients exposed to chronic salt depletion with hypotonic fluid replacement had symptoms of lassitude, fatigue, headache, muscle tremor and muscle cramping but recovered rapidly or avoided symptoms by either ingesting supplemental sodium or purposefully avoiding excess fluid ingestion.^{45,46,47}
- Healthy subjects who were purposely salt depleted to a mean serum sodium concentration of 131 mEq/L reported symptoms of nausea, altered sense of thirst, lack of appetite, taste disturbances, cramps, fatigue, mental “slowing” and social withdrawal. These symptoms reversed when subjects were returned to a normal sodium diet.^{48,49}
- Non-specific symptoms of hyponatremia (nausea, vomiting, headache, ataxia) could be produced without sodium depletion in patients with diabetes insipidus given posterior pituitary extracts (AVP) and asked to drink beyond their sense of thirst.⁵⁰

A causal association between reductions in serum sodium and cognition and a wide range of neurological signs and symptoms has also been demonstrated in psychiatric patients who are at risk of hyponatremia for a variety of reasons.^{8,51,52,53,54,55,56,57} When patients

presenting with symptoms resembling a psychiatric or an affective disorder were treated with antidepressants, there was little or no effect on these symptoms. However, when sodium concentrations were corrected in these patients, the symptoms resolved.^{56,58,59} Similarly, a prospective study of schizophrenic patients with and without hyponatremia showed that when hyponatremia was corrected to normal (mean serum sodium shift from 127 ± 1.4 to 138 ± 2.3 mEq/L), performance improved on neuropsychological tests related to orientation (shift from 3.3 to 4.6, $p < 0.05$). Also improved were attention and mental flexibility as demonstrated by the trail-making test (shift from 25.1 to 19.0 seconds, $p < 0.05$) and verbal fluency (shift from 17.3 to 24.5 words $p < 0.05$).⁵⁴

Similar findings can be found in non-psychiatric patients with hyponatremia:

- Hyponatremia was shown to be associated with attention deficits and gait disturbance.
 - Cognitive and stability deficits observed in moderate hyponatremia (average serum sodium of 128 ± 3 mEq/L) were greater than impairments seen in age-matched healthy subjects given two glasses of wine (blood alcohol concentration of 0.06 g/dL).⁶¹
 - In 122 consecutive elderly patients admitted with chronic hyponatremia (mean serum sodium of 126 ± 5 mEq/L) compared with 244 matched controls (mean serum sodium 139 ± 2 mEq/L), the odds ratio of admissions associated with falls was 9.5 (95% confidence interval [CI] 2.6-34, $p < 0.001$), and when adjusted for age, sex and other covariates, the odds ratio increased to 67 (95% CI 7.5-607, $p < 0.001$). The frequency of falls was the same regardless of the origin of the hyponatremia.⁶¹
- In a retrospective study of patients admitted to the hospital because of hyponatremia (< 135 mmol/L), 31 of 47 had mental status changes such as disorientation, headache, seizures, agitation, obtundation or focal neurological signs. Twenty-two of the 31 patients had pre-admission hyponatremia (mean sodium 128.7 mEq/L), which was untreated and believed to be “asymptomatic”, and which decreased further on admission to a mean sodium of 118.7 mmol/L (mean decrease 10.1 ± 8 mmol/L). Nine of the 31 patients had normal pre-admission sodium concentration (mean 135.5 mmol/L), but at admission mean sodium was 119.4 mmol/L in these patients (mean decrease 16.1 ± 5.5 mmol/L). Resolution of mental status deficits occurred when serum sodium returned at least to pre-admission concentration.⁵

These authors concluded that “asymptomatic” hyponatremia should not be ignored because it is associated with a high risk of worsening of hyponatremia with altered mental status.^{5,61}

Overall, these data demonstrate that many non-specific neurological symptoms such as mental slowing, fatigue, ataxia, and headache are caused by hyponatremia. These

symptoms are initially mild, but may progress to alterations in consciousness, seizure and respiratory arrest. Importantly, these symptoms can be reversed or prevented by correcting serum sodium concentrations, and failure to recognize and appropriately correct hyponatremia may have adverse consequences.

2.2.2 Symptoms of Fluid Overload

As mentioned in [Section 2.1](#), increased release of vasopressin leads to fluid retention in patients with hypervolemic hyponatremia associated with heart failure or liver cirrhosis. As a result, patients may present with signs and symptoms of vascular and interstitial congestion, eg, jugular venous distention, ascites, dyspnea, orthopnea, pulmonary edema, dependent edema, anasarca with integumentary compromise, etc. Current therapies for the management of fluid overload do not address the complicating role played by AVP in these symptoms (see [Section 2.5](#)).

2.3 Morbidity and Mortality Associated with Hyponatremia

Hyponatremia has been shown to be an independent predictor of complications and death in patients with heart disease and cirrhosis.⁶² Epidemiological and clinical studies have shown that chronic hyponatremia is associated with increased morbidity and mortality as well as increased hospital stays.^{11,63,64} In elderly patients, hyponatremia has been shown to be a predictor of in-hospital mortality after adjusting for other risk factors such as age, malignancies, or number of comorbidities.⁶⁵ Similarly, in patients with mild, asymptomatic hyponatremia of diverse origin, the mortality rate was three times higher than in normonatremic patients.^{66,67}

In CHF

Hyponatremia has been found to be a strong and consistent predictor of worsened outcomes in patients with CHF, including increased risk for morbidity and mortality:

- Among 47,647 patients enrolled in the Organized Program to Initiate Life Saving Treatment in Patients Hospitalized for Heart Failure (OPTIMIZE-HF) registry, 25.3% had hyponatremia at admission. Multivariable-adjusted Cox proportional hazards analysis showed that serum sodium on admission, when modeled linearly, predicted increased 60-day mortality: sodium (per 3-mEq/L decrease) was associated with a hazard ratio of 1.18 with a 95% CI of 1.03 to 1.36 (p=0.018).¹¹
- In the OPTIMIZE-HF program, the risk of mortality appeared to rise significantly as serum sodium decreased below 138 mEq/L. After adjusting for other prognostic factors, admission serum sodium concentration remained a significant independent predictor of in-hospital mortality. The risk of in-hospital mortality increased by 19.5% for left ventricular systolic dysfunction (LSDV) patients and by 8.6% for non-

LVSD patients for each 3 mEq/L decrease in admission serum sodium below 140 mEq/L.⁶⁸ of a phase 2 tolvaptan trial conducted in patients hospitalized with worsening heart failure, a modest increase in serum sodium (> 2 mEq/L) was associated with a lower risk of 60-day mortality. Hyponatremia was observed in 69 of 319 (21.6%) of enrolled patients. At hospital discharge, 45 of 68 (66.2%) hyponatremic patients had improvements in serum sodium concentrations (> 2 mEq/L) and a mortality rate of 11.1% at 60 days post discharge, compared with a 21.7% mortality rate in those showing no improvement in serum sodium. After covariate adjustment, change in serum sodium was a statistically significant predictor of 60-day mortality (60-day HR [hazard ratio] 0.74, p<0.0185).⁶⁹

- In the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) study, patients with persistent hyponatremia, defined as serum sodium values 134 mEq/L or lower at baseline and throughout the hospital course, had higher rates of 6-month mortality, rehospitalization, and the composite of death or rehospitalization than patients with corrected hyponatremia or normonatremia.¹²

In Liver Cirrhosis

Hyponatremia has been found to be an independent predictor of worsened outcomes in patients with liver cirrhosis:

- There is clinical and experimental evidence that in acute and chronic liver failure, low serum sodium concentration and brain changes associated with hyponatremia may predispose patients to hepatic encephalopathy.^{70,71,72,73}
- In patients with cirrhosis, the presence and severity of hyponatremia are associated with severity of ascites (high prevalence of refractory ascites, large fluid accumulation rate, frequency of large volume paracentesis), impairment of renal function, and higher rates of hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome.¹³
- In patients with cirrhotic ascites, the presence of hyponatremia was an important determinant of impaired health-related quality of life as evaluated with the Short Form-36 questionnaire. Serum sodium concentration was an independent predictor of 6 out of the 8 domains analyzed, and its value as predictive factor was independent of that of liver function, as determined by liver function tests or Child-Pugh or Model for End-stage Liver Disease (MELD) scores.⁷⁴

2.4 Criteria for the Treatment of Hyponatremia

Serum sodium is an important clinical and therapeutic target and definitively linked to important clinical outcomes; however, the decision to treat an individual patient should

be based not on an absolute serum sodium threshold but on a combination of four critical factors:

- 1) Concentration of serum sodium,
- 2) Rate and magnitude of serum sodium decline,
- 3) Presence of symptoms, and
- 4) Concomitant medical conditions (etiological and non-etiological).

As noted previously, at one end of the spectrum of risks associated with hyponatremia, the need for treatment is unquestioned because of the high risk for serious, irreversible harm. At the other end of the spectrum, hyponatremia presents with subtle neurological symptoms that still warrant treatment. If these milder symptoms are not treated, the patient's symptoms often become severe, leading to more serious outcomes.^{5,61} If the need to treat is not obvious, the physician must balance the risks of withholding effective treatment against the potential for adverse outcomes. Additionally, the need for chronic therapy should be periodically assessed with careful monitoring of patients while on treatment and during drug withdrawal. Importantly, because serum sodium concentrations just outside normal levels may predict risk for subsequent episodes of symptomatic hyponatremia,⁵ ongoing monitoring of serum sodium may be required.

To illustrate these principles, consider the following clinical scenario:

A middle-aged male patient with alcoholic cardiomyopathy and cirrhosis was recently hospitalized for a variceal bleed, hypervolemic hyponatremia and pulmonary edema whose discharge was delayed until severe fluid restriction and reduction of loop-diuretic therapy increased his serum sodium concentration to 132 mEq/L. Two weeks later, he is brought to the office for a post-hospitalization follow up with mild confusion, edema, tense ascites, serum sodium concentration of 123 mEq/L, and a gradual 5 kg weight gain. His wife states that his symptoms of encephalopathy have gradually worsened since discharge, leading to non-compliance with fluid restriction, anorexia, fatigue and malaise.

A decision for treatment of this patient is made based on 1) the absolute serum sodium concentration at presentation (123 mEq/L), 2) the fact that the decline from 132 mEq/L to 123 mEq/L occurred over a short time period, 3) the gradual onset of moderate, non-life-threatening symptoms which 4) complicated his compliance with fluid restriction and exacerbated his fluid overload and hyponatremia.

A brief review (below) of alternatives for managing this patient's condition suggest that currently available therapeutic options are either not appropriate or carry significant risk.

2.5 Current Therapy for Hyponatremia

Current options for the treatment of hyponatremia include the elimination of the underlying cause, fluid restriction, saline infusion/replacement, and drug therapy. Limitations of each of these are discussed below.

Elimination of underlying cause of hyponatremia (medications or disease)

Eliminating or avoiding the cause of hyponatremia, if known, is the obvious first step in treatment (eg, hypothyroidism, hypoadrenalism, polydipsia, iatrogenic fluid supplementation). If caused by medications prescribed for the treatment of a serious underlying condition (eg, antineoplastics, diuretics, anticonvulsants or antipsychotics), it may be impossible to remove or change them safely. Diuretics, commonly used to treat symptoms of fluid overload in CHF and cirrhosis, have major limitations, including the potential exacerbation of hyponatremia and its symptoms (eg, encephalopathy and fatigue).^{75,76,77,78,79,80,81}

Fluid restriction

Typical fluid intake is 2000 - 3000 mL/d. Fluid restriction of no more than 500-700 mL/d in food and drink, or 500 mL less than daily urine output, is necessary to increase serum sodium concentrations in most patients with SIADH.^{52 82} Most practitioners prescribe fluid restriction in the range of 1000-1500 mL/d without regard to the actual diluting ability of the kidney. In some cases of paraneoplastic SIADH, AVP concentrations may increase urine sodium concentration to levels beyond that of the plasma, rendering any level of fluid restriction ineffective.⁸³ Furthermore, even when prescribed, most patients are noncompliant because the thirst drive is too strong, and any level of restriction is unpleasant and therefore difficult to enforce on an outpatient basis.

Hypertonic saline

Administration of hypertonic saline, while life-saving in severely symptomatic cases, may complicate fluid overload.⁵³ Use of hypertonic saline is difficult, dangerous, and for these reasons rarely employed unless the patient's circumstances are dire. Equations used to estimate appropriate volumes and rates of administration are sometimes inaccurate and may lead to inadequate correction in up to 5% and excessively-rapid correction in up to 11% of patients.^{4,35,36,84,85}

Prescription medications

Rarely used today, demeclocycline has an inherent renal toxicity which can be turned to an advantage with variable success in treating certain SIADH patients.⁸⁶ It can produce a form of nephrogenic diabetes insipidus (nDI) in some patients at very high doses. However, its slow onset and offset of action and its potential inhibition of its own renal elimination present a real and significant danger for severe and permanent renal failure and make it unacceptable in many clinical settings. Lithium, which also produces nDI, is avoided for having a similar narrow therapeutic window and toxicity.

Urea is used in some European countries to promote osmotically-driven water excretion. It has been used with some success in patients with SIADH and cirrhosis; however is distasteful, unavailable in the US, and may worsen the condition of patients having azotemia.

Conivaptan, a mixed V_{1a}/V_2 receptor antagonist, is approved in the US for up to 4-day IV, in-hospital use but has limited safety and efficacy data, a high rate of infusion site reactions, and significant drug-drug interactions.⁸⁷ Mozavaptan, a V_2 receptor-specific antagonist is approved for prescription use in Japan but is limited to an orphan indication for the treatment of SIADH due to an ectopic antidiuretic hormone-producing tumor (limited to cases with insufficient clinical response to conventional treatments).

Except for mozavaptan, which is only available in Japan, each of the above therapies is suboptimal because of variable efficacy, slow response, poor compliance, and/or intolerable or dangerous side effects. In our illustrative case study noted above:

- The cause of hyponatremia includes a form of inappropriate antidiuresis likely caused by heart and liver failure. In this patient's case, heart or liver transplantation is unavailable at the current time. His condition is further complicated by the need for natriuresis and aquaresis, but there is a risk of worsening encephalopathy and other symptoms if loop or thiazide diuretics are employed.
- Fluid restriction is only useful if enforced while the patient can be hospitalized. In the non-compliant or disoriented patient, fluid restriction often fails in an outpatient setting.
- Hypertonic saline is not indicated in this patient given the non-life-threatening nature of his current symptoms. Infusion of any extra saline is likely to worsen his hypervolemia.
- Drugs available to produce a relative aquaresis are, in this patient's case, limited to temporary (4-day) in-hospital use (conivaptan), or those with significant toxicity in patients prone to renal insufficiency.

This case is a clear example of the urgent need for a safe and effective therapy targeting the common mechanism of dilutional hyponatremia (inappropriate antidiuresis via overactivity of AVP).

In conclusion, there are no pharmacotherapies currently approved in the US for the treatment of hyponatremia in the outpatient setting. Therapies like hypertonic saline and conivaptan, while effective in treating acute hyponatremia in the hospital, are not appropriate for continued therapy. Treatment with tolvaptan, an oral V₂ receptor antagonist, represents the only potentially reasonable option for such patients. This presents a strong case of the need for an oral therapy that can be used on an inpatient as well as outpatient basis.

2.6 Role of V₂ Receptor Antagonists in the Treatment of Hyponatremia

Literature summarized in this document supports the causal role of sodium in many disease processes, as confirmed by well-understood chemical mechanisms, well-established epidemiological data, and evidence of reversibility of outcomes with normalization of serum sodium. Moreover, the literature supports that failure to effectively treat certain forms of severe, acute hyponatremia can be lethal. There are, however, very few data available in the literature from controlled studies evaluating the clinical outcomes associated with the correction of hyponatremia, especially if the hyponatremia is long-standing and not associated with emergent neurological symptoms. [Section 3](#) of this document will summarize data from the tolvaptan program that demonstrates that mental functioning and clinical outcomes improve with correction in serum sodium regardless of hyponatremia severity. These data provide the most current, well-controlled evidence that correction of hyponatremia improves patient symptoms and health-related outcomes.

Taken together with the literature data, the data presented in [Section 3](#) of this document will support the overall medical utility of using a vasopressin antagonist to treat hyponatremia. Knowledge of an individual patient's risk for hyponatremia is the critical determinant in the decision to treat an individual patient.

Given the high prevalence of hyponatremia among patients with SIADH (2.2 % of hospitalized patients),^{88,89} acute decompensated heart failure (range of 8 to 27%),^{11,68}^{90,91} and patients with cirrhotic ascites (up to 30%),⁹² a safe, effective therapy to treat patients with chronic hyponatremia is urgently needed.

Non-peptide V₂ receptor antagonists offer the first opportunity for oral management of a longstanding unmet medical need. Tolvaptan represents the first orally-administered, receptor-selective V₂ receptor antagonists in the US that would meet this specific need.

Because they address the basic underlying pathophysiological mechanism associated with the disease processes, AVP V₂ receptor antagonists, such as tolvaptan, are ideal treatments for conditions associated with inappropriate antidiuresis such as SIADH, cirrhosis, and heart failure. Moreover, given the limitations of fluid restriction as currently implemented, treatment with a vaptan eliminates the need for fluid restriction and therefore presents a clear advantage over this therapy. V₂ receptor antagonists have favorable safety profiles, and are effective, convenient and well-tolerated. Importantly they address a clear unmet medical need for long-term use. Tolvaptan represent the first orally-administered agent of this class to be considered for approval for this indication by the US FDA.

3 Summary of Studies and Efficacy Outcomes

In the tolvaptan development program, the common efficacy variable of interest in the treatment of hyponatremia is serum sodium, which is the primary extracellular electrolyte to which the osmoreceptors respond and which determines the osmolality and volume of the extracellular compartment. There is medical consensus that serum sodium is the key variable to diagnose various states of hypervolemic and euvolemic hyponatremia (including SIADH, cirrhosis, and CHF), to evaluate the severity of hyponatremia, to determine interventional treatment, and to monitor corrective treatment. Thus, serum sodium is a direct measure of the condition of hyponatremia and therefore an appropriate and adequate study endpoint.

Additionally, an attempt was made to investigate the clinical benefits of treating hyponatremia beyond increase in serum sodium concentrations. The effect of the change of serum sodium on patient-reported outcomes of health status was investigated, with special focus on mental functioning. Hyponatremia is associated with a broad range of neurological symptoms of varying severity, which, logically, would evidence an improvement following improvement in serum sodium concentration. The Short Form-12 (SF-12) Health Survey is a generic, validated instrument and suitable general outcome measurement that was used to evaluate the clinical manifestations of hyponatremia. These measures were supported by neurological examination findings and results of the Hyponatremia Disease-specific Survey (HDS) and Kansas City Cardiomyopathy

Questionnaire (KCCQ). In addition, patients were assessed for other clinical benefits that might be specifically associated with their underlying disease. For example, studies in patients with CHF assessed the signs and symptoms of the disease (eg, body weight, dyspnea, edema, orthopnea, JVD, and fatigue), as well as the combined cardiovascular (CV) mortality and morbidity.

3.1 Description of Tolvaptan Development Program and Patient Demographics

The efficacy of tolvaptan in the treatment of hyponatremia was evaluated in two similarly-designed placebo-controlled phase 3 hyponatremia studies (156-02-235, 156-03-238), one ongoing phase 3 open-label extension hyponatremia study (156-03-244), and two phase 2 hyponatremia studies (156-96-203, 156-97-204). The efficacy of tolvaptan in hyponatremia was also evaluated in one phase 3 (156-03-236) and five phase 2 (156-97-251, 156-97-252, 156-98-213, 156-00-220, 156-01-232) CHF studies as a secondary objective in the subset of patients with heart failure who were also found to have hyponatremia at baseline. The primary objectives and main design features of the tolvaptan studies are summarized in [Table 3.1-1](#). While the phase 2 study results were largely supportive, the sample sizes were relatively small (≤ 50 patients), so this briefing document will focus almost exclusively on the phase 3 controlled and uncontrolled data from the tolvaptan program.

Table 3.1-1 Clinical Studies of Tolvaptan in Hyponatremia Patients					
Protocol Number (Study Phase)	Study Objective	Design	Number of Patients ^a		
			PBO	TLV	Total
Treatment of hyponatremia					
156-02-235 (phase 3)	Treatment of hyponatremia	Randomized, DB, PC, parallel arms; tolvaptan starting dose 15 mg QD, titrated to effect among 15, 30, or 60 mg QD for 30 days	103	102	205
156-03-238 (phase 3)			120	123	243
156-03-244 (phase 3)-ongoing study	Safety and maintenance of efficacy in hyponatremia	OL extension up to 214 weeks for patients completing 156-02-235 or 156-03-238; tolvaptan starting dose 15 mg QD, titrated to effect among 15, 30, or 60 mg QD	-	111	111
156-96-203 (phase 2)	Treatment of hyponatremia secondary to liver disease	Randomized (2:1), DB, PC, sequential cohort, ascending doses; tolvaptan 5, 10, 15, 30, or 60 mg QD for 13 days	15	30	45
156-97-204 (phase 2)	Efficacy, safety, and dose characteristics of titrated doses	Randomized (2:1), OL, active-controlled (placebo with fluid restriction); tolvaptan starting dose 10 mg QD, titrated to effect among 15, 30, 45, and 60 mg up to 26 days	11	17	28
Treatment of CHF in subgroup of patients having hyponatremia (serum sodium < 135 mEq/L) at baseline					
156-03-236 (phase 3)	Long-term safety and efficacy in patients with worsening CHF; morbidity/mortality study	Randomized, DB, PC, parallel arms; tolvaptan 30 mg QD for minimum of 60 days up to 32 months	232	243	475
156-98-213 (phase 2)	Treatment of worsening CHF	Randomized, DB, PC, parallel arms; tolvaptan 30, 60, 90 mg QD for up to 61 days	11	39	50
156-97-251 (phase 2)	Treatment of stable CHF	Randomized (2:1), DB, PC, sequential cohort, ascending doses; tolvaptan 10, 15, 30, 60, 90, and 120 mg QD for 13 days	7	10	17
156-97-252 (phase 2)		Randomized, DB, PC, parallel arms; tolvaptan 30, 45, 60 mg QD for 25 days	12	21	33
156-00-220 (phase 2)		Randomized, DB, PC, parallel arms; tolvaptan 15, 30, 60 mg QD for up to 169 days	5	16	21
156-01-232 (phase 2)		Randomized, DB, PC, parallel arms; tolvaptan 30 mg QD for 54 weeks	3	3	6
Total patients with hyponatremia of any origin (SIADH/other, CHF, cirrhosis)			519	659 ^b	1178

DB = double-blind; OL = open-label; PBO = placebo; PC = placebo-controlled; TLV = tolvaptan.

^aNs shown for CHF studies represent the hyponatremia subgroup (ie, baseline serum sodium < 135 mEq/L).

^bTotal represents unique patient exposures (ie, excludes 56 patients from 156-03-244 who received tolvaptan in more than one trial).

With the exception of the open-label extension phase 3 hyponatremia study (156-03-244) and an open-label, active-controlled (fluid restriction with placebo; 156-97-204) phase 2 hyponatremia study, all of the tolvaptan studies were of a randomized, double-blind, placebo-controlled design. In the phase 3 hyponatremia studies and as agreed to by the FDA Division of Metabolic and Endocrine Products in a Special Protocol Assessment, randomization was stratified based on patients' baseline serum sodium concentration (< 130 mEq/L, and ≥ 130 mEq/L and < 135 mEq/L) and underlying disease (CHF, non-CHF), with enrollment goals of having 50% of patients with baseline serum sodium concentration < 130 mEq/L and no single hyponatremia etiology (eg, SIADH/other, cirrhosis, CHF) representing more than 50% of the study population. (Hereinafter, for simplicity, hyponatremia defined by serum sodium ≥ 130 mEq/L and < 135 mEq/L will be referred to as 130-134 mEq/L).

The hyponatremia studies evaluated tolvaptan doses between 5 and 60 mg in patients having baseline serum sodium concentrations < 135 mEq/L. The patients in the phase 3 studies received a starting dose of 15 mg QD, with a dose titration scheme to increase to 30 or 60 mg QD to achieve a gradual correction of serum sodium concentrations over the first few days or weeks of therapy, as well as to maintain effect by individualized dosing based on tolerability and serum sodium response. The average tolvaptan dose used in the phase 3 hyponatremia studies was 36.9 mg QD. If the correction of serum sodium was too rapid (protocol defined as either > 8 mEq/L in the first 8 hours or > 12 mEq/L over 24 hours) or if the serum sodium concentration exceeded the upper limit of the normal range of 145 mEq/L at any time, the investigator could adjust fluid intake or medication administration. Patients were allowed to continue their existing medications/therapies during the treatment period, as well as initiate fluid restriction if warranted. Use of hypertonic saline infusion or any other therapy for hyponatremia (eg, demeclocycline) was allowed if indicated, but the patient would be withdrawn from the study.

The pivotal phase 3 hyponatremia studies were short-term (30-day) studies. The ongoing open-label extension phase 3 hyponatremia study is a long-term study of up to 214 weeks. As of an October 2007 data cutoff, patients had been exposed over 106+ weeks in this study.

Of the supportive heart failure studies, four were conducted in patients with stable heart failure and two studies were performed in patients hospitalized for the treatment of worsening heart failure. Fixed doses of 10 to 120 mg QD were used in all heart failure studies, with the 30 mg dose being common to all and the most broadly investigated. Treatment duration ranged from 13 days to 32 months.

The primary efficacy variable in the pivotal tolvaptan hyponatremia studies was serum sodium concentration, with co-primary endpoints of average daily area under the concentration-time curve (AUC) of change from baseline in serum sodium concentration up to Day 4 and up to Day 30. Mean change from baseline in serum sodium concentration at Day 4 and Day 30 were secondary endpoints. Analyses were additionally stratified by prespecified patient subgroups, including underlying illness (SIADH, CHF, and cirrhosis) and severity of hyponatremia at baseline (serum sodium < 130 mEq/L, or 130-134 mEq/L). Secondary and exploratory efficacy variables included body weight, urine output, fluid intake, need for fluid restriction and saline infusion, SF-12 Health Survey, Hyponatremia Disease Survey (exploratory; performed in only 156-03-238), and neurological examination (exploratory).

In total, 424 patients were included in the Randomized Dataset of the phase 3 hyponatremia studies, which, as prespecified in the respective study statistical analysis plans, excludes data from 3 sites (Sites 004 and 006 in 156-02-235 [total patient n = 15] and Site 237 in 156-03-238 [patient n = 9]) because of concerns about data reliability stemming from site audits conducted by the sponsor. Approximately half the study patients (217/424; 51.2%) had baseline hyponatremia <130 mEq/L and the distribution of patients by etiology was 27.6% (117/424) cirrhosis, 30.2% (128/424) CHF, and 42.2% (179/424) SIADH/other. The mean age was 62 years (range 18 to 100 years) and the majority of patients were male (251/424, 59.2%) and Caucasian (356/424, 84.0%) (Table 3.1-2).

Table 3.1-2 Demographic and Baseline Characteristics in the Placebo-controlled Phase 3 Hyponatremia Studies; Randomized Patient Dataset				
Parameter	Characteristic	Pooled Patient Population		
		Tolvaptan (N = 216)	Placebo (N = 208)	Total (N = 424)
Age (years)	N	216	208	424
	Mean (SD)	61 (15)	62 (14)	62 (15)
	Range	18 - 92	28 - 100	18 - 100
	< 65 years, n (%)	131 (60.6)	117 (56.3)	248 (58.5)
	≥ 65 years, n (%)	85 (39.4)	91 (43.8)	176 (41.5)
Gender	Male, n (%)	124 (57.4)	127 (61.1)	251 (59.2)
	Female, n (%)	92 (42.6)	81 (38.9)	173 (40.8)

Table 3.1-2 Demographic and Baseline Characteristics in the Placebo-controlled Phase 3 Hyponatremia Studies; Randomized Patient Dataset				
Parameter	Characteristic	Pooled Patient Population		
		Tolvaptan (N = 216)	Placebo (N = 208)	Total (N = 424)
Race	Caucasian, n (%)	181 (83.8)	175 (84.1)	356 (84.0)
	Hispanic, n (%)	16 (7.4)	15 (7.2)	31 (7.3)
	Black, n (%)	13 (6.0)	15 (7.2)	28 (6.6)
	Asian, n (%)	3 (1.4)	1 (0.5)	4 (0.9)
	Other, n (%)	3 (1.4)	2 (1.0)	5 (1.2)
Baseline Serum Sodium ^a	< 130 mEq/L	110 (50.9)	107 (51.4)	217 (51.2)
	130-134 mEq/L	106 (49.1)	101 (48.6)	207 (48.8)
Hyponatremia Origin ^b	Cirrhosis, n (%)	63 (29.2)	54 (26.0)	117 (27.6)
	CHF, n (%)	66 (30.6)	62 (29.8)	128 (30.2)
	SIADH/other, n (%)	87 (40.3)	92 (44.2)	179 (42.2)
Volume Status	Euvolemic, n (%)	119 (55.1)	119 (57.2)	238 (56.1)
	Hypervolemic, n (%)	95 (44.0)	87 (41.8)	182 (42.9)
Use of Diuretics	Yes, n (%)	144 (66.7)	126 (60.6)	270 (63.7)
	No, n (%)	72 (33.3)	82 (39.4)	154 (36.3)

Includes studies 156-02-235 and 156-03-238. SD = standard deviation.

Randomized Patient Dataset comprises data from all patients (excluding patients from Sites 004, 006, and 237) who were randomized to a treatment group.

^aPatients with missing baseline serum sodium results were grouped based on their randomization strata (< 130 or 130-134 mEq/L).

^bPatients with missing values in the Hyponatremia History Panel and randomized to the CHF stratum were considered CHF origin; patients randomized to the non-CHF stratum were considered as SIADH/other origin. Cirrhosis includes patients with cirrhosis hyponatremia origin; CHF includes patients with CHF but not cirrhosis hyponatremia origin; and SIADH/other includes patients with SIADH or other hyponatremia origin but not cirrhosis or CHF.

In the long-term phase 3 study in patients with worsening heart failure (156-03-236), approximately 12% of enrolled study patients had hyponatremia at baseline as defined by serum sodium < 135 mEq/L: 243 (12.1%) patients in the tolvaptan 30 mg group and 232 (11.5%) patients in the placebo group. Demographics for this hyponatremic subgroup are provided in [Table 3.1-3](#).

Table 3.1-3 Demographic and Baseline Characteristics in the Phase 3 Study of Tolvaptan in Worsening Heart Failure; All Patients With Baseline Serum Sodium Concentration < 135 mEq/L				
Parameter	Characteristic	Tolvaptan 30 mg (N = 243)	Placebo (N = 232)	Total (N = 475)
Age (years)	Mean (SD)	64 (14)	64 (14)	64 (14)
	Range	22 - 89	18 - 93	18 - 93
	< 65 years, n (%)	116 (47.7)	109 (47.0)	225 (47.4)
	≥ 65 years, n (%)	127 (52.3)	123 (53.0)	250 (52.6)
Gender	Male, n (%)	208 (85.6)	180 (77.6)	388 (81.7)
	Female, n (%)	35 (14.4)	52 (22.4)	87 (18.3)
Race	Caucasian, n (%)	213 (87.7)	199 (85.8)	412 (86.7)
	Black, n (%)	14 (5.8)	9 (3.9)	23 (4.8)
	Hispanic, n (%)	9 (3.7)	18 (7.8)	27 (5.7)
	Asian, n (%)	0 (0.0)	2 (0.9)	2 (0.4)
	Other, n (%)	7 (2.9)	4 (1.7)	11 (2.3)
Baseline Serum Sodium	< 130 mEq/L, n (%)	38 (15.6)	54 (23.3)	92 (19.4)
	130-134 mEq/L, n (%)	205 (84.4)	178 (76.7)	383 (80.6)

Study 156-03-236. SD = standard deviation.

3.2 Correction of Serum Sodium in Hyponatremia

The data summarized in this section demonstrate the consistently statistically significant effects of tolvaptan on correction of serum sodium concentration in patients with dilutional hyponatremia regardless of the etiology of their underlying disorder (ie, hyponatremia associated with SIADH, CHF, or cirrhosis) and regardless of the severity of the hyponatremia at baseline (ie, sodium < 135 mEq/L, sodium < 130 mEq/L, or sodium between 130 and 134 mEq/L). The differences between the placebo and tolvaptan groups are statistically significant for all analyses. The key results can be summarized as follows:

- Significantly larger average daily AUC of mean change from baseline in serum sodium concentrations were observed in tolvaptan patients as compared with placebo patients.
- There were significantly larger mean increases in serum sodium concentrations in tolvaptan patients compared with placebo patients, which represents a clinically meaningful difference between the two groups.
- A sustained treatment effect was observed in long-term studies, including an open-label study of at least 2 years' duration.

- After discontinuation of tolvaptan, average serum sodium concentrations declined to below 135 mEq/L; following re-introduction of tolvaptan therapy, mean serum sodium concentrations returned to the normal range (≥ 135 mEq/L).
- Prevention of worsening hyponatremia was observed in those patients who were at increased risk for hyponatremia and even in those patients who were normonatremic at baseline.

3.2.1 Primary Endpoint: Average Daily AUC of Mean Change from Baseline

In the two phase 3 hyponatremia studies of tolvaptan, the prespecified co-primary efficacy endpoints were average daily AUC of mean change from baseline in serum sodium up to Day 4 and up to Day 30. The results of the tolvaptan program were remarkably consistent across the 2 pivotal studies, showing highly statistically significant increases in serum sodium concentrations for tolvaptan compared to placebo. In addition, the statistically significant findings were observed for patients with each of the three underlying diseases of SIADH, CHF, and cirrhosis.

In the AUC analyses, both of the pre-specified co-primary efficacy endpoints were significant ($p < 0.0001$) in the individual phase 3 studies (156-02-235, 156-03-238) and in the pooled analysis ([Table 3.2.1-1](#)). As shown in the pooled analysis, the average daily AUC of mean change from baseline in serum sodium concentration was 4.0 mEq/L for tolvaptan and 0.4 mEq/L for placebo (an estimated treatment effect of 3.7 mEq/L) up to Day 4 ($p < 0.0001$) and was 6.2 mEq/L for tolvaptan and 1.8 mEq/L for placebo (an estimated treatment effect of 4.6 mEq/L) up to Day 30 ($p < 0.0001$). Statistically significant results were also observed for these analyses when previously excluded data (from Sites 004, 006, and 237) were included.

Table 3.2.1-1 Average Daily AUC up to Day 4 and Day 30 of Change From Baseline in Serum Sodium Concentration (mEq/L) in the Placebo-controlled Phase 3 Hyponatremia Studies of Tolvaptan; Restricted Intent-to-treat Dataset

Visit	Treatment Group	N	Mean (SD)	Estimated Treatment Effect	P-value ^a
156-03-235					
Baseline Serum Sodium (mEq/L) ^b	Tolvaptan	95	128.54 (4.51)	-	-
	Placebo	89	128.75 (4.07)		
AUC up to Day 4	Tolvaptan	95	3.62 (2.68)	3.41	< 0.0001
	Placebo	89	0.25 (2.08)		
AUC up to Day 30	Tolvaptan	95	6.22 (4.10)	4.57	< 0.0001
	Placebo	89	1.66 (3.59)		
156-03-238					
Baseline Serum Sodium (mEq/L) ^b	Tolvaptan	118	129.36 (3.47)	-	-
	Placebo	114	128.87 (4.45)		
AUC up to Day 4	Tolvaptan	118	4.33 (2.87)	4.04	< 0.0001
	Placebo	114	0.42 (2.56)		
AUC up to Day 30	Tolvaptan	118	6.20 (3.92)	4.54	< 0.0001
	Placebo	114	1.84 (3.83)		
Pooled					
Baseline Serum Sodium (mEq/L) ^b	Tolvaptan	213	128.99 (3.98)	-	-
	Placebo	203	128.82 (4.28)		
AUC up to Day 4	Tolvaptan	213	4.01 (2.80)	3.73	< 0.0001
	Placebo	203	0.35 (2.36)		
AUC up to Day 30	Tolvaptan	213	6.21 (3.99)	4.57	< 0.0001
	Placebo	203	1.77 (3.72)		

Restricted intent-to-treat (ITT) Dataset comprises data from all randomized patients (excluding patients from Sites 004, 006, and 237) treated with study medication and having a baseline serum sodium observation and at least one postbaseline serum sodium observation within the study treatment period or no more than one day after the day of last dose. SD = standard deviation.

^aP-values were derived from an analysis of covariance (ANCOVA) model with factors of treatment, baseline hyponatremia origin and severity, and baseline serum sodium concentration as covariate. An additional factor of study was added to the ANCOVA model for the pooled data.

^bActual serum sodium concentration at baseline.

As shown in [Figure 3.2.1-1](#) (a prespecified subgroup analysis), AUC results up to Day 4 and up to Day 30 were similarly highly significant ($p < 0.0001$ in all analyses) in the pooled (from the two studies) patient subgroups stratified by etiology (SIADH, cirrhosis, CHF). The largest effect on serum sodium was observed for the SIADH patients, which is consistent with the underlying hormonal condition associated with their disorder. For patients with SIADH and CHF, the magnitude of response based on estimated treatment

effect (ie, difference between tolvaptan and placebo groups) was greater at Day 30 than Day 4, whereas, for cirrhosis patients, the response was greater at Day 4 than Day 30.

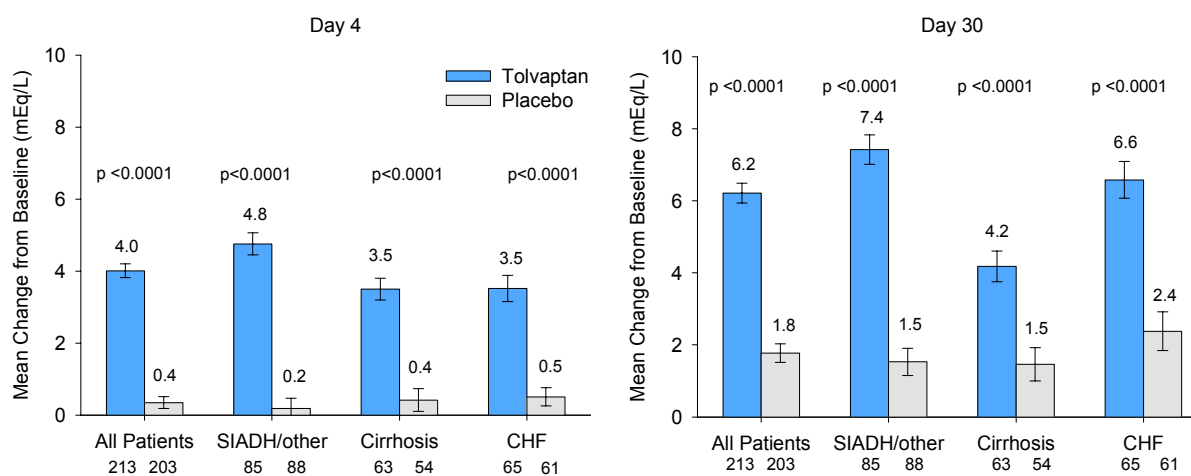


Figure 3.2.1-1 Average Daily AUC up to Day 4 and Day 30 of Change From Baseline in Serum Sodium Concentration (mEq/L) by Hyponatremia Etiology in the Pooled Placebo-controlled Phase 3 Hyponatremia Studies of Tolvaptan

Restricted ITT dataset.

3.2.2 Secondary Endpoints

3.2.2.1 Mean Change From Baseline in Serum Sodium

The mean change from baseline in serum sodium concentration is shown in [Figure 3.2.2.1-1](#) for the pooled analysis of patients enrolled in the placebo-controlled phase 3 hyponatremia studies for tolvaptan at the pre-specified endpoints of Day 4 and Day 30. Of patients with serum sodium < 135 mEq/L, tolvaptan patients showed significantly greater mean increases from baseline at both time points relative to patients receiving placebo. Similarly, analyses stratified by underlying disease showed significantly greater increases from baseline for all three etiologies (ie, SIADH, CHF, and cirrhosis). The greatest effect (based on estimated treatment effects) was observed in patients with SIADH, followed by patients with CHF and then patients with cirrhosis.

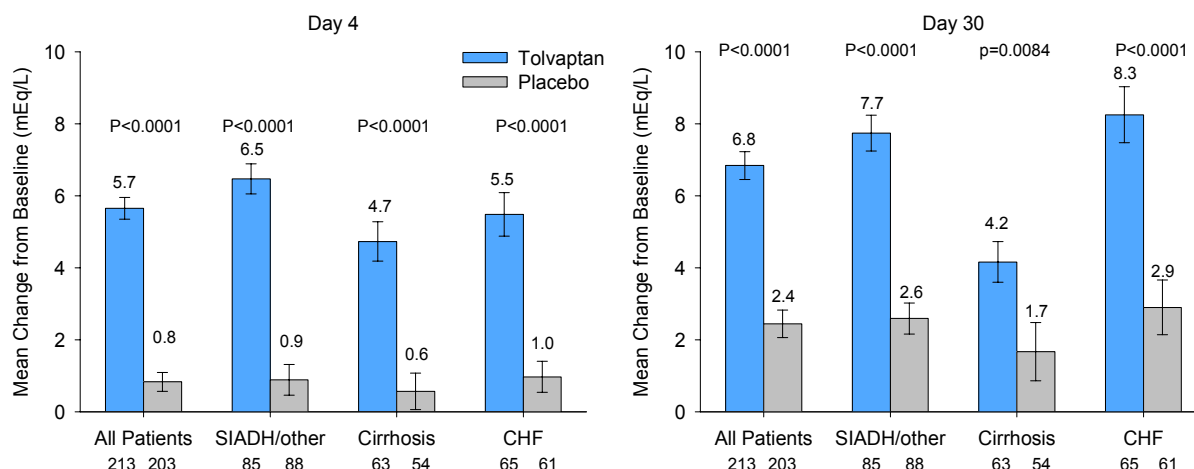


Figure 3.2.2.1-1 Mean Change from Baseline in Serum Sodium Concentration (mEq/L) at Day 4 and Day 30 by Etiology in the Pooled Placebo-controlled Phase 3 Hyponatremia Studies of Tolvaptan

ITT Dataset, LOCF analysis.

Baseline serum sodium concentrations: All patients - Placebo=128.8 mEq/L; Tolvaptan=129.0 mEq/L.

SIADH - Placebo=129.0 mEq/L; Tolvaptan=129.5 mEq/L.

Cirrhosis - Placebo=128.6 mEq/L; Tolvaptan=128.8 mEq/L.

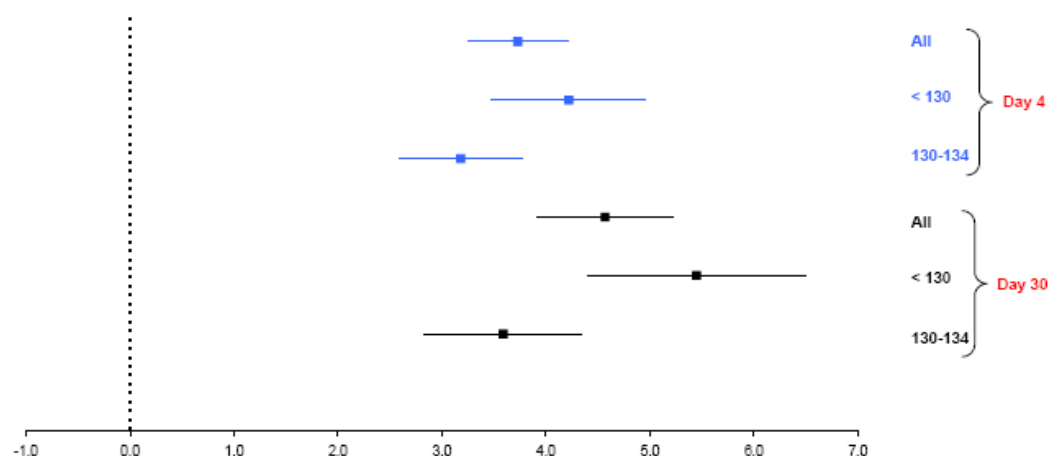
CHF - Placebo=128.8 mEq/L; Tolvaptan=128.5 mEq/L.

3.2.2.2 Stratification by Baseline Severity of Hyponatremia

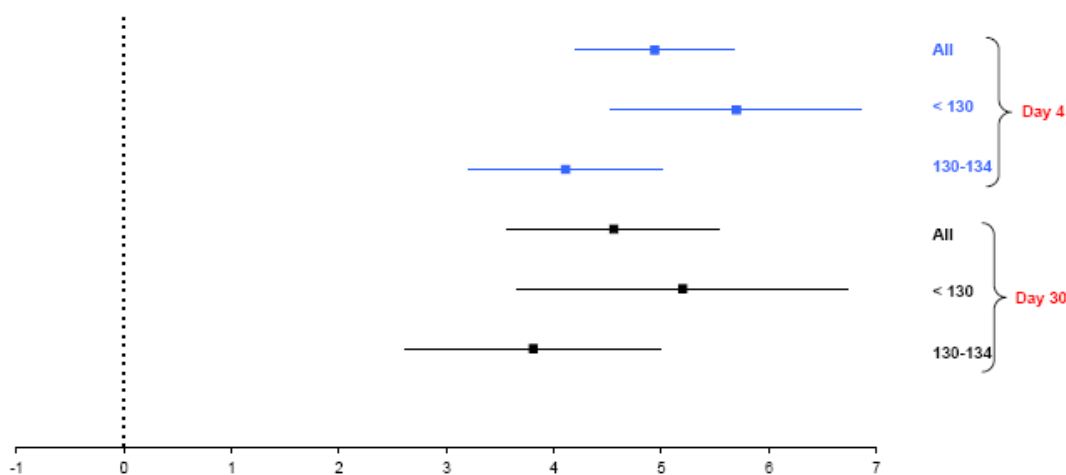
Throughout the tolvaptan clinical development program, Otsuka sought and received guidance from the FDA Division of Metabolic and Endocrine Products. The feedback from FDA had consistently advised the sponsor that while an all-patient dataset (ie, serum sodium < 135 mEq/L) could be used as the primary analysis for change in serum sodium concentration, the focus of the NDA review would be on those patients with baseline serum sodium concentration of < 130 mEq/L, where the need for treatment was well established. Conversely, FDA clearly indicated that the need for treatment of patients with serum sodium concentration of 130-134 mEq/L would be assessed during the review process. Thus, an important analysis for understanding the effects of tolvaptan on serum sodium concentrations is the stratification by baseline severity of hyponatremia.

When the data for tolvaptan are stratified by baseline severity, statistically significant differences between tolvaptan and placebo are observed for AUC and mean change from baseline for both patients with baseline serum sodium concentrations < 130 mEq/L and those with baseline serum sodium concentrations of 130-134 mEq/L. The data are shown below in Figure 3.2.2.2-1. The effects for each of the three endpoints are consistently in

favor of tolvaptan. These data clearly indicate the benefit of tolvaptan in the improvement of serum sodium concentrations in patients with baseline concentrations < 130 mEq/L. The data also show very similar effects in patients with hyponatremia 130-134 mEq/L at baseline. The effect size was smaller in the patients with baseline serum sodium concentrations of 130-134 mEq/L because their baseline values were higher and therefore required smaller increases to achieve normalization.



a) Average daily AUC of change from baseline to endpoint



b) Mean change from baseline

Figure 3.2.2.2-1 Analyses of Serum Sodium Response by Hyponatremia Severity (< 130 mEq/L, 130-134 mEq/L) in the Pooled Placebo-controlled Phase 3 Hyponatremia Studies of Tolvaptan

3.2.2.3 Time to First Normalization in Serum Sodium

An analysis was performed of the time to first normalization in serum sodium concentration (ie, > 135 mEq/L) in the placebo-controlled phase 3 hyponatremia studies. In this analysis, the relative risk was the factor by which tolvaptan subjects were more likely than placebo subjects to have normalized serum sodium concentrations at any point in time during the trial. A relative risk > 1 favored tolvaptan. The relative risk favored tolvaptan over placebo for the individual trials and the pooled analysis and the differences between groups were consistently statistically significant. In the pooled analysis, the relative risk was 3.203 ($p < 0.0001$), indicating that tolvaptan subjects were 3.2 times more likely than placebo subjects to have normalized serum sodium concentrations at any point during the trial.

3.2.2.4 Categorical Change in Serum Sodium Concentration

[Table 3.2.2.4-1](#) presents the categorical changes in serum sodium concentrations at selected time points for the overall hyponatremia population in the placebo-controlled phase 3 hyponatremia studies, as well as in the subgroups by baseline serum sodium concentration < 130 mEq/L and 130-134 mEq/L.

In the overall population, more patients in the tolvaptan group than in the placebo group achieved normalization of serum sodium at Day 4 and Day 30. Also, fewer tolvaptan patients were categorized as “severe” (< 130 mEq/L) at Day 4 and Day 30. The overall categorical analysis demonstrated tolvaptan was superior to placebo in achieving better serum sodium concentrations ($p < 0.0001$). Within 7 days following discontinuation of study medication (Day 37), there were no differences in the distribution of tolvaptan or placebo patients by serum sodium category. Analysis of the patients stratified by baseline severity (ie, < 130 mEq/L and 130-134 mEq/L) were consistent with the overall population ([Table 3.2.2.4-1](#)).

Table 3.2.2.4-1 Analysis of Categorical Change in Serum Sodium Level at Selected Time Points for the Overall Hyponatremia Population and by Baseline Hyponatremia Severity in the Pooled Placebo-controlled Phase 3 Hyponatremia Studies; Intent-to-treat Dataset (OC)							
Visit	Treatment Group	Normalized (> 135 mEq/L) n (%)	Remained or Became Mild (130-134 mEq/L) n (%)	Remained or Became Severe (< 130 mEq/L) n (%)	Chance for TLV to be Better than Placebo ^a	95% CI ^a	P-value ^b
Total Hyponatremia Population (Serum Sodium < 135 mEq/L at Baseline)							
Day 4	Tolvaptan	100 (48.5)	83 (40.3)	23 (11.2)	0.7499	0.697 - 0.803	< 0.0001
	Placebo	21 (11.2)	87 (46.3)	80 (42.6)			
Day 30	Tolvaptan	100 (59.9)	53 (31.7)	14 (8.4)	0.6940	0.636 - 0.752	< 0.0001
	Placebo	39 (26.5)	68 (46.3)	40 (27.2)			
Day 37 ^c	Tolvaptan	45 (26.6)	81 (47.9)	43 (25.4)	0.5044	0.446 - 0.563	0.8758
	Placebo	40 (26.5)	71 (47.0)	40 (26.5)			
Patients Having Serum Sodium < 130 mEq/L at Baseline							
Day 4	Tolvaptan	37 (34.9)	46 (43.4)	23 (21.7)	0.7797	0.706 - 0.854	< 0.0001
	Placebo	4 (4.2)	26 (27.1)	66 (68.8)			
Day 30	Tolvaptan	46 (55.4)	24 (28.9)	13 (15.7)	0.7184	0.634 - 0.803	< 0.0001
	Placebo	13 (18.3)	28 (39.4)	30 (42.3)			
Day 37 ^c	Tolvaptan	18 (21.2)	42 (49.4)	25 (29.4)	0.5189	0.436 - 0.602	0.6118
	Placebo	16 (21.1)	34 (44.7)	26 (34.2)			
Patients Having Serum Sodium 130-134 mEq/L at Baseline							
Day 4	Tolvaptan	63 (63.0)	37 (37.0)	0 (0.0)	0.7480	0.675 - 0.821	< 0.0001
	Placebo	17 (18.5)	61 (66.3)	14 (15.2)			
Day 30	Tolvaptan	54 (64.3)	29 (34.5)	1 (1.2)	0.6733	0.594 - 0.753	< 0.0001
	Placebo	26 (34.2)	40 (52.6)	10 (13.2)			

Table 3.2.2.4-1 Analysis of Categorical Change in Serum Sodium Level at Selected Time Points for the Overall Hyponatremia Population and by Baseline Hyponatremia Severity in the Pooled Placebo-controlled Phase 3 Hyponatremia Studies; Intent-to-treat Dataset (OC)							
Visit	Treatment Group	Normalized (> 135 mEq/L) n (%)	Remained or Became Mild (130-134 mEq/L) n (%)	Remained or Became Severe (< 130 mEq/L) n (%)	Chance for TLV to be Better than Placebo^a	95% CI^a	P-value^b
Day 37 ^c	Tolvaptan	27 (32.1)	39 (46.4)	18 (21.4)	0.4925	0.409 - 0.576	0.8299
	Placebo	24 (32.0)	37 (49.3)	14 (18.7)			

ITT Dataset comprises data from all randomized patients (excluding patients from Sites 004, 006, and 237) who had a baseline and a postbaseline efficacy evaluation.

^aBased on Section 6.1.2 of: Fleiss JL. The design and analysis of clinical experiments. New York: John Wiley & Sons, Inc.; 1999. A value > 0.5 favors tolvaptan.

^bDerived from the CMH test stratified by baseline hyponatremia origin.

^cAssessment performed 7 days after discontinuation of trial medication.

3.2.2.5 Worsening of Hyponatremia

In the prespecified categorical analysis of serum sodium data (Section 3.2.2.4), it was observed that a relatively high percentage of placebo subjects fell from a baseline serum sodium concentration of 130-134 mEq/L to < 130 mEq/L at any post-baseline time point. This prompted post hoc analyses to explore clinically relevant declines in serum sodium concentrations while on treatment, where it became apparent that tolvaptan prevents worsening of hyponatremia. Although these analyses were largely post hoc, they speak to the importance of treating hyponatremia and to the potential dangers of withholding therapy. To quantify this benefit, different analyses of worsening hyponatremia were performed and are summarized in Table 3.2.2.5-1.

Table 3.2.2.5-1 Incidence of Worsening Hyponatremia in the Pooled Placebo-controlled Phase 3 Hyponatremia Studies of Tolvaptan			
Treatment Group	N	Percentage of Patients with Worse Serum Sodium Concentration n (%)	p-value
Patients with serum sodium concentration 130-134 mEq/L at baseline whose sodium concentration decreased to < 130 mEq/L ^a			
Tolvaptan	103	16 (15.53)	< 0.0001
Placebo	98	48 (48.98)	
Patients with serum sodium concentration < 130 mEq/L at baseline in whom sodium concentrations decreased by ≥3 mEq/L ^a			
Tolvaptan	110	11 (10.00)	< 0.0001
Placebo	105	46 (43.81)	
Patients in whom sodium concentration decreased by ≥ 3 mEq/L or who fell to < 130 mEq/L from ≥ 130 mEq/L at baseline (at any post-baseline visit) ^b			
Tolvaptan	213	34 (15.96)	< 0.0001
Placebo	203	106 (52.22)	
Patients in whom sodium concentration decreased by ≥ 3 mEq/L or who fell to < 130 mEq/L from ≥ 130 mEq/L at baseline at two consecutive visits ^c			
Tolvaptan	213	5 (2.35)	< 0.0001
Placebo	203	25 (12.32)	

Includes studies 156-02-235 and 156-03-238.

^a ITT dataset, OC analysis. Patients with decreases at any post-baseline time point are included. P-values are derived from CMH test.

^b ITT dataset, observed cases (OC) analysis. P-values are derived from Cochran-Mantel-Haenszel test.

^c ITT dataset, LOCF analysis. P-values were derived from the Cochran-Mantel-Haenszel test, stratified by baseline disease etiology, severity, and study.

Overall, fewer tolvaptan patients with baseline serum sodium concentrations 130-134 mEq/L fell to concentrations < 130 mEq/L at any point while on treatment (15.53% tolvaptan patients versus 48.98% placebo patients) (relative risk [RR] 0.3173, 95% CI 0.19-0.52, $p < 0.0001$).

In another analysis that quantified the patients with baseline serum sodium concentrations < 130 mEq/L who exhibited decreases of at least 3 mEq/L, significantly fewer tolvaptan patients declined by ≥ 3 mEq/L at any post-baseline time point (10.0% tolvaptan patients versus 43.8% placebo patients; RR 0.2286, 95% CI 0.13-0.42, $p < 0.0001$).

Another analysis defined worsening as the patients in whom, at any post-baseline visit, sodium concentrations decreased by ≥ 3 mEq/L or fell to < 130 mEq/L from ≥ 130 mEq/L at baseline. Using these criteria, the rate of worsening with placebo was more than 3 times greater than that with tolvaptan (ITT dataset, observed cases [OC] analysis; RR [relative risk] = 0.3053, 95% CI of RR 0.22-0.43, $p < 0.0001$). At the behest of the FDA, another criteria investigated the persistence of worsening hyponatremia by requiring patients to exhibit decreases in sodium concentrations of ≥ 3 mEq/L or decreased sodium concentrations to < 130 mEq/L from ≥ 130 mEq/L at baseline and to do so for at least 2 consecutive visits. While the absolute rates using these more stringent criteria were lower, over 5 times more placebo patients exhibited persistent worsening (12.3%) than did patients treated with tolvaptan (2.4%) (ITT data set, last observation carried forward [LOCF] analysis; $p < 0.0001$).

Similar findings were also seen in a long-term, placebo-controlled phase 3 heart failure study (156-03-236). Patients with sodium concentrations 130-134 mEq/L at baseline were analyzed to determine the percentage who worsened to sodium < 130 mEq/L at any post-baseline time point during the course of this long-term study. The data demonstrate that 45/203 (22.2%) tolvaptan patients shifted sodium concentrations (ie, 130-134 mEq/L to < 130 mEq/L) at at least one post-baseline visit compared to 66/176 (37.5%) of placebo patients (RR = 0.5911, $p = 0.0011$). In addition, in this study, patients with normal sodium concentrations at baseline were analyzed to determine if they became hyponatremic at any post-baseline visit. The analysis demonstrated that 19% of the patients (N=1821) receiving tolvaptan exhibited a serum sodium concentration of < 135 mEq/L in at least one post-baseline visit compared to 32% of patients (N=1825) receiving placebo (RR = 0.546, $p < 0.0001$), while 4% of tolvaptan patients shifted to sodium concentrations < 130 mEq/L compared to 7% of placebo patients (RR = 0.531, $p < 0.0001$). These data support tolvaptan's ability to prevent worsening of hyponatremia

in both those patients who are at increased risk (by having either sodium concentrations < 130 mEq/L or 130-134 mEq/L at baseline) and even in those patients who are normonatremic at baseline.

3.2.2.6 Effects of Discontinuation of Therapy

To assess the effects of discontinuation of tolvaptan treatment on serum sodium concentrations, patients in the 30-day phase 3 studies had their serum sodium concentrations analyzed 7 days after withdrawal from therapy. The data for the pooled dataset (from 156-02-235 and 156-03-238) are shown in [Figure 3.2.2.6-1](#).

At Day 37 of the studies (7 days following treatment discontinuation), a decline in serum sodium concentrations to those approximately equivalent to the placebo group was observed (ie, mean < 135 mEq/L). This decline occurred despite instructions to institute measures such as fluid restriction for patients at risk of recurrent hyponatremia < 130 mEq/L. Similar effects were observed in the subsets of patients stratified by baseline sodium concentrations (ie, < 130 mEq/L and 130-134 mEq/L) and stratified by underlying disease (ie, SIADH, cirrhosis and CHF).

Similarly, in the open-label extension phase 3 hyponatremia study (156-03-244), withdrawal from tolvaptan therapy was consistently associated with a decline in mean serum sodium concentration at follow up, approximately to the concentrations observed at baseline (see [Figure 3.2.3-1](#)).

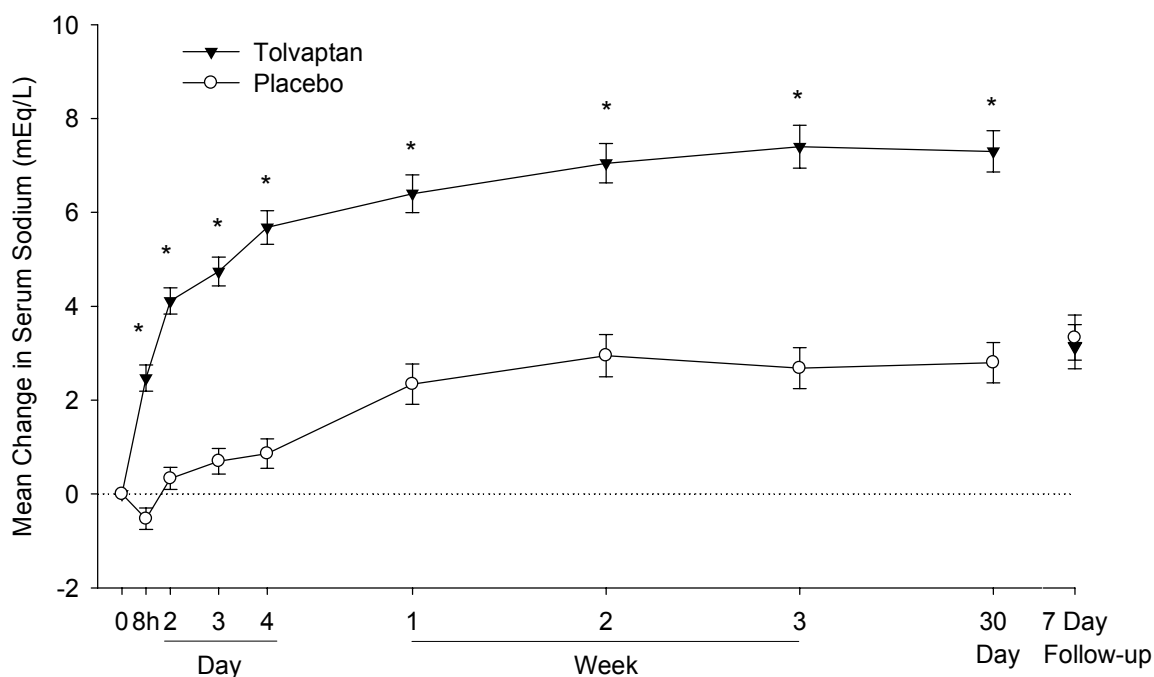


Figure 3.2.2.6-1 Mean Change From Baseline in Serum Sodium Concentration (mEq/L) Over Time in the Pooled Placebo-controlled Phase 3 Hyponatremia Studies of Tolvaptan

ITT Dataset, OC analysis; * $p < 0.0001$.

Note: 0=Baseline; 8h=8 hours post-first dose.

3.2.2.7 Percentage of Patients Requiring Strict Fluid Restriction

In the pivotal hyponatremia studies of tolvaptan, the option of initiating fluid restriction for patients with serum sodium concentrations < 130 mEq at baseline was available at the investigator's discretion depending on the clinical condition of the patient. Fluid restriction was defined in the tolvaptan program as < 1000 mL/day, and the prescription of fluid restriction was recorded at each visit. Two definitions were used for the variable of fluid restriction. Using the first definition, a patient was defined as requiring fluid restriction if the patient had no baseline fluid restriction but had fluid restriction imposed during the double-blind treatment period of the study (excluding Day 30). This definition treated all patients who had baseline fluid restriction as patients who did not require fluid restriction during the double-blind treatment period. Using the second definition, a patient was defined as requiring fluid restriction if the patient had no baseline fluid restriction but had fluid restriction imposed during the double-blind treatment period, or

the patient had fluid restriction imposed at baseline and maintained the fluid restriction (maybe at different levels) throughout the double-blind treatment period.

For the pooled analysis, the percentage of patients prescribed fluid restriction was statistically significantly lower in the tolvaptan group than in the placebo group, regardless of the definition used for fluid restriction. Using the first definition, 7.9% of tolvaptan patients required fluid restriction, compared to 15.5% of patients receiving placebo ($p=0.0117$). Using the second definition, 14.0% of patients receiving tolvaptan received fluid restriction, while 24.8% of placebo patients received fluid restriction ($p=0.0017$). The largest treatment effect was observed in the SIADH population, where statistical significance was attained by both definitions (definition 1, 4.7% tolvaptan versus 18.9% placebo; definition 2, 4.7% tolvaptan versus 22.2% placebo; $p < 0.01$ for both analyses). Effects in the CHF and cirrhosis populations are described in [Section 3.3.2](#). These data further reinforce the benefits of tolvaptan for the treatment of hyponatremia.

3.2.2.8 Urine Output, Fluid Intake, and Fluid Balance

In an analysis of urine output, fluid intake and fluid balance in the pivotal hyponatremia trials for tolvaptan, fluid intake and urine output were significantly greater in the tolvaptan group compared to placebo ($p \leq 0.0086$). As expected, overall fluid balance (IV/oral fluid intake minus urine output) was significantly decreased in the tolvaptan group compared with placebo ($p < 0.0001$).

3.2.3 Maintenance of Efficacy

In the ongoing hyponatremia phase 3 open-label extension study (156-03-244), patients who were randomized to tolvaptan or placebo in the short-term, double-blind placebo-controlled phase 3 hyponatremia studies (156-02-235 and 156-03-238) and completed the 30-day treatment course were given open-label tolvaptan after at least 7 days off study drug. As of an October 2007 data cutoff date, results are available up to Week 106+. The mean change from baseline in serum sodium concentrations over time is shown side-by-side in [Figure 3.2.3-1](#) for the short-term double-blind studies and the open-label extension study. In the open-label study, statistically significant increases in serum sodium concentrations over baseline values were observed, and these improvements were maintained over the long term.

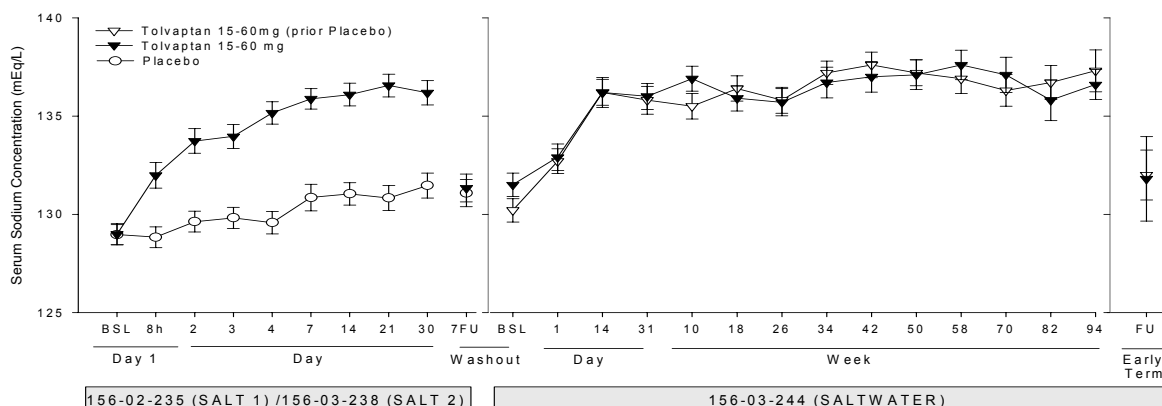


Figure 3.2.3-1 Mean Serum Sodium Concentration (mEq/L) Over Time For Patients in the Pooled Placebo-controlled Phase 3 Hyponatremia Studies and the Open-label Extension Phase 3 Hyponatremia Study of Tolvaptan

All patients dataset; OC analysis.

Note: figure is cut at Week 94 due to small numbers of patients beyond this time point.

In the phase 3 heart failure study (156-03-236), 475 patients had a baseline serum sodium concentration < 135 mEq/L, of whom 243 received tolvaptan 30 mg QD and 232 received placebo. Differences in the change from baseline in serum sodium between treatment groups were greater for tolvaptan compared with placebo and were statistically significant up to Week 40 (OC) (Figure 3.2.3-2).

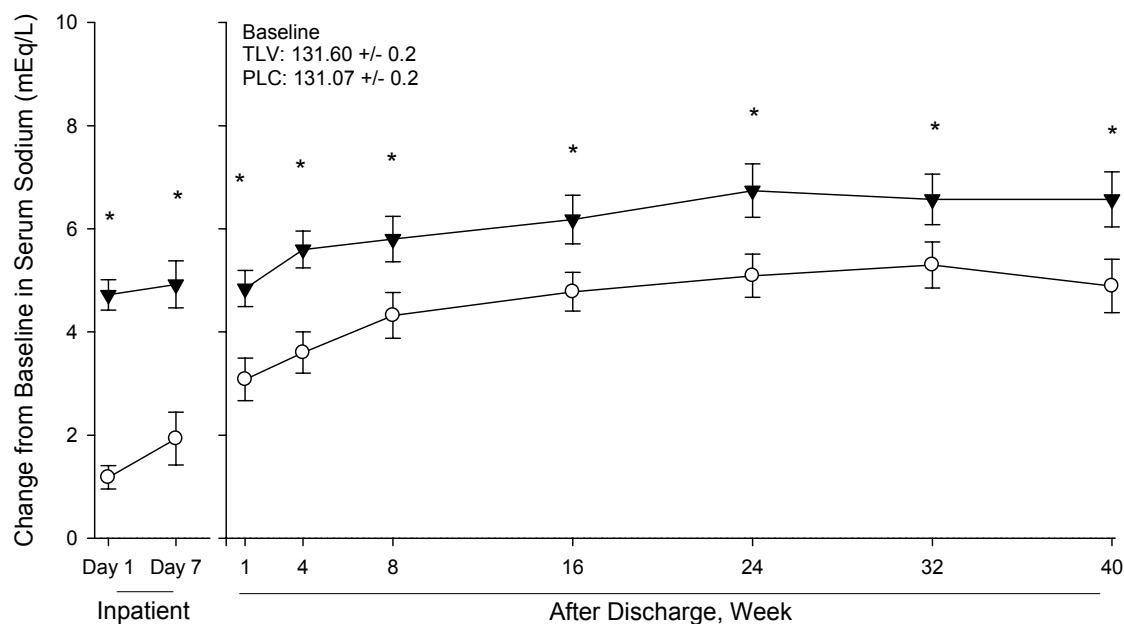


Figure 3.2.3-2 Mean Serum Sodium Concentration (mEq/L) Over Time for the Hyponatremia Subgroup (Baseline Serum Sodium < 135 mEq/L) in the Phase 3 Study of Tolvaptan in Worsening Heart Failure

ITT dataset; OC analysis.

3.3 Clinical Outcomes

3.3.1 Health-related Patient-reported Outcomes

In the tolvaptan program, health-related patient-reported outcomes were assessed in the phase 3 hyponatremia studies in all patient subtypes using the Short-Form-12 (SF-12) Health Survey. Supportive data were obtained from the phase 3 heart failure trial where the Kansas City Cardiomyopathy Questionnaire (KCCQ) was utilized. The SF-12 is a general health instrument, whereas the KCCQ is specific for heart failure. Additionally in the tolvaptan program, the HDS was used in one of the hyponatremia studies to evaluate hyponatremia-specific symptoms. With the exception of the HDS, these scales were pre-specified secondary efficacy variables in the studies in which they were assessed. This program represents the first application of the SF-12 general health instrument in hyponatremia patients.

3.3.1.1 Methodology, Including Subscales

3.3.1.1.1 Short-form-12 Health Survey

The SF-12 general health questionnaire is completed independently by patients and provides data on 4 concepts relating to physical health (ie, physical functioning, role limitations due to physical health problems, bodily pain, and general health) and 4 concepts relating to mental health (ie, vitality, social functioning, role limitations due to emotional problems, and mental health). Two scores, Mental Component Summary (MCS) Score and Physical Component Summary (PCS) Score, which are composite measures respectively for mental and physical health concepts, are derived using norm-based methods and transformed to have a mean of 50 and a standard deviation (SD) of 10 in the general US population.⁹³

The SF-12 is validated with US normative data available for age, gender, and a variety of clinical conditions including heart and liver disease.^{94,95} Therefore, while this instrument is not specifically targeted for hyponatremia symptoms, it can provide insights into the general health status of the hyponatremia study population as compared to normal and similar diseased populations. The sponsor has worked with patient-reported outcomes experts from QualityMetric, Inc. (Lincoln, RI), including the co-creators of the SF scale. Validation of the SF-12 scale in the hyponatremia population has been undertaken and is discussed briefly in [Section 3.3.1.4](#).

In the two placebo-controlled phase 3 hyponatremia studies of tolvaptan, patients completed the SF-12 at predose on Day 1, and at Week 1 (156-03-235) or Week 2 (156-03-238), Day 30/early termination (ET), and (Trial 156-03-238 only) at the 7-day follow-up visit. Because each of these studies was considered underpowered for this tool, a meta-analysis of the combined data was prespecified as the endpoint of interest. In the open-label extension phase 3 tolvaptan study (156-03-244), patients completed the SF-12 at baseline, Days 14 and 31, and Weeks 10, 18, 26, 34, 42, 50, 58, 70, 82, 94, 106, and 214/ET. Data were analyzed as change from baseline in MCS and PCS Scores using an analysis of covariance (ANCOVA) model with treatment, baseline hyponatremia severity and etiology as factors, and baseline score as covariate. All studies used the SF-12 acute version (1 week time recall).

3.3.1.1.2 Hyponatremia Disease-specific Survey

The HDS was implemented in the second of the pivotal tolvaptan hyponatremia studies as an exploratory endpoint (multinational study 156-03-238; also in the long-term, open-

label extension study, 156-03-244, as a secondary endpoint) to collect hyponatremia-specific data and use it to assess the validity of the SF-12 for use in the hyponatremic population. This is a 13-item self-directed patient questionnaire, with an overall health status question also rated by the investigator. The HDS was developed by the sponsor in collaboration with academic and medical experts. Questions were formulated to assess mental and physical domains reportedly influenced by chronic hyponatremia, as well as to assess issues related to general health, thirst, and hyponatremia awareness.

Patients were asked to rate themselves on the following:

- Their general health over the past 2 days (excellent, very good, good, fair, or poor);
- How their thinking ability had been limited, specifically in concentrating, calculating, language, and memory activities (not at all, slightly, moderately, quite a bit, or extremely). (These items constituted the MCS component of the HDS.);
- How their strength or coordination had been limited, specifically in endurance, strength, gross coordination, and fine coordination activities (not at all, slightly, moderately, quite a bit, extremely). (These items constituted the PCS component of the HDS.);
- Their self-perception, without prompting by knowledge of their laboratory test, of their current sodium concentration (very low, a little low, or normal);
- Their thirst sensation, disregarding the amount of fluid ingested, over the past 2 days (not thirsty, little thirsty, normal thirst, extra thirsty, or very thirsty); and
- Assessments of how the patient and how the investigator believed the study treatment affected their activity, symptoms, and overall well-being (much better, somewhat better now, about the same, somewhat worse now, or much worse now).

A lower score indicated improved functioning, but scores were sometimes presented with an opposite sign for ease of direct comparison with SF-12 data, where a higher score represented improvement.

This instrument was further refined according to best practice questionnaire design principles with input from patient-reported outcomes experts from QualityMetric, Inc. The applicability and sensitivity of the HDS on the effects of hyponatremia and its correction were validated based on the results of study 156-03-238, which is discussed further in [Section 3.3.1.4](#).

The HDS was completed by patients in study 156-03-238 at baseline (Day 1 predose), Week 2, Day 30/ET, and at the 7-day follow-up visit; and in study 156-03-244 at baseline, Days 14 and 31, Weeks 10, 18, 26, 34, 42, 50, 58, 70, 82, 94, 106, and 214/ET, and at the 7-day follow-up visit. Shift analyses were performed for each HDS item on the

ITT Dataset and < 130 mEq/L hyponatremia subgroup. In addition, changes from baseline of the MCS and PCS Scores were summarized, with p-value derived from ANCOVA with treatment and baseline hyponatremia origin and severity (3x2) as factors and baseline MCS/PCS as covariate.

3.3.1.1.3 Kansas City Cardiomyopathy Questionnaire

The KCCQ, a validated instrument used to assess health outcomes in heart failure patients, was administered in the tolvaptan phase 3 worsening heart failure study (156-03-236) and specifically selected because of its relatively short evaluation interval (2 weeks). The KCCQ is a self-administered, 23-item questionnaire that quantifies physical limitations, symptoms, self-efficacy, social limitations, and quality of life.⁹⁶ Five domains were analyzed: Physical Limitation (question 1 with 6 parts, which pertains to the way in which heart failure is limiting for the patient); Symptom (questions 3 through 9, which pertain to frequency and bothersomeness of heart failure symptoms); Social Limitation (question 15 with 4 parts, which pertains to the degree to which heart failure limits the patient's lifestyle); Self Efficacy (questions 10 and 11, which pertain to the patient's understanding about how to manage worsening heart failure symptoms); and Quality of Life (questions 12, 13, 14, which pertain to the patient's feelings about the effects of their heart failure). For all domain and composite scores, higher scores indicated a better level of functioning and/or greater satisfaction. The KCCQ was administered to patients at screening; Outpatient Weeks 1, 4, 8 and every 8 weeks thereafter; and end of treatment (or early termination). It was performed where available in the local language and only for patients randomized under protocol Amendment 1. The analysis was performed using an ANCOVA model with terms of treatment, (pooled) center and baseline score as covariate. Type III sum of squares from SAS was used for the treatment comparison. The KCCQ overall summary score was constructed based on the outlines provided by C. Patrick Green et al.⁹⁶

3.3.1.2 Analysis of SF-12 Health Survey

3.3.1.2.1 Health Burden of Hyponatremia Based on Baseline SF-12

In the placebo-controlled phase 3 hyponatremia studies where patients had baseline serum sodium concentrations < 135 mEq/L, baseline SF-12 MCS and PCS Scores were low and similar between the tolvaptan and placebo groups (Table 3.3.1.2.2-1), approximately 44 for MCS and 33 for PCS. These data were compared to the general US population for which scores are equated to a mean of 50 and SD of 10, meaning a one point difference is equated to one-tenth of a SD. In a post hoc analysis to obtain an estimate of the disease

burden in hyponatremia, normative data were adjusted to the age and gender of the hyponatremia study sample using separate least squares multiple regression models for each of the SF-12 component scores, with Student's t-test used to test for significant differences between hyponatremia patients and the adjusted norms. The benchmarks for the representative normal population are based on findings from the 1998 National Survey of Functional Health Status, a sample of non-institutionalized US adults.⁹⁷ In the context of comparing group differences, it has been suggested that a 0.2 SD (ie, 2 points) represents a small effect size, a 0.5 SD represents a moderate effect size, and a 0.8 SD represents a large effect size.⁹⁸ The minimally important difference (MID) established for the MCS and PCS Scores is 0.3 SD (ie, 3 points), which is between the small and moderate effect sizes.^{99,100}

The above-mentioned baseline scores in the phase 3 tolvaptan studies represent a significant mental and physical burden compared to the normal US population. For the MCS, a score of 53 has been shown to correlate with the “average well” adult patient, whereas a score of 50 represents the mental health status for the average adult. Similarly, for the PCS, a score of 55 correlated with the “average well adult” and a score of 50 correlated with the average adult. The MCS Score of 44 was at the 20th percentile (about 8 points or 0.8 SD difference from normal, a large effect size difference) and associated with an increased likelihood of receiving mental health specialty care and diagnosis of depression.¹⁰¹ The PCS Score of 33 in hyponatremia patients was at the 11th percentile compared to the general US population (about 15 points or 1.5 SD from normal, also a large effect size difference), and scores this low have been linked to increased likelihood of hospitalizations, lost jobs due to health reasons, and increased medical expenditures and mortality.^{101,102} The observation that the PCS scores were significantly lower than the MCS scores at baseline is likely a representation of the underlying illnesses; SIADH and more notably CHF and cirrhosis, are associated with significant physical burdens independent of their effects on mental functioning (see [Section 3.3.1.2.4](#) for a more detailed discussion).

The observed health burden at baseline as described above can not solely be attributed to hyponatremia, as enrolled patients in the phase 3 hyponatremia studies had comorbidities of CHF, cirrhosis, and SIADH, and the SF-12 has extensively documented the health burden of the first two referenced conditions. The benchmarks for the representative disease populations were based on findings from the Medical Outcomes Study, a 4-year observational study of chronically ill patients and adjusted for age and gender of the

hyponatremia sample.^{103,104} The hyponatremia study patients with CHF showed an comparable physical health burden compared to CHF patients in the general US population (baseline score of 31 vs. population score of 34), whereas their mental health burden was comparably much greater. While the general CHF population appears comparable to the average US population on mental status (score of approximately 50), the hyponatremia-CHF trial patients had a 6-point deficit on the MCS Score (43.9), which is close to the clinical cut point score for depression (42).¹⁰¹ In contrast, the hyponatremia trial patients with cirrhosis exhibited scores somewhat lower than the kidney/renal disease general population on both physical (baseline score of 31 vs. population score of 40) and mental (baseline score of 43 vs. population score of 45) component measures. Again, the MCS Score in hyponatremia-cirrhosis trial patients was closer to the depression cut point of 42. Finally, while there were no benchmark scores for SIADH patients in the general US population, the baseline scores for SIADH were comparable to those of CHF and cirrhosis patients for both the physical (baseline score of 37) and mental (baseline score of 45) component measures. These data collectively suggest that while the underlying diseases appear to have a greater impact on the physical component scores, the presence of hyponatremia in addition to the underlying disease has a greater impact on the mental health status of patients. This conclusion leads to the hypothesis that the effects of treatment of hyponatremia are more likely to impact the mental health of patients than the physical health. This hypothesis is consistent with a long-held understanding within the medical community that CNS and peripheral nervous system symptoms manifest as the earliest signs of both acute and chronic forms of hyponatremia.¹⁰⁵ In the acute circumstance, prominent, life-threatening consequences of a shift in the osmotic state, brain edema and potential herniation may manifest precipitously. In the chronic circumstance, changes in nerve function due to altered electrolyte and neurotransmitter levels may produce subtle, yet significant effects on nervous system function.

3.3.1.2.2 Impact of Tolvaptan Treatment on SF-12 Health Status at Day 30

While positive mean change scores at Day 30 demonstrate that both tolvaptan and placebo groups had improvements in their MCS and PCS Scores (Table 3.3.1.2.2-1), the magnitude of improvement was greater for the MCS Score and achieved statistical significance ($p = 0.0113$).

The statistically greater mean improvement observed in the tolvaptan group compared to placebo group for MCS Score (5.3 in the tolvaptan group compared to 1.6 in the placebo group; $p = 0.0113$) also represented a clinically meaningful improvement in mental functioning. The mean value at Day 30 of 48.8 approaches the range of the average adult (approximately 50) and represents a restoration of mental function and well-being to near normal levels. This improvement has been correlated to a 29% reduction in the likelihood of receiving mental health specialty care within 6 months, a 62% reduction in the percentage of the general population that reported a need to cut down time at work due to psychiatric problems, and a 45% reduction in percentage of the general population that reported accomplishing less at work due to psychiatric problems (data on file).

The changes between groups were not significantly different for the PCS Score. Tolvaptan exhibited an improvement of 1.15 compared to an improvement with placebo of 0.29 ($p=0.3047$). While the improvement was 4-times greater with tolvaptan than with placebo, the change was small, especially when considering the magnitude of difference from the typical US adult. The typical US adult exhibits a score of approximately 50, while the PCS for the patients in these studies was 33; a one-point improvement is not relevant in light of the 17 point difference from “normal.” The magnitude of change was most likely related to the underlying illnesses, especially CHF and cirrhosis. As would be expected, improvement of hyponatremia in these chronic illnesses does not dramatically change the overall physical burden of the disease.

Table 3.3.1.2.2-1 Mean Change From Baseline at Day 30 in the SF-12 PCS Score and MCS Score in the Pooled Placebo-controlled Phase 3 Hyponatremia Studies of Tolvaptan; Randomized Patient Dataset (LOCF)								
Visit	Treatment Group	Value		Change From Baseline		P-value ^a	Estimated Treatment Effect	95% CI
		N	Mean (SD)	N	Mean (SD)			
PCS Score ^b								
Baseline ^c	Tolvaptan	203	33.17 (10.65)	-	-	-	-	-
	Placebo	198	33.43 (10.67)	-	-	-	-	-
Day 30	Tolvaptan	188	35.06 (11.01)	184	1.15 (9.42)	0.3047	0.90	-0.82 - 2.62
	Placebo	177	34.44 (10.72)	174	0.29 (9.50)			
MCS Score ^b								
Baseline ^c	Tolvaptan	203	43.51 (11.78)	-	-	-	-	-
	Placebo	198	44.85 (11.72)	-	-	-	-	-
Day 30	Tolvaptan	188	48.81 (11.47)	184	5.33 (12.20)	0.0113	2.86	0.65 - 5.08
	Placebo	177	46.75 (12.23)	174	1.63 (12.85)			

Includes studies 156-02-235 and 156-03-238.

MCS = Mental Component Summary Score; PCS = Physical Component Summary Score.

Randomized Patient Dataset comprises data from all patients (excluding patients from Sites 004, 006, and 237) who were randomized to a treatment group.

^aP-values were derived from an ANCOVA model with treatment and baseline hyponatremia severity and origin as factors and covariate baseline score. An additional factor of trial was added to the ANCOVA model for the pooled data.

^bA positive score indicates improvement.

^cOriginal score at baseline.

Since mean change scores can mask the underlying variability in health status outcomes, a post hoc responder analysis was also used to evaluate the impact of treatment on health status using the MID established for the SF-12 MCS and PCS scales (ie, 3 points): scores were categorized as “better,” (ie, change > 3 points) “same,” (ie, change between +3 and -3 points) or “worse” (ie, change > -3 points) than the baseline scores. Multinomial (polytomous) logistic regression methods were used to compare the categorical changes in SF-12 MCS and PCS scores between tolvaptan and placebo groups. Adjusted percentages for change categories were generated with statistical adjustments for baseline hyponatremia severity, disease etiology, and study. Chi-square tests of significance were computed to determine whether the percentages across change categories differed between groups. The analysis was conducted using the ITT sample and the categories of change scores were based on LOCF. Sensitivity testing using other analyses accounting for missing data showed similar results.

Significantly more patients in the tolvaptan group had an improved outcome in MCS Score as compared to placebo ($X^2=9.58$, $p=0.008$): 44% of tolvaptan patients showed meaningful improvement in MCS Score compared to 32% of placebo patients, and more importantly, the percentage of patients showing meaningful decline was double in the placebo group (24%) compared to the tolvaptan group (12%). In contrast, roughly one-third of hyponatremia patients in both treatment groups showed meaningful improvement (“better”) in PCS Score, while the majority stayed the same; about one-fourth of patients in either group showed meaningful decline ($X^2 = 0.64$, $p=0.726$).

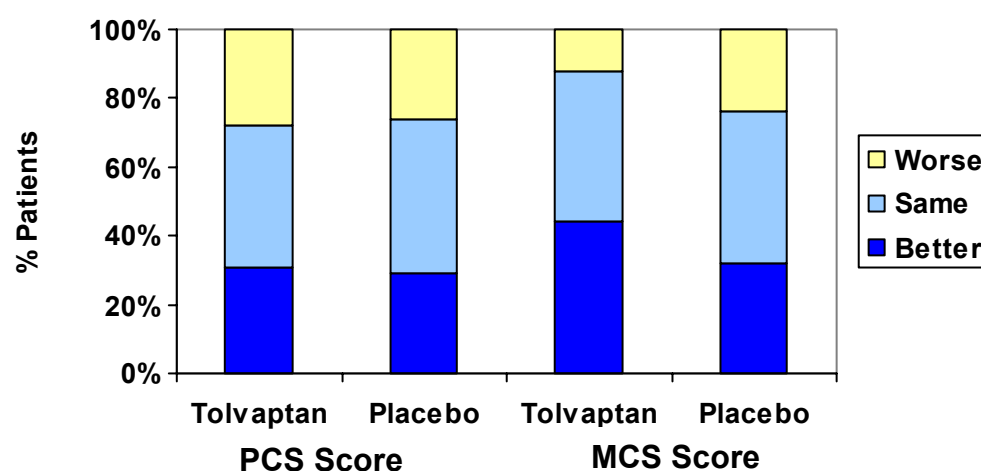


Figure 3.3.1.2.2-1 Impact of Treatment on Health Status as Measured by SF-12 at Day 30 in the Pooled Placebo-controlled Phase 3 Hyponatremia Studies of Tolvaptan

MCS = Mental Component Summary Score; PCS = Physical Component Summary Score.

Over the long-term course of treatment, SF-12 results from the 106+ week open-label extension study (156-03-244) showed that changes from baseline in the parent double-blind trial showed improved scores (ie, increases compared to baseline) at all visits. Improvements during treatment ranged from 1.6 to 7.2 for MCS Scores and 1.3 to 4.3 for PCS Scores (OC). These data show that effects observed in the parent trial were generally maintained in the long-term open-label study.

3.3.1.2.3 Link Between Changes in Serum Sodium and SF-12 Health Status

In the pooled phase 3 hyponatremia studies, the MCS Score results were found to be correlated with serum sodium concentrations. Post hoc analyses using the ITT Dataset (LOCF) revealed statistically significant correlations between the AUC of mean change

from baseline in serum sodium concentration at Day 30 and the change from baseline in SF-12 MCS Scores at Day 30 using placebo patients only (ie, independent of drug effect; correlation coefficient 0.1940, $p = 0.0103$) and using tolvaptan plus placebo patients (ie, inclusive of drug effect; correlation coefficient 0.1603, $p = 0.0021$).

To further investigate the association between changes in SF-12 MCS and PCS scores and the observed clinically meaningful changes in serum sodium concentrations (as discussed in [Section 3.3.1.2.2](#)), SF-12 results using the MID categories were evaluated in terms of clinically meaningful categories of change in serum sodium concentrations from baseline to Day 30, ie, as “better” (increased by 5 mEq/L or more), “same” (changed between +5 and -3 mEq/L), and “worse” (decreased by 3 mEq/L or more). Mean changes in MCS and PCS Scores from baseline to Day 30 were analyzed across these three categories using analysis of variance (ANOVA) methods. It was hypothesized that SF-12 MCS and PCS scores would show significantly greater improvement among those patients categorized as “better” on changes in serum sodium levels compared to patients categorized as the “same” or “worse” in serum sodium level changes.

Results are summarized in [Table 3.3.1.2.3-1](#) and bear out this hypothesis for MCS but not PCS Score, as evidenced by statistically significant results for mean change score and categorical change. MCS Scores improved by nearly 6 points for patients whose serum sodium concentration improved by a clinically meaningful amount (> 5 mEq/L), which represents a moderate effect size change in MCS Score and exceeds the MID score established for the MCS. Likewise, the percentages of patients whose SF-12 MCS Scores were rated as “better” was highest for the patients in whom the serum sodium concentration had improved, moderate in those whose sodium concentration had remained unchanged, and lowest in those whose sodium concentration had worsened. The converse is observed for the patients who were rated as “worse” by their SF-12 MCS Scores: the percentage of patients exhibiting worsening SF-12 scores was lowest in the patients with improvement in serum sodium concentration, moderate for those whose sodium concentration remained unchanged, and highest in those patients whose serum sodium concentration had worsened.

In contrast, changes in PCS Score were not meaningfully related to changes in serum sodium concentration. Approximately the same percentages of patients showed categorical improvement or worsening, regardless of the change in serum sodium concentration. Similar results were observed for the mean change in SF-12 PCS Scores.

In conclusion, these data clearly indicate that improvement in mental functioning (as indicated by improving MCS Scores) is positively correlated with improvement in serum sodium concentration, and worsening of mental functioning is correlated with additional reductions in serum sodium concentration. These data in conjunction with the data in the previous sections indicate that tolvaptan-mediated improvements in serum sodium concentration are likely to lead to restoration of mental functioning to a level consistent with the US population at large.

Table 3.3.1.2.3-1 Change in SF-12 PCS Score and MCS Score Across Clinically Meaningful Changes in Serum Sodium Concentrations at Day 30 in the Pooled Placebo-controlled Phase 3 Hyponatremia Studies of Tolvaptan								
Score	Serum Sodium Changes		N	Mean SF-12 Score		SF-12 Categorical Change ^a		
				Mean	SD	Better	Same	Worse
PCS	≥5 mEq/L improvement	Better	160	1.9	9.8	40.0%	30.6%	29.4%
	-2 to +4 mEq/L change	Same	113	0.6	9.3	38.9%	25.7%	35.4%
	≤ 3 mEq/L loss	Worse	21	2.4	10.2	47.6%	23.8%	28.6%
Significance Test of Differences				F=0.72, df=2, p=0.49		X ² = 1.9, p=0.76		
MCS	≥5 mEq/L improvement	Better	160	5.8	12.0	53.8%	27.5%	18.7%
	-2 to +4 mEq/L change	Same	113	2.0	12.3	43.4%	22.1%	34.5%
	≤ 3 mEq/L loss	Worse	21	0.4	13.7	38.1%	9.5%	52.4%
Significance Test of Differences				F=4.1, df=2, p=0.018		X ² = 17.2, p=0.002		

Includes studies 156-02-235 and 156-03-238.

df = degrees of freedom; MCS = Mental Component Summary Score; PCS = Physical Component Summary Score.

^aRepresents MID categories in comparison to baseline SF-12 scores as better,” (ie, change > 3 points), “same,” (ie, change between +3 and -3 points), and “worse” (ie, change > -3 points).

3.3.1.2.4 Analysis of SF-12 by Underlying Etiology (SIADH, Cirrhosis, CHF) and by Baseline Severity (Baseline Sodium < 130 mEq/L, Baseline Sodium 130 - 134 mEq/L)

The impact of treatment on the health status of hyponatremia patients was investigated post hoc in order to rule out that the changes in health status outcomes differed by etiology or severity. Separate ANOVA analyses with interaction terms for treatment by disease etiology and treatment by baseline severity were conducted with changes in SF-12 MCS and PCS scores from baseline to Day 30 as dependent variables. Estimated

marginal mean changes in SF-12 MCS and PCS scores were output from the model in order to assess the estimated treatment effects by disease origin and by baseline disease severity. The analysis was conducted using the ITT sample with LOCF. Results of both models revealed no significant interactions of disease etiology or disease severity and treatment suggesting neither etiology nor baseline severity are predictors of health status outcomes.

SF-12 data were analyzed in the placebo-controlled phase 3 hyponatremia studies for subgroups by hyponatremia etiology (SIADH/other, cirrhosis, CHF), as depicted in [Figure 3.3.1.2.4-1](#).

By etiology, consistent improvements of greater magnitude were observed in MCS Scores, regardless of underlying etiology. While the differences between tolvaptan and placebo groups for the SIADH and CHF patients were not significantly different ($p=0.0886$ and 0.5825 , respectively), statistically significantly greater improvement in MCS Scores were observed in tolvaptan cirrhosis patients (4.68) compared to placebo cirrhosis patients (0.16 ; $p = 0.0339$). The improvement in MCS Scores are consistently approximately 5 points or about 0.5 SD and are independent of the underlying disease etiology. These data suggest that improving hyponatremia is associated with a consistent improvement in mental functioning that is independent of the underlying etiology and likely dependent on the improvement in serum sodium concentrations.

While cirrhosis and CHF patients had small and not statistically different improvements between groups in PCS Scores at Day 30, a trend toward greater improvement was observed in tolvaptan SIADH/other patients (3.10) compared to placebo SIADH/other patients (0.18 ; $p = 0.0788$). This observation again is likely consistent with the underlying physical burden of each illness. The PCS scores are dependent on the underlying etiology and only in SIADH, where increased vasopressin activity is the primary underlying physical impairment, is there differential improvement of those scores between tolvaptan and placebo.

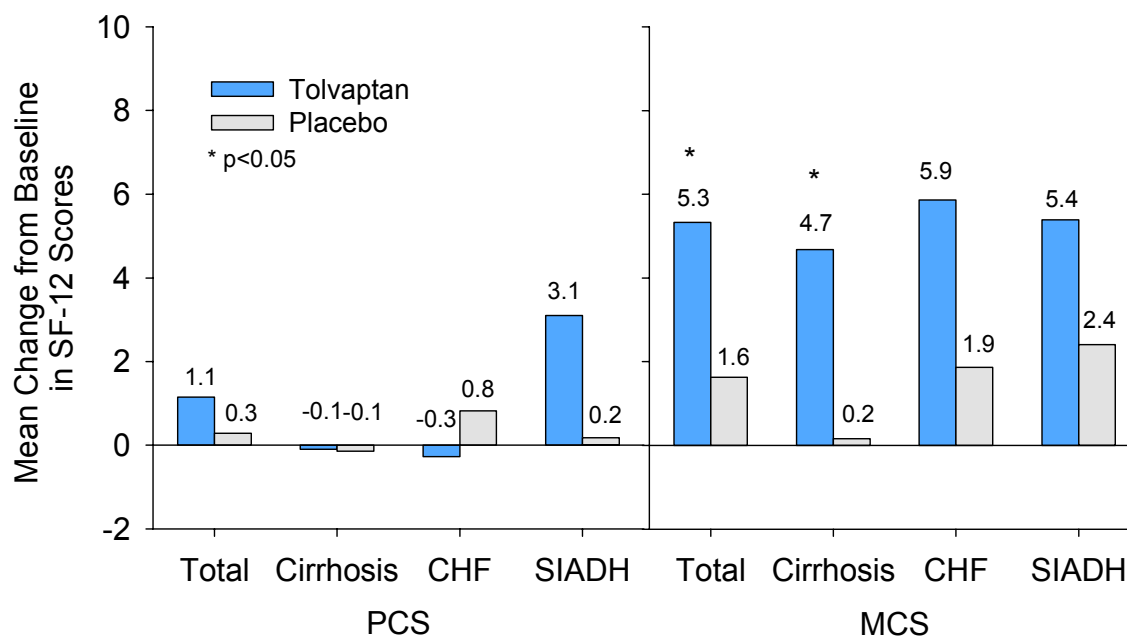


Figure 3.3.1.2.4-1 Mean Change From Baseline in SF-12 PCS and MCS Scores by Etiology in the Pooled Placebo-controlled Phase 3 Hyponatremia Studies of Tolvaptan; Randomized Patient Dataset (LOCF)

* $P \leq 0.05$.

MCS = Mental Component Summary Score; PCS = Physical Component Summary Score.

For MCS Score, tolvaptan patients again showed consistently greater improvements than placebo patients, regardless of the severity of hyponatremia at baseline (Figure 3.3.1.2.4-2). For the hyponatremia patients with baseline serum sodium concentrations < 130 mEq/L, the tolvaptan group exhibited a mean improvement of 5.10 compared to 1.43 in the placebo group ($p = 0.0275$). The patients with serum sodium concentrations of 130-134 mEq/L at baseline showed very similar effects (tolvaptan 5.58, placebo 1.83), albeit without achieving statistical significance ($p=0.1709$).

By severity, differences in PCS Score were not statistically different between tolvaptan and placebo patients having hyponatremia of 130-134 mEq/L or < 130 mEq/L. Again, differences between tolvaptan and placebo were relatively small, indicating that the PCS Score was more dependent on the underlying disease state. It is interesting to note, however, that the placebo patients with hyponatremia < 130 mEq/L at baseline showed

the largest decrease from baseline of any of the prespecified subgroups, suggesting that hyponatremia may be a predictor for worsening of illness if not corrected.

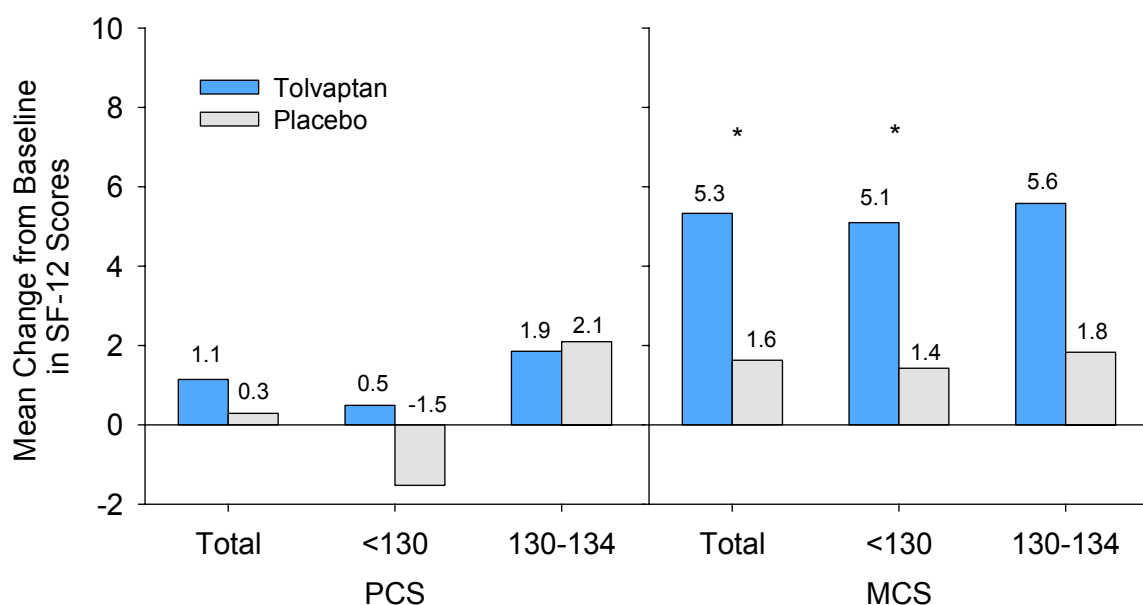


Figure 3.3.1.2.4-2 Mean Change in SF-12 PCS and MCS Scores for Patients With Baseline Sodium Concentrations < 130 mEq/L and 130-134 mEq/L in the Pooled Placebo-controlled Phase 3 Hyponatremia Studies of Tolvaptan (LOCF)

* $P \leq 0.05$.

MCS = Mental Component Summary Score; PCS = Physical Component Summary Score.

As observed in the overall hyponatremia patients, patients having baseline sodium concentrations < 130 mEq/L who improved most in their serum sodium concentrations were associated with the most improved SF-12 MCS Scores irrespective of treatment arm. Over one-third (36.3%) of patients having baseline sodium concentrations < 130 mEq/L had their serum sodium concentrations at Day 30 improve by ≥ 5 mEq/L and also showed the most improved MCS Scores (ie, change > 3).

3.3.1.3 Analysis of Hyponatremia Disease-specific Survey

Post-hoc analyses were performed using the HDS data from the one placebo-controlled phase 3 tolvaptan trial in which it was collected, 156-03-238. Change from baseline in the HDS MCS and PCS Scores were analyzed for the overall population and subgroup of patients having baseline sodium concentrations < 130 mEq/L. The changes in HDS MCS Scores were statistically significant in favor of tolvaptan at Day 30 for the overall

population (estimated treatment effect = -1.9 ; $p = 0.0296$) and for the < 130 mEq/L sodium subgroup (estimated treatment effect = -2.7 ; $p = 0.0129$) (LOCF). Interestingly, the effects observed at Day 30 were greatly diminished one week following withdrawal of therapy, with no statistically significant differences observed between treatment groups. The importance of this finding cannot be overstated, as it directly demonstrates that improvements in the HDS were dependent on therapy with tolvaptan. Additionally, a correlation analysis between average daily AUC of mean change from baseline in serum sodium concentration at Day 30 and the change from baseline in HDS MCS Score at Day 30 (ITT, LOCF) was significant (correlation p -value = 0.0029 ; partial correlation p -value = 0.0151). No statistically significant differences were observed between treatment groups in PCS Score for the overall population or the < 130 mEq/L sodium subgroup.

Given the correlation between HDS and SF-12 results and the significantly greater improvement observed for the MCS Score in tolvaptan patients having baseline serum sodium concentrations < 130 mEq/L, the HDS results of particular interest are from the subgroup of patients with baseline sodium < 130 mEq/L. The following statistically significant improvements favoring tolvaptan over placebo in study 156-03-238 were evident for the < 130 mEq/L sodium subgroup: concentrating activities (Day 30, $p = 0.0016$); calculating activities (Week 2, $p = 0.0172$; Day 30, $p = 0.0150$); memory activities (Week 2, $p = 0.0254$; Day 30, $p = 0.0343$); and the patient self-assessed overall hyponatremia status (Day 30, $p = 0.0025$).

For the patient self-assessment at Day 30 in the subgroup of patients with baseline serum sodium concentrations < 130 mEq/L, 69.2% of tolvaptan patients improved and 30.8% were about the same; whereas, in the placebo group, 30.0% of patients improved, 60.0% were about the same, and 10.0% were worse at Day 30. The physician assessment, however, did not reach statistical significance for the < 130 mEq/L sodium subgroup.

Over the long-term course of treatment, HDS results from the 106+ week open-label extension study (156-03-244) showed that the majority of hyponatremia patients in the < 130 mEq/L sodium subgroup improved based on the patient self-assessment at all on-treatment visits through the data cutoff at Week 106, except for at Week 42, when an equal percentage (44%) of patients either improved or were about the same. The percentages of hyponatremia patients in the < 130 mEq/L sodium subgroup who improved ranged from 55 to 90%.

Though HDS results did not completely discriminate tolvaptan's effects on neuromuscular functioning, specifically on balance through cerebellar integration of vision, vestibular, and proprioceptive inputs, evidence is available from Romberg's Test, which was performed as part of the neurological examination in the phase 3 pivotal hyponatremia studies, that tolvaptan has a beneficial effect in some patients. At baseline, 14 (12.4%) patients in the tolvaptan group and 11 (9.7%) patients in the placebo group could stand erect, feet together, with eyes open but not with eyes closed, a sign of cerebellar dysfunction. In a responder analysis derived from Wilson score method for single proportion, the proportion of patients with a positive Romberg's Test outcome (ie, positive Romberg's sign at baseline but negative result on follow-up visit) was significantly greater in the tolvaptan group compared to placebo at Week 2 (9 vs 1; $p = 0.0188$, Fisher Exact test) and approached statistical significance at Day 30 (9 vs 2; $p = 0.0590$, Fisher Exact test). A similar outcome was observed for the subgroup of hyponatremia patients with baseline serum sodium concentrations < 130 mEq/L at Week 2 (5 vs 0; $p = 0.0257$) but not at Day 30 (5 vs 1; $p = 0.1096$), which likely can be attributed to the small number of patients. For the overall population, the positive outcome was no longer evident one week after the last dose of tolvaptan was taken, during which time patients' serum sodium concentrations had returned to near baseline (low) levels. Similar but non-significant findings were found in an analysis of tandem walking.

3.3.1.4 Validity of SF-12 and HDS for Use in Hyponatremia

Results described above and in reports prepared by QualityMetric (data on file) demonstrate that the SF-12, and (as discussed below) to a more limited degree, HDS, are valid health instruments for measuring symptoms of hyponatremia.

The SF-12 was valid in a disease context (CHF, cirrhosis) based on normative data from the US general population. Component SF-12 scores, particularly MCS, correlated with questions designed to match hyponatremia-specific symptoms (ie, from the HDS). The MCS Scores from both instruments detected and responded to serum sodium changes. Further, hyponatremia etiology, baseline hyponatremia severity and also region/language were not confounders of SF-12 outcomes.

The applicability and sensitivity of the HDS on the effects of hyponatremia and its correction were validated (data on file) based on the SF-12 results of study 156-03-238. In general, the HDS items performed well in the hyponatremia population, showing properties of roughly normal distribution, equality of variance, and acceptable ceiling and

floor effects. Results of factor analyses suggested that there are potentially three factors (Cognitive, Physical, Coordination) in the instrument based on 8 items of the original survey that make sense conceptually. The three factors were scaled using the method of simple summated rating scales and results of psychometric testing revealed a well performing set of items and factor scales with good structural validity. Correlations were performed of the HDS scales with the baseline SF-12 MCS and PCS Scores, where it was expected the HDS physical items would correlate at least moderately (correlation coefficient > 0.4) with the SF-12 PCS and conversely the HDS cognitive items would correlate with the SF-12 MCS. As hypothesized, the HDS Cognitive Scale was significantly but modestly correlated with the SF-12 MCS (0.30) but not with the SF-12 PCS (0.06). The HDS Physical Scale was moderately (0.63) correlated with the SF-12 PCS and modestly on the SF-12 MCS (0.30). Additionally, the HDS Coordination Scale was generally equally correlated with the SF-12 MCS (0.41) than the SF-12 PCS (0.35).

HDS correlation analyses were also performed against clinical measures such as serum sodium change at Day 30 and clinical responders defined as patients (overall and by disease severity) achieving normalized sodium concentrations (>135 mEq/L) by Day 30. The HDS Cognitive and Coordination scales were significantly correlated (correlation coefficients of 0.37 and 0.26, respectively) with serum sodium change at Day 30, whereas the HDS Physical or Overall Health scales were not, indicating that the HDS does detect the effects of hyponatremia on mental function. In the responder analyses, while only one comparison in HDS scores reached statistical significance (ie, HDS Physical Scale) due in part to the lack of statistical power from having small sample sizes in each comparison group, in general, all HDS scales showed greater improvement among patients who reached normal serum sodium concentrations at Day 30 compared to patients who did not.

The validity of these patient-reported outcome measures in the hyponatremia population and their respective sensitivities to serum sodium change support the conclusion that patients' improved mental functioning as measured by the surveys is a real and direct response to the tolvaptan-mediated improvements in serum sodium concentration.

3.3.1.5 Analysis of KCCQ

Additional evidence from patient-reported outcome data of the disease burden associated with heart failure was observed with the KCCQ, which is a validated instrument specific for heart failure. The KCCQ results in the tolvaptan phase 3 heart failure study (156-03-236) suggested an additional disease burden at baseline in patients with hyponatremia

beyond that seen in the general population of acutely decompensated heart failure patients. The baseline scores of patients with hyponatremia, particularly of those with serum sodium concentration < 130 mEq/L, were lower than the overall population. Numeric trends of improvements were observed in all patients with CHF, but the largest numeric differences between tolvaptan and placebo patients were observed in those patients with hyponatremia, with the largest differences occurring in the Quality of Life and Social Limitation domains ([Appendix 1, Table 1](#)). However, there were not sufficient numbers of patients to detect a significant treatment effect.

3.3.2 Clinical Effects in Hypervolemic Hyponatremia

In patients with hypervolemic hyponatremia associated with disease states such as heart failure or liver cirrhosis, hyponatremia is associated with fluid overload and accompanying symptoms, eg, dyspnea in patients with heart failure. The aquaretic effects of tolvaptan may correct fluid overload and permit more effective treatment when added to standard therapy.

Evidence from the development program of tolvaptan includes data relating to the effects of managing hyponatremia on associated symptoms and outcomes in patients with fluid overload. The results are based on clinical studies involving over 700 patients with heart failure and hyponatremia and over 150 patients with cirrhosis and hyponatremia. For patients with heart failure, improvements were shown in:

- Fluid balance and body weight,
- Requirement for fluid restriction,
- Dyspnea,
- Fatigue,
- Length of hospital stay, and
- Morbidity/mortality (risk of CV events).

For patients with cirrhosis, improvements were shown in body weight and fatigue.

The correction of hyponatremia in patients with edematous states, such as cirrhosis or worsening heart failure, can prove to be especially difficult. Treating the most pressing clinical condition, ie, fluid overload, may actually worsen the hyponatremia and contribute to adverse outcomes, particularly with diuretics commonly thought of as “saluretics” (diuretics that inhibit sodium reabsorption).¹⁰⁶ Diuretic-induced hyponatremia is a well-known complication of diuretic therapy and most likely results from impaired urinary diluting capacity, ie, blockade of sodium and chloride

reabsorption. Compounding the challenge of treating volume overload in hyponatremic patients is the fact that conventional diuretics have also been reported to be less effective in the setting of low plasma sodium.¹⁰⁶ In contrast, vasopressin receptor antagonists may be useful in the management of hypervolemic hyponatremia because they induce a proportionally greater free water excretion than electrolyte excretion.

The tolvaptan development program was designed to assess effects of therapy in patients with hypervolemic hyponatremia (irrespective of etiology) and, separately, in patients with worsening heart failure (including those with hyponatremia). Results presented in this section are drawn from both tolvaptan development programs and represent findings most relevant to the management of patients with hyponatremia and fluid overload.

3.3.2.1 Management of Fluid Overload in Patients with Heart Failure

Patients with hyponatremia and heart failure represented significant subgroups in the double-blind, placebo-controlled phase 3 hyponatremia (156-02-235, 156-03-238) and worsening heart failure (156-03-236) tolvaptan studies, comprising a total of 603 patients. Assessments relating to congestive symptoms and outcomes represented primary and secondary efficacy variables in both the hyponatremia and heart failure development programs. Pre-specified endpoints included, for example, measurement of fluid balance and health-related patient-reported outcomes in the hyponatremia studies,² and mortality/morbidity and patient-assessed dyspnea in the heart failure study.^{68,107} Analyses of these endpoints in subgroups of patients with baseline serum sodium <135 and <130 mEq/L were not pre-specified in the heart failure program, but are included as evidence of supportive efficacy.

3.3.2.1.1 Fluid Balance, Fluid Restriction, and Body Weight

The use of tolvaptan in patients with heart failure and hyponatremia was associated with improvements in clinically relevant parameters of fluid management, including fluid balance and body weight. The achievement of a net fluid loss is a primary objective in patients with heart failure and hyponatremia, particularly those with associated congestive symptoms. The collection of fluid intake and urine output in the phase 3 hyponatremia studies permitted calculation of fluid balance, demonstrating a statistically significant net additional loss (over SOC) of approximately 1 liter of fluid ([Figure 3.3.2.1.1-1](#)).

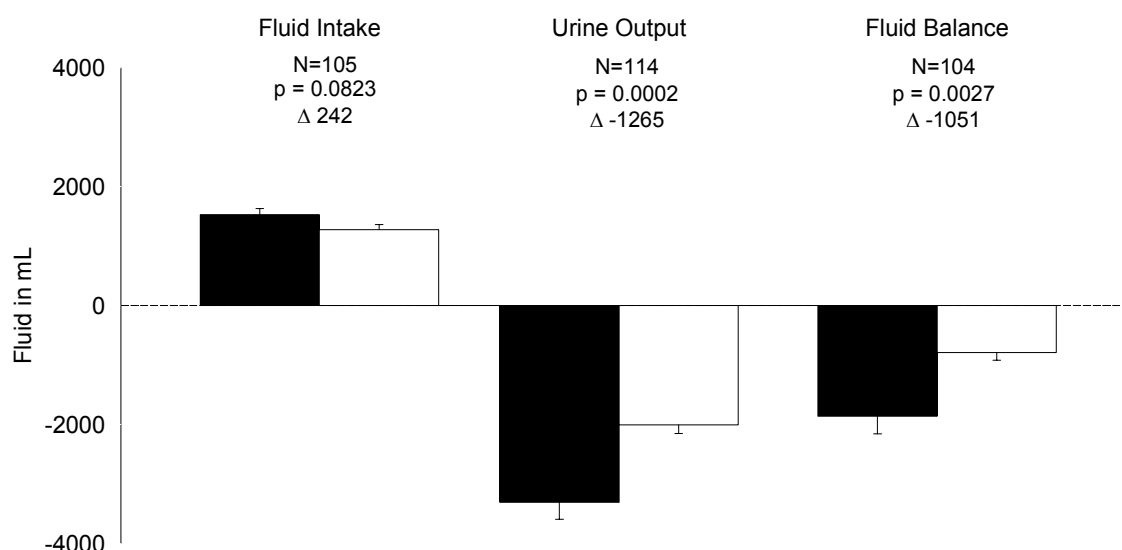


Figure 3.3.2.1.1-1 Fluid Balance (Mean ± SE) at 24 Hours in Patients with Hyponatremia and Heart Failure in the Pooled Placebo-controlled Phase 3 Hyponatremia Studies of Tolvaptan

A net fluid loss was achieved in the context of a statistically significant reduction in the proportion of patients prescribed fluid restriction. As discussed in [Section 3.2.2.7](#), statistically significantly fewer tolvaptan patients than placebo patients were prescribed fluid restriction in the overall population. A similar numerical reduction was observed in the subgroup of tolvaptan patients with heart failure, which did not achieve statistical significance likely because of small sample size ([Figure 3.3.2.1.1-2](#)). Difficulties in maintaining fluid restriction represent a common complaint from patients treated for heart failure, so reduction in the need for fluid restriction represents a potentially important improvement in patients' quality of life.

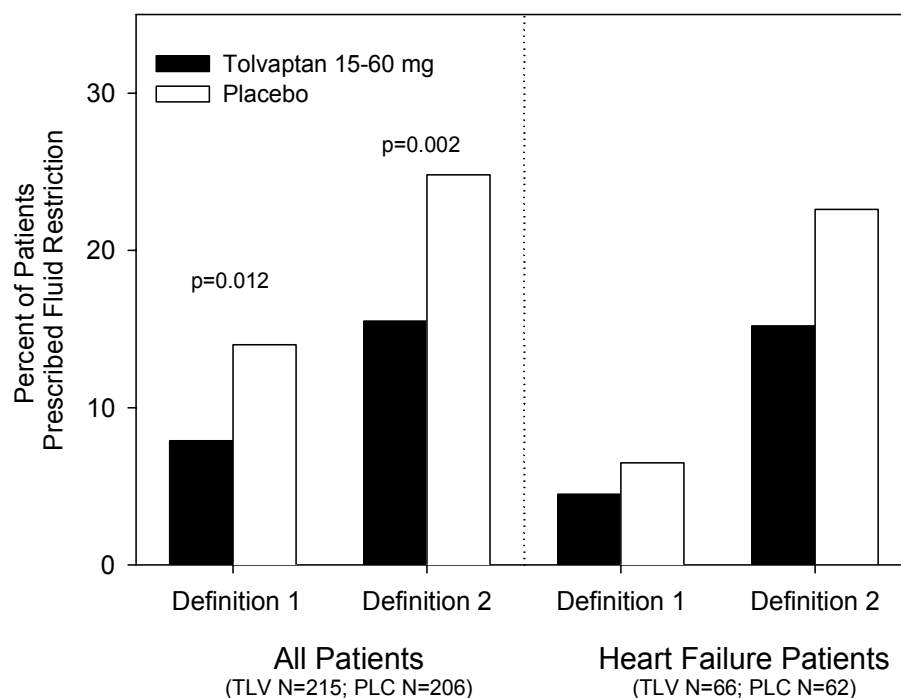


Figure 3.3.2.1.1-2 Fluid Restriction in All Patients with Hyponatremia and Heart Failure Subgroup in the Pooled Placebo-controlled Phase 3 Hyponatremia Studies of Tolvaptan

Definition 1: no fluid restriction at baseline but during double-blind study.

Definition 2: no fluid restriction at baseline but during double-blind study period or from baseline through double-blind study period.

The additional loss of approximately 1 liter of fluid most likely gave rise to the net additional loss in body weight observed among tolvaptan patients in the phase 3 studies. Increases in body weight are perhaps the most easily quantifiable and most commonly-measured indicator of progressive volume retention in heart failure patients. In the pivotal phase 3 study in worsening heart failure (156-03-236), change from baseline in body weight at Inpatient Day 1 and at Inpatient Day 7/discharge if earlier were key pre-specified secondary endpoints. Significant reductions in body weight in patients receiving tolvaptan plus SOC compared with patients receiving placebo plus SOC were demonstrated at both time points. At Inpatient Day 1, the mean change from baseline (LOCF) was -1.76 kg in the tolvaptan 30 mg group compared with -0.97 kg in the placebo group ($p < 0.0001$, 95% CI = -0.89 to -0.66). At Inpatient Day 7/discharge if earlier, the mean change from baseline was -3.56 kg in the tolvaptan 30 mg group compared with -2.76 kg in placebo group ($p < 0.0001$, 95% CI = -0.97 to -0.58). The results also significantly favored tolvaptan 30 mg over placebo on each of the other

inpatient days. Analyses of body weight by visit in the pivotal phase 3 study in worsening heart failure showed that the effects on body weight were sustained through much of the outpatient period.⁶⁸

Similarly, in the hyponatremic subgroup of the pivotal phase 3 study in worsening heart failure, at Inpatient Day 1, the mean change from baseline (LOCF) was -1.69 kg in the tolvaptan 30 mg group compared with -0.96 kg in the placebo group ($p < 0.0001$, 95% CI = -1.06 to -0.37). At Inpatient Day 7/discharge if earlier, the mean change from baseline was -3.47 kg in the tolvaptan 30 mg group compared with -2.63 kg in placebo group ($p = 0.0193$, 95% CI = -1.48 to -0.13 ; Figure 3.3.2.1.1-3). The results also significantly favored tolvaptan 30 mg over placebo on each of the other inpatient days.

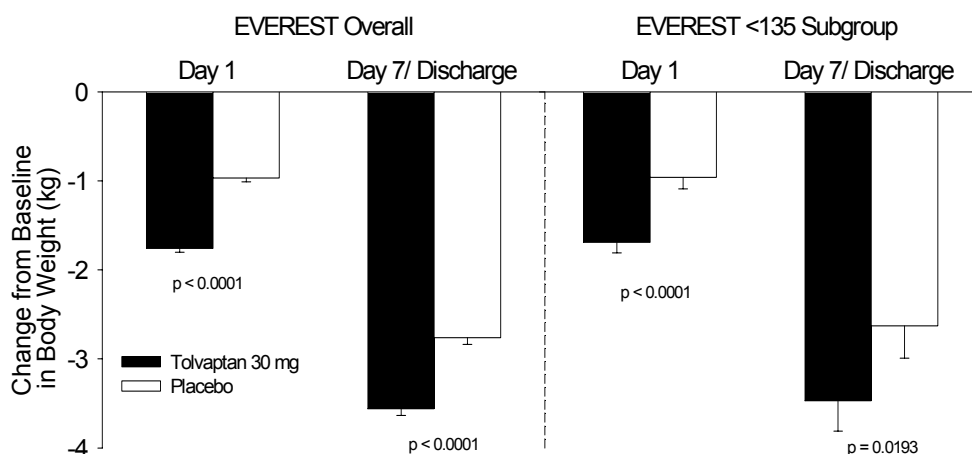


Figure 3.3.2.1.1-3 Mean (SE) Change in Body Weight at Inpatient Day 1 and Day 7/Discharge in Patients with Hyponatremia and Heart Failure in the Phase 3 Study of Tolvaptan in Worsening Heart Failure

EVEREST = study 156-03-236.

Analysis of mean change from baseline in body weight at Day 2 (24 hours post first-dose) was also a prespecified secondary endpoint in the pivotal phase 3 hyponatremia tolvaptan studies (156-02-235, 156-03-238). Statistically significantly greater mean decreases in body weight were observed in hypervolemic (CHF and cirrhosis, as prespecified) patients at Days 2, 3, and 4 for the tolvaptan group compared with the placebo group in the pooled analysis. On Day 2, the mean change from baseline was -1.08 kg in the tolvaptan group compared with -0.65 kg in the placebo group ($p=0.0033$); on Day 3 the change in the tolvaptan group was -1.17 kg compared to -0.05 kg in the placebo group ($p=0.0006$); and on Day 4 the change in tolvaptan patients was -0.58 kg compared to -0.06 kg in

placebo patients ($p=0.006$; p -values derived from Wilcoxon Rank Sum test to mitigate the influence of outliers in the data).

3.3.2.1.2 Patient-Assessed Dyspnea

Dyspnea is the most common symptom in patients hospitalized with worsening heart failure, and an urgent clinical treatment priority for both patients and clinicians.¹⁰⁸ As a source of tremendous fear and anxiety among patients, dyspnea is a symptom that compels patients to seek medical care.¹⁰⁹ In the tolvaptan program, patient-assessed dyspnea status at Day 1 was evaluated as a pre-specified key secondary efficacy endpoint in the pivotal phase 3 study in patients with worsening heart failure (156-03-236).⁶⁸ The majority of patients (approximately 90%) had frequent or continuous dyspnea at baseline, and in these patients, tolvaptan plus SOC, compared with placebo plus SOC, significantly improved patient-assessed dyspnea (1364/1835 [74.3%] versus 1243/1829 [68.0%], $p < 0.0001$; p -values are for the distribution of scores across 7 categories of improvement, no change, and worsening). Dyspnea improved regardless of the patients' baseline dyspnea status.

In the subset of patients with hyponatremia and dyspnea (frequent or continuous) at baseline, the significant improvement observed in the overall population was amplified, more than double in patients with hyponatremia (151/211 [71.6%] tolvaptan versus 115/198 [58.1%] placebo, $p < 0.0280$, [Figure 3.3.2.1.2-1](#)).

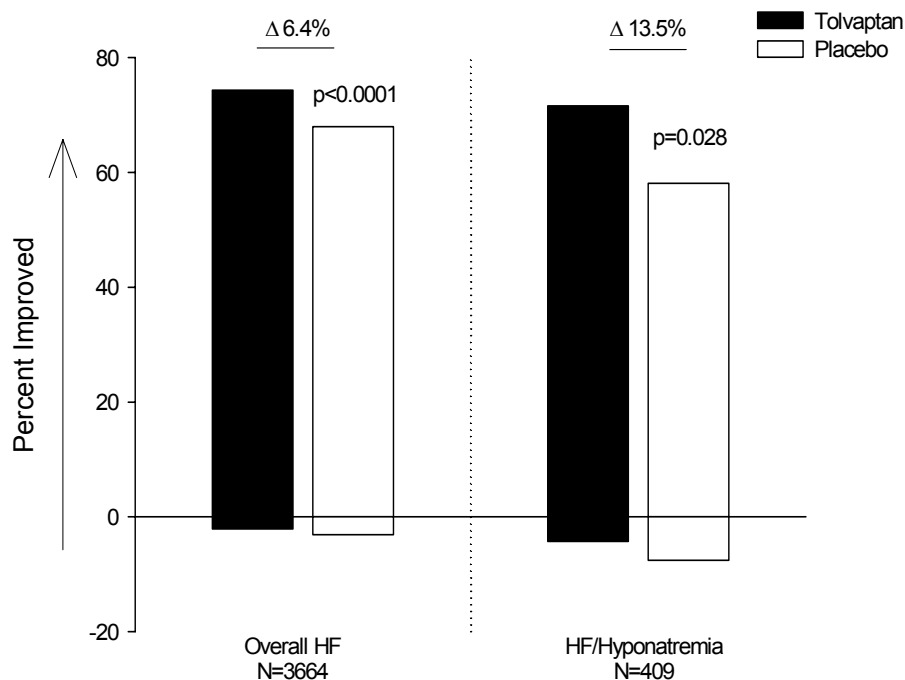


Figure 3.3.2.1.2-1 Patient-assessed Dyspnea Status at Inpatient Day 1 in Patients With Frequent or Continuous Dyspnea at Baseline - Overall and in the Hyponatremia Subgroup in the Phase 3 Study of Tolvaptan in Worsening Heart Failure

Note: Patients were asked “Compared to how much difficulty you were having with your breathing just before study drug was started, how is your breathing now?”

Typical “responder” analyses, ie, analyses of patients with “improvement,” often fail to give a complete picture of the range and distribution of responses for a particular outcome variable. Dyspnea--as a subjective sensation of “breathlessness”--can exist with varying degrees of severity, and, consequently, varying degrees of improvement. Depending on the instrument used to assess dyspnea, it may be possible to further characterize the proportions of patients experiencing various degrees of improvement or worsening to determine the distribution of effect of a particular intervention. In the phase 3 study in worsening heart failure, the improvement in dyspnea was measured using a subjective, patient-assessed instrument, consisting of seven different categories, with each of the categories of improvement showing an advantage associated with tolvaptan therapy in the overall population and further enhanced in the subpopulation of patients with hyponatremia (p = 0.028; [Figure 3.3.2.1.2-2](#)).

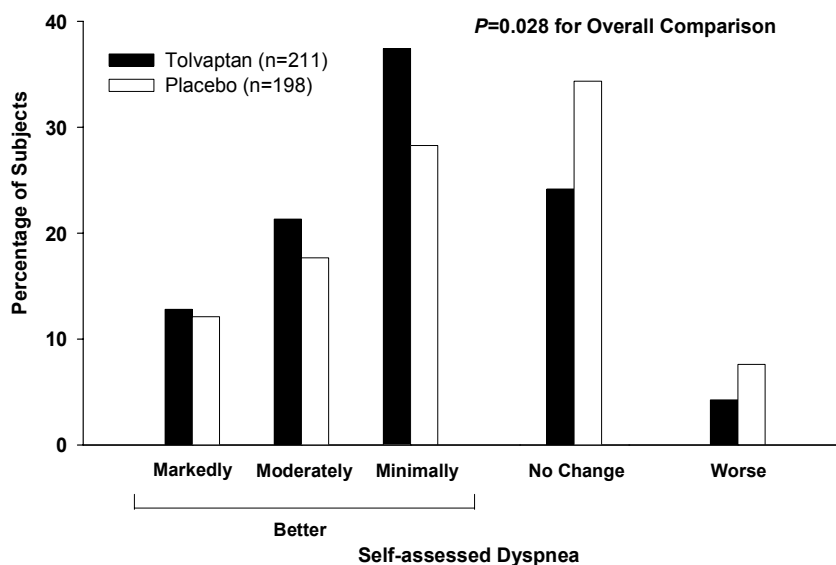


Figure 3.3.2.1.2-2 Distribution of Patient-assessed Dyspnea Status at Inpatient Day 1 in Patients With Frequent or Continuous Dyspnea at Baseline - Hyponatremia Subgroup of the Phase 3 Study of Tolvaptan in Worsening Heart Failure

Note: Patients were asked “Compared to how much difficulty you were having with your breathing just before study drug was started, how is your breathing now?”

Note: Worse includes minimally worse, moderately worse, and markedly worse.

Body weight remains a clinically relevant guide to fluid management therapy, forming the foundation of most patient management programs, and correlating strongly with other parameters of congestion. The relationship between improvements in dyspnea and reductions in body weight was evaluated post hoc in the phase 3 heart failure study in patients with worsening heart failure. In the overall population, a strong association ($p < 0.0001$) was observed between change in body weight and change in patient-assessed dyspnea, suggesting a strong association between reductions in body weight and improvements in patient-assessed dyspnea (Figure 3.3.2.1.2-3).

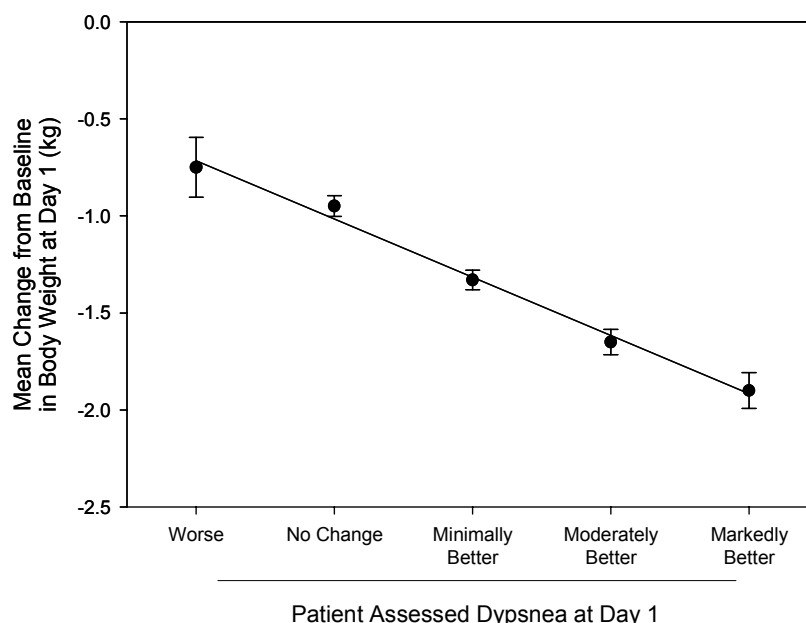


Figure 3.3.2.1.2-3 Association Between Patient-assessed Dyspnea Status and Mean (SE) Change From Baseline in Body Weight at Inpatient Day 1 in the Phase 3 Study of Tolvaptan in Worsening Heart Failure

Includes patients who recorded both patient-assessed dyspnea status and body weight change at Inpatient Day 1.

Note: Worse includes minimally worse, moderately worse, and markedly worse.

Note: For association between weight change and treatment: $p < 0.0001$ for dyspnea status adjusted from treatment; $p < 0.0001$ adjusted from dyspnea status; $p = 0.3008$ for dyspnea-treatment interaction.

In patients with hyponatremia and heart failure, the effects of managing hyponatremia with tolvaptan extend to improvement of symptoms such as dyspnea.

3.3.2.1.3 Physician-assessed Signs and Symptoms

Exploratory analyses of physician-assessed signs and symptoms (collected as CV assessments) were conducted in the pivotal phase 3 heart failure and hyponatremia tolvaptan studies. These data were analyzed only for symptoms which are broadly applicable to a particular subpopulation, ie, fatigue is relevant to overall populations, whereas, jugular venous pressure (JVP) and dyspnea are only relevant for heart failure or hypervolemic patients, and were therefore only analyzed for those subgroups.

The results of analyses of physician-assessed dyspnea in the pivotal phase 3 study in patients with worsening heart failure (156-03-236) were supportive of the pre-specified

endpoint (patient-assessed dyspnea at Inpatient Day 1, [Section 3.3.2.1.2](#)) and showed that the effects of tolvaptan on dyspnea may persist beyond Day 1.¹⁰⁷ Among the patients with frequent or continuous baseline dyspnea, the change in physician-assessed dyspnea numerically favored tolvaptan 30 mg over placebo on each inpatient day, and the differences were statistically significant, favoring tolvaptan over placebo on Inpatient Days 1 to 4. Physician-assessed dyspnea demonstrated improvements regardless of the patients' baseline dyspnea status.

Also in the phase 3 study in patients hospitalized for worsening heart failure, post hoc analyses demonstrated that treatment with tolvaptan was associated with statistically significant short-term improvement in several of the signs and symptoms of heart failure (including JVP, rales, fatigue, and orthopnea) as assessed by physicians during the inpatient period of the study.¹⁰⁷ However, in the smaller subset of patients with hyponatremia, no consistent effect was observed.

In the pivotal phase 3 hyponatremia studies of tolvaptan (156-02-235, 156-03-238), the results of analyses of physician-assessed signs and symptoms in hyponatremia showed improvements in dyspnea, orthopnea, JVP, and NYHA class for patients with heart failure and are included in [Appendix 1, Table 2](#) to [Appendix 1, Table 5](#), respectively. The analysis of fatigue, a symptom that may be observed in all patients with hyponatremia, showed improvements favoring tolvaptan especially through Day 4 of treatment in patients with hyponatremia and heart failure ([Figure 3.3.2.1.3-1](#)).

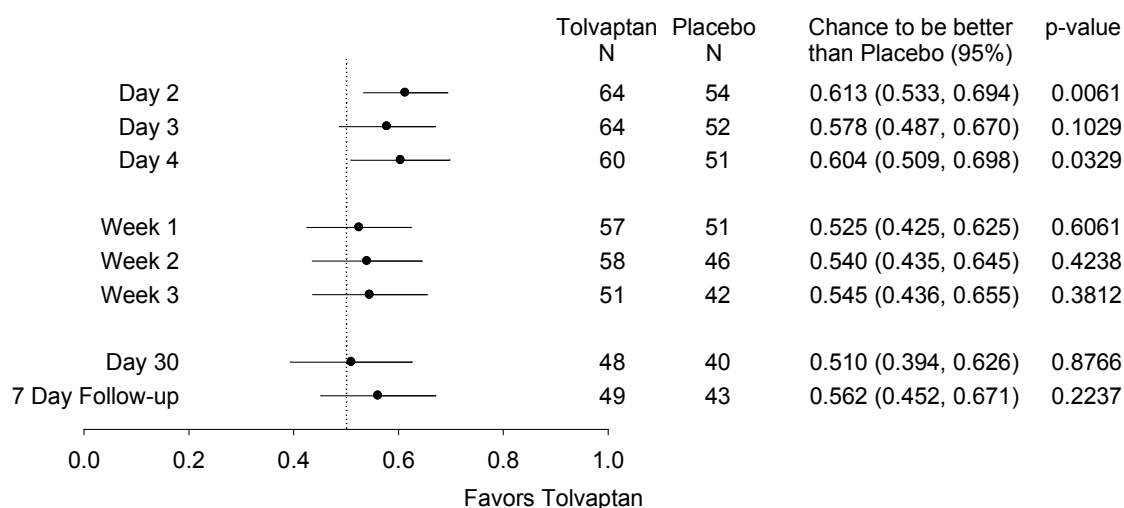


Figure 3.3.2.1.3-1 Change from Baseline (95% CI of Mean Ridit) in Fatigue in Heart Failure Patients in the Pooled Placebo-controlled Phase 3 Hyponatremia Studies of Tolvaptan

3.3.2.1.4 Length of Hospital Stay

In a retrospective chart review of 1046 patients with a principal discharge diagnosis of CHF conducted in 1996, the overall mean length of stay was 4.9 ± 0.9 days. In multivariate regression models, hyponatremia (sodium < 135 mEq/L) was one of several factors that were independently associated with a significantly longer length of stay. Bivariate analyses were conducted to examine the correlation between individual factors and length of stay. The mean length of stay among patients with hyponatremia was 5.68 ± 5.0 days; among patients without hyponatremia, the mean length of stay was 4.72 ± 4.0 days ($p < 0.0001$).²³

In the phase 3 study in worsening heart failure (156-03-236), an exploratory analysis of length of hospital stay (LOS) in patients with hyponatremia (< 135 mEq/L and < 130 mEq/L) suggested that tolvaptan patients had shorter initial hospitalization LOS than placebo patients (Table 3.3.2.1.4-1).

Table 3.3.2.1.4-1 Length of Initial Hospital Stay in Patients with Hyponatremia and Heart Failure in the Phase 3 Study of Tolvaptan in Worsening Heart Failure					
Baseline Sodium	Treatment Group^a	N	LS Mean Hospital Days^b	Mean Difference Days (95% CI)	p-Value^c
< 135 mEq/L	TLV 30 mg	225	9.77	-1.49	0.0887
	Placebo	216	11.26	(-3.195-0.226)	
< 130 mEq/L	TLV 30 mg	32	12.00	-0.78	0.7806
	Placebo	48	12.78	(-6.343-4.782)	

Study 156-03-236. LS = least squares; TLV=tolvaptan.

^a All study treatment was in addition to standard of care.

^b Length of initial hospital stay was calculated as number of days from randomization to discharge from initial hospitalization (subjects who died without a discharge record are treated as missing).

^c ANOVA model with factors of treatment and region was used for LS mean and p-value calculations.

3.3.2.1.5 Cardiovascular Mortality/morbidity

The relationship between hyponatremia and outcomes in patients with heart failure is well established.^{68,69} However, to date, no prospective, controlled study conducted in patients with hyponatremia has been powered to detect the effect of increasing serum sodium on outcomes. Analyses of all-cause mortality and the composite of CV mortality/hospitalization for heart failure were prespecified, co-primary endpoints in the tolvaptan phase 3 study in worsening heart failure. Overall, long-term treatment with tolvaptan 30 mg had no effect, either favorable or unfavorable, on all-cause mortality or the combined endpoint of CV mortality/hospitalization for worsening heart failure. The results demonstrated the noninferiority of tolvaptan treatment for mortality within the prespecified confidence limits.⁶⁸

However, in an exploratory analysis of patients with hyponatremia, using the cut-off of sodium <130 mEq/L, numeric improvements in all-cause mortality and in CV mortality/HF hospitalization were observed (Figure 3.3.2.1.5-1). For the composite endpoint of time to CV mortality/CV morbidity, the improvements reached statistical significance for the subset of patients with serum sodium < 130 mEq/L.

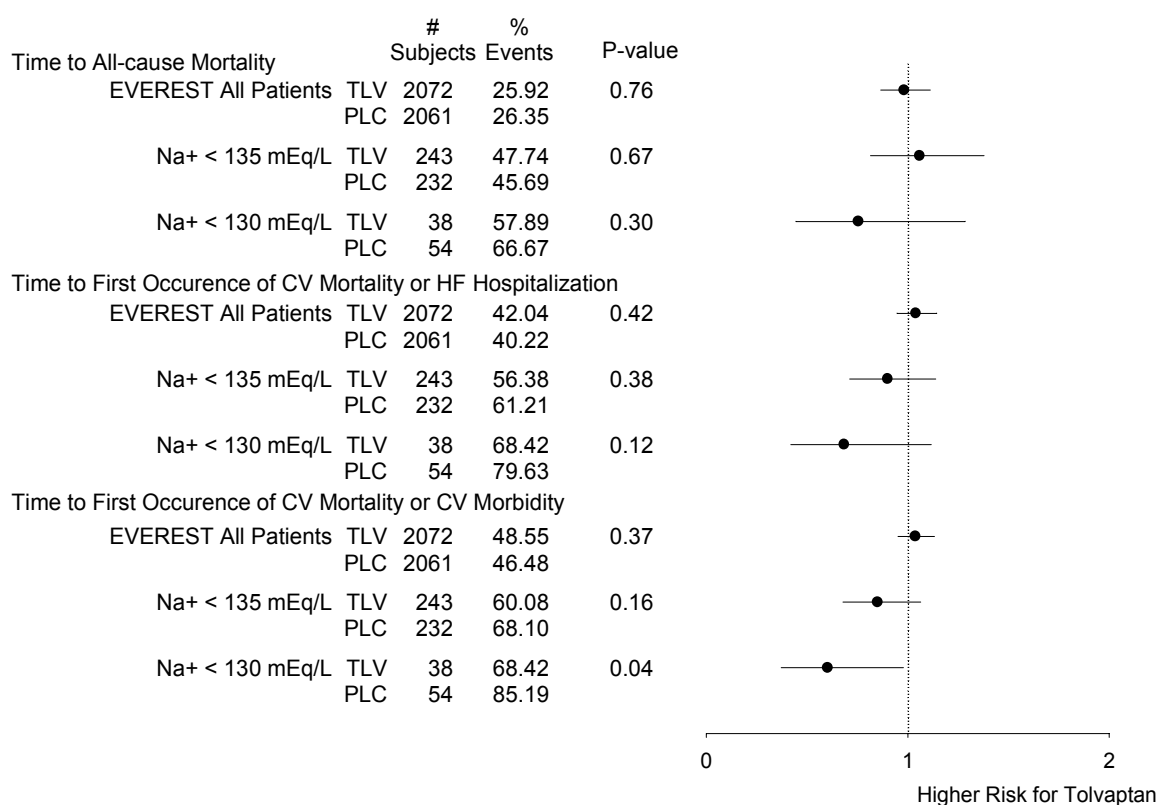


Figure 3.3.2.1.5-1 Time to All-Cause Mortality and Cardiovascular Mortality/Morbidity (HR; 95% CI) in All Heart Failure and Hyponatremia Heart Failure Patients in the Phase 3 Study of Tolvaptan in Worsening Heart Failure

P-values are based on log rank test. EVEREST = study 156-03-236; HF = heart failure; TLV = tolvaptan.

A Kaplan-Meier analysis of event-free survival in patients with serum sodium < 130 mEq/L suggested that the improvement may be observed as early as 2 months, albeit the analysis is based on relatively few patients (HR 0.603, 95% CI 0.372 - 0.979, p=0.0380, [Figure 3.3.2.1.5-2](#)).

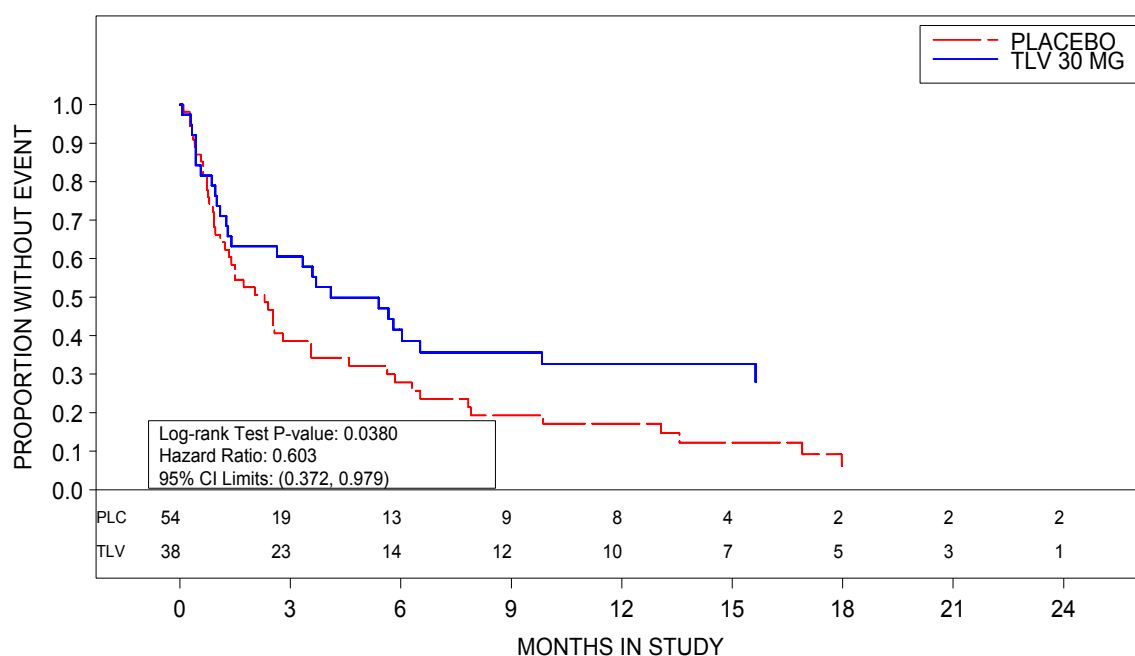


Figure 3.3.2.1.5-2 Kaplan Meier Curve of Time to Adjudicated Cardiovascular Mortality or Cardiovascular Hospitalization in Patients With Baseline Serum Sodium Concentrations < 130 mEq/L in the Phase 3 Study of Tolvaptan in Worsening Heart Failure

TLV = tolvaptan.

3.3.2.2 Management of Fluid Overload in Cirrhotic Patients

In patients with cirrhosis and hyponatremia, the effects on fluid overload were documented in the short term by changes in body weight supported by changes in fluid balance and fatigue. The overall impact on the patients' health was investigated by assessing quality of life.

Patients with hyponatremia and cirrhosis represented a significant subgroup in the double-blind, placebo-controlled phase 3 hyponatremia tolvaptan studies, comprising over 100 patients. Assessments relevant to congestive symptoms represented secondary efficacy variables in the tolvaptan hyponatremia development program. Pre-specified endpoints included measurement of fluid balance, body weight and health-related quality of life in the phase 3 hyponatremia studies.⁶⁸

3.3.2.2.1 Fluid Balance, Fluid Restriction and Body Weight

The use of tolvaptan in addition to SOC in patients with cirrhosis and hyponatremia was associated with improvements in clinically relevant parameters of fluid management,

including fluid balance and body weight. A statistically significant net additional loss of fluid (over SOC) was observed after 24 hours, although patients only received the 15-mg tolvaptan dose during the first day of dosing ([Figure 3.3.2.2.1-1](#)).

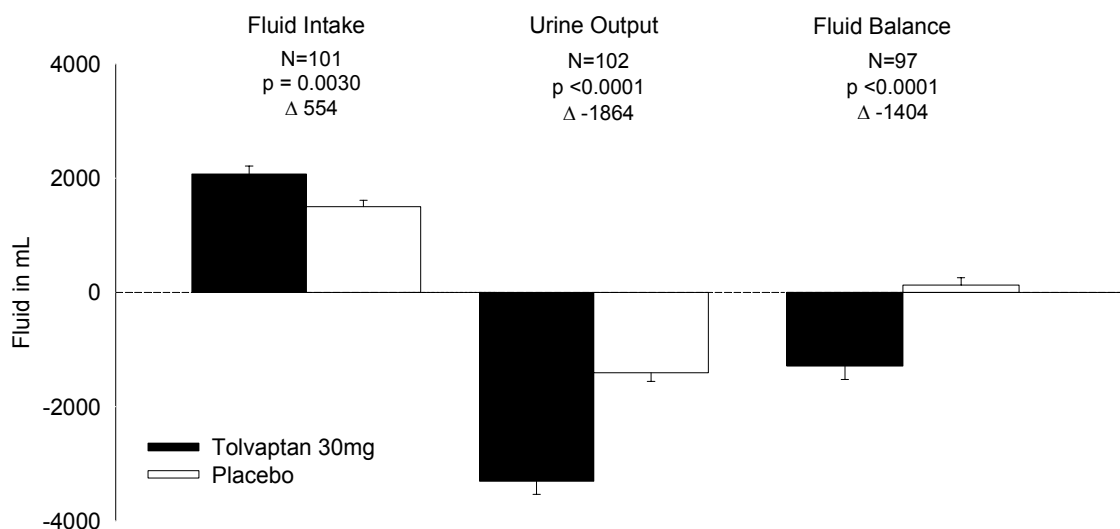


Figure 3.3.2.2.1-1 Fluid Balance in Patients with Cirrhosis From the Pooled Placebo-controlled Phase 3 Hyponatremia Studies of Tolvaptan

Many of the cirrhosis patients had fluid restriction imposed at baseline and maintained it during treatment or had fluid restriction imposed during treatment (definition 2). For cirrhosis patients, this represents 17/54 (31.5%) patients in the placebo group and 16/63 (25.4%) patients in the tolvaptan group. The percentage of patients requiring fluid restriction during double-blind treatment (definition 1) was 20.4% (11/54) in the placebo group and 15.9% (10/63) in the tolvaptan group. In general, use of fluid restriction was greatest in cirrhosis patients, regardless of treatment group. As a result of the small sample size, no statistically significant differences were observed between the tolvaptan and placebo treatment groups in the percentage of cirrhosis patients requiring fluid restriction, regardless of the definition used for fluid restriction ([Table 3.3.2.2.1-1](#)).

Table 3.3.2.2.1-1 Percentage of Patients with Cirrhosis Who Required Fluid Restriction in the Pooled Placebo-controlled Phase 3 Hyponatremia Studies of Tolvaptan (OC)					
	Tolvaptan		Placebo		P-Value^a
	N	n (%)	N	n (%)	
Definition 1	63	10 (15.9)	54	11 (20.4)	0.5199
Definition 2	63	16 (25.4)	54	17 (31.5)	0.4223

Includes studies 156-02-235 and 156-03-238.

Definition 1 = patients having no fluid restriction at baseline but for whom fluid restriction was imposed during the double-blind study period (excluding Day 30); Definition 2 = patients who had no baseline fluid restriction but a fluid restriction imposed during the double-blind study period, or patients who had fluid restriction imposed at baseline and maintained the fluid restriction (maybe at different levels) throughout the double-blind study period.

^aP-values were derived from the Cochran-Mantel-Haenszel test, stratified by study and baseline hyponatremia severity.

In hypervolemic patients with cirrhosis in the pooled analysis of phase 3 hyponatremia studies, the mean decreases from baseline in body weight at Day 2 (24 hours postdose) were small in both treatment groups, but still statistically significant for tolvaptan over placebo, with a difference of -0.24 kg ($p = 0.0116$). No other statistically significant differences between groups in body weight were seen.

3.3.2.2.2 Physician-assessed Signs and Symptoms

As described in [Section 3.3.2.1.3](#), exploratory analyses of physician-assessed signs and symptoms (collected as CV assessments) were conducted in the pivotal phase 3 hyponatremia tolvaptan studies. The only parameter from this assessment specifically relevant in patients with cirrhosis and hyponatremia, physician-assessed fatigue, was assessed post hoc in this subgroup of patients. The analysis of fatigue in patients with hyponatremia and cirrhosis showed improvements favoring tolvaptan throughout the treatment period, with significant improvements at some point points ([Figure 3.3.2.2.2-1](#)).

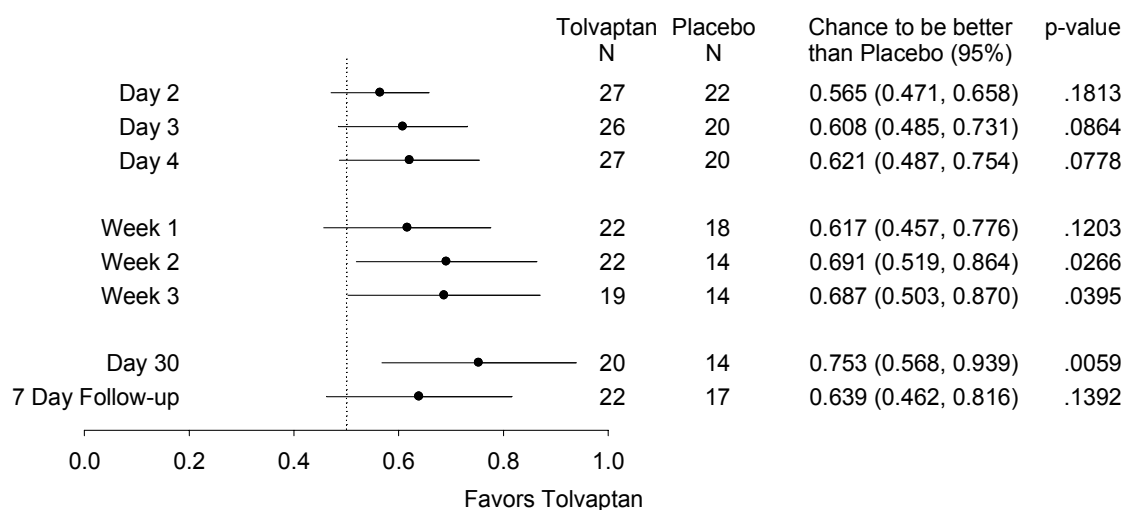


Figure 3.3.2.2.2-1 Change from Baseline (95% CI of Mean Ridit) in Fatigue in Cirrhosis Patients From the Pooled Placebo-controlled Phase 3 Hyponatremia Studies of Tolvaptan

4 Summary of Tolvaptan Safety

This section presents the sponsor's analysis of overall safety data available from the tolvaptan clinical development programs for hyponatremia and heart failure. Included are analyses based on all available safety data and details of AEs, clinical laboratory and electrocardiographic data from placebo-controlled studies. This section also includes analyses describing evidence in support of, or against, an effect of tolvaptan on the identified potential risks such as

- Potential risks associated with the antagonism of AVP V₂ receptors, ie, risks related to mode of action,¹¹⁰
- Analyses focusing on patients by baseline hyponatremia severity,
- Drug-drug interactions, and
- Electrophysiological properties of tolvaptan.

4.1 Exposure, Disposition and Demographics

The primary tolvaptan safety population consists of patients with a baseline diagnosis of hyponatremia or heart failure treated in any completed placebo-controlled phase 2 and 3 clinical study of tolvaptan. Additional analyses were performed separately on the hyponatremia (<135 mEq/L serum sodium) subpopulation.

Most patients in the primary safety population received total daily doses of tolvaptan ranging from 15-60 mg (N=3181 patients). Additionally, a small subset of patients received tolvaptan doses greater than 60 mg/day or less than 15 mg/day. Overall disposition and demographic characteristics were similar between treatment groups. The majority of patients in the primary safety population were male and Caucasian (approximately 70% and 80%, respectively). The mean age ranged across dose groups from 58.0 to 65.2 years ([Appendix 1, Table 6](#)).

Study completion rates in the primary safety population were 65.5% in tolvaptan patients and 64.1% in placebo patients. Discontinuation rates were similar for tolvaptan and placebo groups. In both treatment groups, discontinuations were most often due to AEs, death, or patient withdrawal of consent.

[Appendix 1, Table 7](#) summarizes the demographic and baseline characteristics for all hyponatremic patients, focusing on those tolvaptan dose groups with the largest populations (tolvaptan 30 mg and 15 to 60 mg), as well as all tolvaptan patients (any dose), and placebo patients. The tolvaptan 30 mg group was mostly composed of hyponatremia patients from the phase 3 worsening heart failure trial and the tolvaptan 15 to 60 mg dose group was composed of patients from the 2 placebo-controlled phase 3 hyponatremia studies. As in the primary population, the majority of patients were male (70%) and Caucasian (82%), with a mean age of 62 years. The majority of patients had baseline serum sodium 130-134 mEq/L (68.9% in the any tolvaptan dose group and 65.5% in the placebo group), and the remaining patients had baseline serum sodium < 130 mEq/L. CHF was the predominant underlying etiology (67.5% in the any tolvaptan dose group), and patients with cirrhosis and SIADH/other accounted for the remaining 33% of patients (approximately 16% each).

The extent of exposure for all patients enrolled in phase 1 -3 studies of tolvaptan is summarized in [Appendix 1, Table 8](#). Overall, a total of 4423 patients have been exposed to tolvaptan in 63 ongoing or completed clinical studies. Overall exposure in the primary safety population, as well as the all hyponatremia population is summarized in [Table 4.1-1](#).

Of the 1125 patients with hyponatremia included in this analysis, 607 received tolvaptan (any dose) and 518 received placebo ([Appendix 1, Table 9](#)). Over 10% of patients with hyponatremia were exposed for at least one year, and the maximal duration of exposure as of the October 2007 data cutoff was over 2 years in placebo-controlled studies. Only the heart failure subgroup of patients with hyponatremia had significant exposure greater

than 6 months and 1 year (128/410 and 67/410 in the tolvaptan group and 123/336 and 68/336 in the placebo group, respectively).

Table 4.1-1 Summary of Exposure in Heart Failure and Hyponatremia Patients From Multiple-dose Placebo-controlled Studies of Tolvaptan				
Parameter	Primary Safety Population		All Hyponatremia Patients	
	Any Tolvaptan Oral Dose	Placebo	Any Tolvaptan Oral Dose	Placebo
N	3294	2738	607	518
Patient days of drug exposure ^a	683036	656051	71,695	65,062
Patient years of drug exposure ^b	1870.1	1796.2	196.3	178.1
Long-Term Exposure n (%)				
≥ 180 days	1372 (41.7)	1400 (51.1)	132 (21.7)	125 (24.1)
≥ 360 days	817 (24.8)	798 (29.1)	69 (11.4)	69 (13.3)
≥ 720 days	72 (2.2)	94 (3.4)	6 (1.0)	10 (1.9)
Long-Term Exposure by Baseline Sodium n (%)				
Serum Sodium 130 -134 mEq/L				
N	--	--	418	340
≥ 180 days	--	--	111 (26.6)	103 (30.3)
≥ 360 days	--	--	56 (13.4)	56 (16.5)
Serum Sodium <130 mEq/L				
N			189	178
≥ 180 days	--	--	21 (11.1)	22 (12.4)
≥ 360 days	--	--	13 (6.9)	13 (7.3)

Primary safety population: studies 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.

Dose group assignment in study 156-97-204 is based on the patients' maintenance dose.

All hyponatremia patients: same as above, excluding 156-03-001. Hyponatremia patients from heart failure studies have baseline serum sodium < 135 mEq/L.

^aPatient days of drug exposure duration is computed based on the actual number of days of medication use (excluding days when dose was missed).

^bYears of drug exposure = Days of drug exposure/365.25.

4.2 Safety Overview in Hyponatremia Patients

This section presents an overview of the safety profile of tolvaptan observed in patients with hyponatremia including event rates from the primary safety population. It includes in each population, common AEs, deaths, SAEs and discontinuations due to AEs for all doses. In addition to an in-depth review of expected pharmacological effects of this therapeutic class, the potential risks associated with tolvaptan are also summarized.

4.2.1 Summary of Adverse Events

Approximately 89% of patients in the tolvaptan groups and 85% of patients in the placebo group of the primary safety population reported TEAEs across 1870.1 and 1796.2 exposure years, respectively (Table 4.2.1-1). Approximately half of all patients reported SAEs, with more events reported in the placebo group (47.2% tolvaptan versus 51.1% placebo). Discontinuations due to AEs were more common in the overall tolvaptan group (9.4% tolvaptan versus 7.1% placebo).

In the all hyponatremia patients population, the overall incidence of TEAEs was similar among patients exposed to any dose of tolvaptan (524/607, 86.3%) and patients exposed to placebo (441/518, 85.1%). The incidence of discontinuation of study medication due to AEs was slightly higher in the any-tolvaptan-dose group (74, 12.2%) as compared to the placebo group (52, 10.0%).

Table 4.2.1-1 Summary of Number of Patients with Treatment-emergent Adverse Events in Heart Failure and Hyponatremia Patients From Multiple-dose Placebo-controlled Studies of Tolvaptan

Parameter	Primary Safety Population		All Hyponatremia Patients	
	Any Tolvaptan Oral Dose (N = 3294)	Placebo (N = 2738)	Any Tolvaptan Oral Dose (N = 607)	Placebo (N = 518)
Patients with treatment-emergent adverse events, n (%)	2917 (88.6)	231 (84.6)	524 (86.3)	441 (85.1)
Patients with potentially drug-related treatment-emergent adverse events, n (%)	1609 (48.8)	840 (30.7)	275 (45.3)	166 (32.0)
Patients with serious treatment-emergent adverse events, n (%)	1555 (47.2)	1400 (51.1)	281 (46.3)	273 (52.7)
Patients discontinued study medication due to adverse events, n (%)	308 (9.4)	195 (7.1)	74 (12.2)	52 (10.0)

Primary safety population: studies 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.

Dose group assignment in study 156-97-204 is based on the patients' maintenance dose.

All hyponatremia patients: same as above, excluding 156-03-001. Hyponatremia patients from heart failure studies have baseline serum sodium < 135 mEq/L.

Patients treated with tolvaptan alone or in combination with other trial medication are counted once in the corresponding tolvaptan dose group. Patients treated with placebo alone, other trial medication or in combination of placebo and other trial medication are counted once in the placebo dose group.

4.2.1.1 Common Adverse Events

Commonly-reported AEs in the primary safety population and the all hyponatremia population (those occurring in at least 2% of patients and with an incidence of $\geq 1\%$ more than placebo) associated with tolvaptan are reported in [Table 4.2.1.1-1](#).

For the all hyponatremic patients population, events greater than 5% and occurring at least twice as often in the any-tolvaptan-dose group are consistent with the mechanism of action of the drug: thirst (85/607, 14.0% compared with 20/518, 3.9% in the placebo group), dry mouth (54/607, 8.9% compared with 17/518, 3.3% in the placebo group), and pollakiuria (33/607, 5.4% compared with 8/518, 1.5% in the placebo group).

Additional analyses of AE incidences by age, gender, race, concomitant medication use, and disease severity were performed for the primary safety population. Additional groupings by disease etiology and volume status were also assessed in all hyponatremia patients. The safety profile in any of these subgroups was not significantly different than the overall profile.

Table 4.2.1.1-1 Common TEAEs Reported in Greater Than or Equal to 2% of Patients Treated in Any Oral Tolvaptan Group (Regardless of Causality) and With an Incidence of Greater Than or Equal to 1% More Than Placebo by System Organ Class and MedDRA Preferred Term in All Heart Failure and Hyponatremia Patients From Multiple-dose Placebo-controlled Studies of Tolvaptan				
System Organ Class Preferred Term	Primary Safety Population		All Hyponatremia Patients	
	Any Tolvaptan Oral Dose (N = 3294) n (%)	Placebo (N = 2738) n (%)	Any Tolvaptan Oral Dose (N = 607) n (%)	Placebo (N = 518) n (%)
Reporting ≥ 1 event	2917 (88.6)	2316 (84.6)	524 (86.3)	441 (85.1)
Cardiac Disorders				
Cardiac arrest	50 (1.5)	28 (1.0)	14 (2.3)	6 (1.2)
Gastrointestinal Disorders				
Nausea	342 (10.4)	302 (11.0)	87 (14.3)	61 (11.8)
Dry mouth	312 (9.5)	67 (2.4)	54 (8.9)	17 (3.3)
Diarrhoea	237 (7.2)	205 (7.5)	51 (8.4)	37 (7.1)
Abdominal Pain	132 (4.0)	108 (3.9)	38 (6.3)	26 (5.0)
Dyspepsia	57 (1.7)	56 (2.0)	16 (2.6)	8 (1.5)
General Systems Disorders				
Thirst	597 (18.1)	74 (2.7)	85 (14.0)	20 (3.9)

Table 4.2.1.1-1 Common TEAEs Reported in Greater Than or Equal to 2% of Patients Treated in Any Oral Tolvaptan Group (Regardless of Causality) and With an Incidence of Greater Than or Equal to 1% More Than Placebo by System Organ Class and MedDRA Preferred Term in All Heart Failure and Hyponatremia Patients From Multiple-dose Placebo-controlled Studies of Tolvaptan				
System Organ Class Preferred Term	Primary Safety Population		All Hyponatremia Patients	
	Any Tolvaptan Oral Dose (N = 3294) n (%)	Placebo (N = 2738) n (%)	Any Tolvaptan Oral Dose (N = 607) n (%)	Placebo (N = 518) n (%)
Fatigue	203 (6.2)	118 (4.3)	36 (5.9)	32 (6.2)
Asthenia	118 (3.6)	111 (4.1)	34 (5.6)	19 (3.7)
Pyrexia	109 (3.3)	88 (3.2)	23 (3.8)	10 (1.9)
Oedema	56 (1.7)	31 (1.1)	20 (3.3)	12 (2.3)
Investigations				
Blood creatinine increased	115 (3.5)	79 (2.9)	20 (3.3)	12 (2.3)
Metabolism and Nutrition Disorders				
Hyperkalaemia	219 (6.6)	160 (5.8)	43 (7.1)	30 (5.8)
Dehydration	106 (3.2)	66 (2.4)	20 (3.3)	8 (1.5)
Anorexia	57 (1.7)	40 (1.5)	17 (2.8)	3 (0.6)
Diabetes mellitus	80 (2.4)	62 (2.3)	12 (2.0)	4 (0.8)
Nervous System Disorders				
Dizziness	299 (9.1)	225 (8.2)	59 (9.7)	43 (8.3)
Renal and Urinary Disorders				
Pollakiuria	203 (6.2)	35 (1.3)	33 (5.4)	8 (1.5)
Polyuria	108 (3.3)	17 (0.6)	14 (2.3)	2 (0.4)
Skin and Subcutaneous Tissue Disorders				
Ecchymosis	73 (2.2)	54 (2.0)	26 (4.3)	13 (2.5)
Pruritis	82 (2.5)	77 (2.8)	25 (4.1)	16 (3.1)

Primary safety population: studies 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.

Dose group assignment in study 156-97-204 is based on the patients' maintenance dose.

All hyponatremia patients: same as above, excluding 156-03-001. Hyponatremia patients from heart failure studies have baseline serum sodium < 135 mEq/L.

Patients are counted once, per term, for the most severe of multiple occurrences of a specific MedDRA preferred term.

4.2.1.2 Serious Adverse Events

Approximately 50% of patients reported SAEs; however, relatively few of these events were reported in 1% or more of patients receiving tolvaptan and with a greater incidence

than in patients receiving placebo (Table 4.2.1.2-1). The overall incidence of SAEs was higher in the placebo group.

Table 4.2.1.2-1 Treatment-emergent Serious Adverse Events With Incidence Greater Than or Equal to 1% in Any Tolvaptan Oral Dose Group (Regardless of Causality) and With Greater Incidence Than Placebo by System Organ Class and MedDRA Preferred Term in All Heart Failure and Hyponatremia Patients From Multiple-dose Placebo-controlled Studies of Tolvaptan				
System Organ Class MedDRA Preferred Term	Primary Safety Population		All Hyponatremia Patients	
	Any Tolvaptan Oral Dose (N = 3294) n (%)	Placebo (N = 2738) n (%)	Any Tolvaptan Oral Dose (N = 607) n (%)	Placebo (N = 518) n (%)
Reporting an Event	1555 (47.2)	1400 (51.1)	281 (46.3)	273 (52.7)
Cardiac Disorders				
Cardiac arrest	50 (1.5)	26 (0.9)	14 (2.3)	5 (1.0)
Cardiogenic shock	35 (1.1)	25 (0.9)	10 (1.6)	8 (1.5)
Ventricular fibrillation	26 (0.8)	25 (0.9)	8 (1.3)	2 (0.4)
Cardiac failure chronic	13 (0.4)	12 (0.4)	6 (1.0)	3 (0.6)
Gastrointestinal Disorders				
Ascites	11 (0.3)	3 (0.1)	7 (1.2)	2 (0.4)
General Disorders and Administration Site Conditions				
Sudden death	51 (1.5)	50 (1.8)	10 (1.6)	8 (1.5)
Sudden cardiac death	46 (1.4)	44 (1.6)	8 (1.3)	5 (1.0)
Infections and Infestations				
Sepsis	32 (1.0)	23 (0.8)	10 (1.6)	5 (1.0)
Metabolism and Nutrition Disorders				
Dehydration	41 (1.2)	27 (1.0)	11 (1.8)	4 (0.8)
Renal and Urinary Disorders				
Renal failure	55 (1.7)	59 (2.2)	10 (1.6)	8 (1.5)
Respiratory, Thoracic, and Mediastinal Disorders				
Respiratory failure	29 (0.9)	24 (0.9)	8 (1.3)	4 (0.8)

Primary safety population: studies 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.

Dose group assignment in study 156-97-204 is based on the patients' maintenance dose.

All hyponatremia patients: same as above, excluding 156-03-001. Hyponatremia patients from heart failure studies have baseline serum sodium < 135 mEq/L.

Patients are counted once, per term, for the most severe of multiple occurrences of a specific MedDRA preferred term.

4.2.1.3 Deaths

In all hyponatremia patients (N=1125), the percentages of patients with TEAEs leading to death were similar between the any-tolvaptan-dose (131/607, 21.6%) and placebo (108/518, 20.8%) groups (Appendix 1, Table 10). Nearly all of the deaths (103/131)

were reported from the phase 3 heart failure trial (156-03-236) conducted in patients hospitalized for worsening CHF; as such, most TEAEs leading to death resulted from the underlying CV disease. The TEAEs leading to death with an incidence of $\geq 1\%$ in the any-tolvaptan-dose group versus placebo included cardiac failure (5.1% versus 4.4%), congestive cardiac failure (3.8% versus 3.1%), cardiac arrest (1.8% versus 0.8%), sudden death (1.6% versus 1.5%), sudden cardiac death (1.3% versus 1.0%), and cardiogenic shock (1.0% versus 1.0%) (all reported as incidence on tolvaptan versus incidence on placebo).

In the 156-03-236 CV outcomes trial, 4133 patients were treated for a median duration of 9.9 months. Overall, long-term treatment with tolvaptan 30 mg had no effect, either favorable or unfavorable, on all-cause mortality or the combined endpoint of CV mortality or subsequent hospitalization for worsening heart failure. The results demonstrated the noninferiority of tolvaptan 30 mg treatment for mortality within the prespecified confidence limits (HR 0.98; 95% CI 0.87-1.11; [Figure 4.2.1.3-1](#)). All-cause mortality in the hyponatremia population of this trial is reported in [Section 3.3.2.1.5](#).

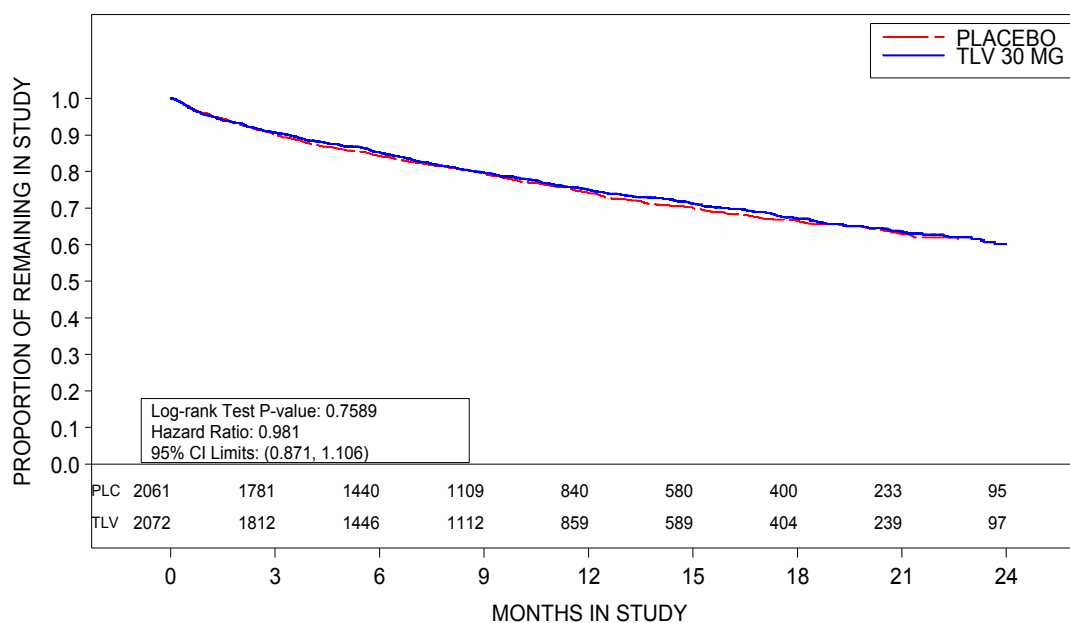


Figure 4.2.1.3-1 Time to All-cause Mortality (Kaplan-Meier Curve) in the Phase 3 Study of Tolvaptan in Worsening Heart Failure

4.2.1.4 Discontinuations Due to Adverse Events

In the hyponatremia population, the percentages of patients with TEAEs leading to discontinuation were similar between the any-tolvaptan-dose and placebo groups. A total of 74/607 (12.2%) patients in the any-tolvaptan-dose group and 52/518 (10.0%) in the placebo group experienced a TEAE which led to the discontinuation of trial medication. Events that occurred in at least 1% of patients in the any-tolvaptan-dose group and with greater incidence than placebo were cardiac failure and congestive cardiac failure. The incidence of cardiac failure was slightly higher in the any-tolvaptan-dose group compared with placebo (10, 1.6% in any-tolvaptan-dose group versus 2, 0.4% in the placebo group), and the incidence of congestive cardiac failure was the same for both treatment groups (7, 1.2% in any-tolvaptan-dose group versus 6, 1.2% in the placebo group).

4.2.2 Risks Related to Antagonism of V2 Vasopressin Receptors

4.2.2.1 Variables Related to Aquaresis (Increases in Serum Sodium Concentrations, Serum Osmolality, and Dehydration)

4.2.2.1.1 Serum Sodium

Vaptans promote aquaresis (excretion of electrolyte-free water) by inhibiting insertion of the aquaporin 2 water channel in the luminal surface of the renal collecting duct. By preventing these cells from reabsorbing filtered free water, they necessarily increase the serum sodium concentration and serum osmolality, and decrease intravascular, extravascular and intracellular water at a rate proportional to effective renal perfusion and filtration. Besides the desired correction of excess body fluid and serum sodium concentration, a number of adverse consequences of this action were anticipated; therefore, the following variables were examined:

- Overly rapid increases in serum sodium concentration (≥ 12 mEq/L/24 hours) and the potentially associated clinical symptoms (ie, risk of neurological complications due to the shift in osmolality in the brain).
- Frequency of increase in serum sodium concentration above the upper limit of the normal range (>145 mEq/L and >160 mEq/L) and/or reported as AEs.
- Thirst, hypovolemia (expressed by hypotensive-related events) and dehydration (as a possible consequence).

4.2.2.1.1.1 Overly-rapid Correction of Serum Sodium

In the pivotal hyponatremia studies (156-02-235 and 156-03-238), where doses were started at tolvaptan 15 mg QD with possible titration up to 60 mg QD, 7/222 (3.2%) patients in the tolvaptan group exceeded the desirable rates of correction of 12 mEq/L/24 hours or 8 mEq/L/initial 8 hours, compared to 0/220 for placebo. The maximal rates of correction during tolvaptan treatment were 17 mEq/L in approximately 27 hours in 156-02-235 and 14 mEq/L in approximately 25 hours in 156-03-238.

In the hyponatremia subgroup of the phase 3 worsening heart failure study (156-03-236), where patients were randomized to tolvaptan 30 mg QD or placebo QD, 20/226 (8.8%) tolvaptan patients exceeded the desirable rates of correction of > 1 mEq/L/hr by Day 1 versus 5/223 (2.2%) in the placebo group. In patients with normal sodium at baseline (between 135-145 mEq/L), 75/1558 (4.8%) tolvaptan patients exceeded the desired rate of correction versus 9/1561 (0.6%) in the placebo group.

A review of clinical symptoms observed in the patients revealed no evidence of osmotic demyelination syndrome or permanent neurological sequelae as a result of the overly rapid correction.

4.2.2.1.1.2 Hypernatremia

Hypernatremia was reported at a 4-fold higher rate for tolvaptan patients compared to placebo in the primary safety population (1.8% tolvaptan versus 0.4% placebo) but at nearly equal frequency in hyponatremia patients (0.7% versus 0.6%). This population difference is likely due to the fact that, by definition, hyponatremia patients had serum sodium <135 mEq/L at baseline, and, therefore, excursions into the supranormal range were rare and typically mild. None of the AEs of hypernatremia were reported as serious in the all hyponatremia patient population, and only one patient discontinued study medication due to hypernatremia.

4.2.2.1.2 Dehydration and Hypotension-related Events

Tolvaptan produces a marked secretion of free water, resulting in a number of physiologic consequences, eg, thirst, polyuria, and dehydration. As expected, the aggregate incidences of thirst and dry mouth were greater for tolvaptan compared to placebo (14.0% and 8.9%, respectively, for hyponatremia patients receiving tolvaptan compared to 3.9% and 3.3%, respectively, for those receiving placebo). Similarly, pollakiuria, polyuria, and dehydration were observed more frequently in tolvaptan patients compared to placebo. Importantly, these events were mild to moderate in nature and generally did not lead to discontinuation of treatment.

In the hyponatremia population, hypotension was reported by 56/607 (9.2%) hyponatremia patients compared to 61/518 (11.8%) placebo patients. Blood pressure decreased was reported by 2/607 (0.3%) hyponatremia patients compared to 1/518 (0.2%) placebo patients. The results indicate that blood pressure is not adversely affected by tolvaptan therapy.

4.2.2.2 Variables Related to Renal Water Clearance and Volume Contraction

Since the vaptans' primary site of action is the kidney, increased renal water clearance and concomitant volume contraction may affect renal function, especially if a vaptan is given to patients at risk, ie, patients with underlying renal disease, cirrhotic ascites or CHF, or in combination with diuretics which might promote pre-renal azotemia. Therefore, the following variables were examined:

- Renal function parameters using specific indicators of renal impairment;
- AE reports of renal impairment using a grouped term approach with the Medical Dictionary for Regulatory Activities (MedDRA) (eg, renal failure or oliguria).

AEs related to decreased renal function/renal failure were assessed in the primary safety population, as well as the all hyponatremia patient population. AEs in this category pertain to symptoms of decreased urine output, presence of protein in urine, changes in serum chemistry (uric acid, creatinine, electrolytes) and renal failure. The aggregate incidence rate in this category for all patients was 24.9% (821/3294) for all tolvaptan patients and 24.3% (664/2738) for placebo patients. The incidence rates for terms related to decreases in urine output (oliguria, anuria, decreased urine output, decreased urine flow) or fluid overload were low and similar for tolvaptan and placebo in both populations.

Analysis of protein (albuminuria, proteinuria, protein urine, protein urine present) or presence of red blood cells (hematuria, hemoglobinuria, red blood cells in urine) demonstrated similar and low incidence rates for tolvaptan and placebo.

The incidences of “blood urea increased” for tolvaptan compared to placebo were 2.6% and 2.6%, respectively, in the primary safety population, and were similar in the all hyponatremia patient population (2.1% versus 1.7%). The incidence of azotemia was lower for tolvaptan (0.7%) compared with placebo (0.9%) in the primary safety population. For the all hyponatremia patient population, the incidence rates were 1.0% and 0.8% for tolvaptan and placebo, respectively.

The incidences of “blood creatinine increased” for tolvaptan compared with placebo were similar across all analysis groups (primary safety population 3.5% versus 2.9%; all hyponatremia patients 3.3% versus 2.3%). The mean change from baseline in serum creatinine was 0.06 mg/dL in the tolvaptan group compared with 0.02 mg/dL for placebo group in the all hyponatremia patient population.

The combined incidences for renal failure overall for all tolvaptan doses versus placebo, respectively, were as follows: primary safety population, 9.3% and 11.1%; all hyponatremia patients, 9.0% and 9.2%.

Tolvaptan use was not associated with decreases in urine output/fluid overload, proteinuria, elevated blood urea or increased rates of renal failure. However, tolvaptan is associated with small increases in serum creatinine concentrations that were observed in the pooled population of patients with hyponatremia in multiple-dose studies. The

magnitude of the increase in creatinine is relatively consistent (mean increase over placebo < 0.1 mg/dL) and does not change markedly with duration of treatment or worsen at any specific time point. The increase was not associated with increases in AEs associated with renal function (renal failure, acute renal failure, chronic renal failure) or increased all-cause mortality. Tolvaptan was also associated with reduction in blood urea nitrogen concentrations. The overall incidence of AEs appears to be comparable, specifically in AEs relating to decreased renal function. In a single-dose study focusing on the effects of tolvaptan on renal function, tolvaptan had no adverse effects on renal hemodynamics in patients with mild to moderate heart failure.¹¹¹

4.2.2.3 Variables Related to Electrolyte Disturbances, Including Hyperkalemia

AEs related to tolvaptan's effects on sodium and other electrolytes were also analyzed as potential events related to tolvaptan's mechanism of action. Disturbances in electrolyte balance have been associated with diuretic therapy, which is commonly prescribed in patients with heart failure. However, there were no depleting effects on electrolytes (potassium, magnesium, and calcium) with tolvaptan treatment in conjunction with SOC (including loop diuretics). Regarding other electrolytes analyzed (potassium, magnesium, and calcium), generally no appreciable changes were observed between treatment groups.

4.2.2.3.1 Variables Related to Hyperkalemia

In the context of a potential change in renal function and the administration of drugs known to increase serum potassium (eg, spironolactone, ACE [angiotensin-converting enzyme] inhibitors), there is a risk of hyperkalemia. In addition, the antinatriuretic and kaliuretic effects of aldosterone are augmented by vasopressin. As a consequence, vasopressin, which acts primarily to regulate water balance, is also an antinatriuretic and kaliuretic hormone.^{110,112} Blocking the V₂ receptor with a vaptan may therefore result in natriuretic and antikaliuretic effects. Therefore, the following variables were examined:

- Serum potassium concentration (defined as ≥ 5.5 mEq/L).
- AE reports of hyperkalemia using a grouped MedDRA term approach (eg, increased kalemia).

AEs related to potential effects on potassium were analyzed in the primary safety population. The aggregate incidence rate for this category was similar for the tolvaptan and placebo groups: 11.0% (362/3294) for any tolvaptan dose versus 10.4% (284/2738) for placebo.

Of the aggregate terms used in the analysis, hyperkalaemia was the potassium-related AE with the highest incidence rate and was reported at a slightly higher rate for tolvaptan patients compared with placebo patients, respectively, for each analysis group (primary safety population, 6.6%, 219/3294 versus 5.8%, 160/2738; all hyponatremia patient population, 7.1%, 43/607 versus 5.8%, 30/518). The AE of muscle spasms was also reported by greater than 2% of tolvaptan and placebo patients in each analysis group; however, for each of the populations, the incidence rate was greater for the placebo group than the tolvaptan group. All other AEs included in this grouping were reported by less than 2% of tolvaptan and placebo patients in each analysis groups. Among these, spastic neuromuscular events which might be associated with hyperkalemia were all nearly equal or less frequent in the tolvaptan group.

In the hyponatremia population, the incidence of potentially clinically significant abnormal increases in serum potassium concentrations was slightly higher in the tolvaptan group (94/542, 17.3%) than in the placebo group (73/467, 15.6%). During the course of treatment, the minimum and maximum serum potassium concentrations in the total tolvaptan group were 2.1 mEq/L and 7.6 mEq/L, respectively, and the mean change from baseline was 0.08 mEq/L (range, -3.6 to 3.3 mEq/L). In the placebo group, the minimum and maximum serum potassium concentrations were 2.4 mEq/L and 7.3 mEq/L, respectively, and the mean change from baseline was 0.05 mEq/L (range, -4.5 to 3.4 mEq/L).

In well-controlled phase 1 and 2 studies where urinary potassium excretion was carefully measured, no effects of tolvaptan treatment were noted in contrast to the effects of furosemide or thiazide use.

A more in-depth analysis of TEAEs and concomitant drug use in patients with events related to potassium changes was performed and is presented in [Table 4.2.2.3-1](#). Event rates of hyperkalemia were higher in patients taking potassium supplementation or potassium-sparing diuretics, particularly in patients with an estimated baseline GFR ≤ 60 mL/min. In both these groups, incidences in tolvaptan patients were higher than in placebo patients. While a numerically higher incidence of TEAEs related to potassium increase was seen in the tolvaptan group, no associated increase in arrhythmia events was observed in these patients.

Table 4.2.2.3-1 Incidence of Adverse Events Related to Potassium and the Effects of Concomitant Drug Use and Renal Impairment in the Primary Safety Population of Tolvaptan				
Category	Included MedDRA Preferred Terms	N Tolvaptan/ N Placebo	Any Oral Tolvaptan n (%)	Placebo n (%)
Adverse Events Related to Potassium				
Hyperkalemia	Increased Blood Potassium; Hyperkalemia	3294/2738	223 (6.7)	149 (5.4)
Hypokalemia	Decreased Blood Potassium; Hypokalemia	3294/2738	174 (5.2)	191 (7.0)
Hyperkalemia and Hypokalemia	Increased Blood Potassium; Hyperkalemia; Decreased Blood Potassium; Hypokalemia	3294/2738	44 (1.3)	35 (1.3)
Potassium TEAEs and Arrhythmia				
Hyperkalemia with Arrhythmia	Increased Blood Potassium; Hyperkalemia; Arrhythmia SMQ	223/149	64 (28.7)	60 (40.3)
Hypokalemia with Arrhythmia	Decreased Blood Potassium; Hypokalemia; Arrhythmia SMQ	174/194	87 (50.0)	85 (44.5)
Hyperkalemia, Hypokalemia with Arrhythmia	Increased Blood Potassium; Hyperkalemia; Decreased Blood Potassium; Hypokalemia; Arrhythmia SMQ	44/35	18 (40.9)	14 (40.0)
Arrhythmia only	Arrhythmia SMQ	2853/2363	557 (19.5)	492 (20.8)
Concomitant Potassium Supplement or Potassium-sparing Diuretic use				
Hyperkalemia Overall	Increased Blood Potassium; Hyperkalemia	897/838	111 (12.4)	80 (9.5)
Hyperkalemia in patients with a baseline GFR ≤60 mL/min	Increased Blood Potassium; Hyperkalemia	353/358	66 (18.7)	49 (13.6)

SMQ=Standardized MedDRA Query.

Primary safety population: studies 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.

Dose group assignment in study 156-97-204 is based on the patients' maintenance dose.

Analyses of laboratory and clinical AE data suggest that while there is little effect of tolvaptan on renal potassium clearance, a tendency toward elevation of serum potassium concentrations exists for some patients, as reflected by increased reports of AEs of hyperkalemia. The exact mechanisms whereby this elevation might occur in a particular patient are not clear, but differences appeared consistent across indications of heart failure and hyponatremia and between etiologies and severity of hyponatremia. Despite these

modest differences, there appear to be no signals for relevant, commonly-associated consequences of hyperkalemia.

4.2.2.4 Hemostatic Disorders

Vasopressin may affect blood coagulation via V_2 receptor agonist activity resulting in an increase in plasma tissue plasminogen activator, factor VIII and von Willebrand factor. Vasopressin may also promote platelet aggregation through the V_{1a} receptor. Inhibition of V_2 receptor activity, or reflex increases in AVP could result in disorders of hemostasis. Arguing against these potential effects are studies in patients with nephrogenic diabetes insipidus who have inactivating mutations of the V_2 vasopressin receptor and no clinical evidence of coagulopathy and clinical studies indicating no significant effect of AVP infusion. Even so, in order to evaluate the potential for hemostatic disorders, the grouping of AEs related to bleeding events (eg, any bleeding or hemorrhage or ecchymosis) was examined.¹¹³

In order to evaluate potential effects of V_2 antagonism related to circulating von Willebrand factor, AEs associated with increased bleeding and hemostatic disorders were analyzed. Ecchymosis and haematuria were reported more frequently than other AEs in this category; however, differences between the any tolvaptan and placebo groups were similar for ecchymosis (primary safety population, 2.2% versus 2.0%; all hyponatremia patients, 4.3% versus 2.5%) and hematuria (primary safety population, 2.1% versus 1.9%; all hyponatremia patients, < 2.0% in both treatment groups). Therefore, tolvaptan does not appear to be associated with increased bleeding or coagulation/hemostatic disorders.

In the primary safety population, the incidence of cerebrovascular AEs (11 MedDRA terms related to stroke) was 2.0% for patients receiving tolvaptan (N = 3294) versus 1.9% for patients receiving placebo (N = 2738). For the all hyponatremia patients population, the incidence of cerebrovascular AEs for the any-oral-dose-tolvaptan group was 1.3% (8/607) compared with placebo 0.8% (4/518).

4.2.2.5 Neurological Effects

Alterations in sodium concentration may affect neurological function resulting in an array of symptoms, eg, lethargy, apathy, disorientation, muscle cramps, anorexia, nausea, and agitation. Physical signs of hyponatremia can include abnormal sensorium, decreased reflexes, seizures, and coma. Correction of hyponatremia has been found to improve cognitive function, suggesting that presumably “asymptomatic” hyponatremia may be subclinically symptomatic;⁶¹ therefore an evaluation of neurological AEs was performed

in the tolvaptan program. The aggregate incidence rate for AEs related to neurological disturbances for the primary safety population was 16.5% for any oral tolvaptan dose versus 17.1% for placebo, with headache, confusional state, depression, and syncope being the most common (reported in >2% of patients). In the all hyponatremia patient population, these events were examined for differences among hyponatremia etiology and hyponatremia severity. Confusional state was most often reported in patients with CHF or cirrhosis etiologies. The severity of hyponatremia had an unexpected contrary association on the incidence of confusional state and its distribution among treatment groups: For tolvaptan and placebo patients, reports of the AE of confusional state were less frequent in the patient subgroup by baseline sodium < 130 mEq/L than the subgroup by baseline sodium 130-134 mEq/L.

No evidence for trends in any significant neurological consequences of tolvaptan treatment were detected. The incidence of seizures and other extreme symptoms sometimes associated with hyponatremia or its treatment were low. There were no reports of central pontine or peripheral myelinolysis.

4.2.2.6 Glucose Metabolism

AVP-mediated effects on glycogenolysis and gluconeogenesis have been demonstrated in ex-vivo and in-vivo animal models. Disturbances in glucose homeostasis have been reported in the clinical program for conivaptan, a non-selective vasopressin antagonist, but attributed to glucose-containing vehicle during its infusion. Therefore the potential impact of tolvaptan on glucose control was evaluated.^{114,115,116,117}

In the primary safety population, the aggregate incidence for events related to increases in glucose (eg, hyperglycemia and diabetes mellitus) was 10.4% for tolvaptan compared to 9.4% for placebo. The aggregate incidence for events related to decreases in glucose (eg, hypoglycemia) was 3.6% for tolvaptan versus 3.1% placebo. Hyperglycemia was reported more frequently in hyponatremia patients receiving tolvaptan (3.8%) compared to placebo (3.1%), as was diabetes mellitus, reported in 2.0% of tolvaptan patients compared to 0.8% of placebo patients. These events were generally mild to moderate in severity, and no hyponatremia patients discontinued for glucose-related events.

Analysis of incidences by etiology (CHF, cirrhosis, and SIADH/other, respectively) within the all hyponatremia population gave the following rates of glucose-related AEs for any oral dose tolvaptan versus placebo (Table 4.2.2.6-1).

Table 4.2.2.6-1 Frequency of Glucose-related TEAEs in Hyponatremia Patients						
MedDRA Term	CHF		Cirrhosis		SIADH/Other	
	Tolvaptan (N=410) n(%)	Placebo (N=336) n(%)	Tolvaptan (N=100) n(%)	Placebo (N=83) n(%)	Tolvaptan (N=97) n(%)	Placebo (N=99) n(%)
Hyperglycaemia	14 (3.4)	15 (4.5)	5 (5.0)	1 (1.2)	4 (4.1)	0 (0.0)
Diabetes mellitus	9 (2.2)	4 (1.2)	2 (2.0)	0 (0.0)	1 (1.0)	0 (0.0)
Hypoglycaemia	21 (5.1)	13 (3.9)	1 (1.0)	0 (0.0)	0 (0.0)	1 (1.0)

All hyponatremia patients: studies 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. Dose group assignment in study 156-97-204 is based on the patients' maintenance dose. Hyponatremia patients from heart failure studies have baseline serum sodium < 135 mEq/L.

Patients are counted once, per term, for the most severe of multiple occurrences of a specific MedDRA preferred term.

Overall, these events occurred at relatively low frequencies, and incidences varied based on differences of only a few patients in each subgroup. Hyperglycemic events were more common in all hyponatremia patients (particularly those with cirrhosis or SIADH/other) receiving tolvaptan.

Laboratory data suggest a small (< 7 mg/dL) difference in circulating glucose concentrations during treatment with tolvaptan, but the differences vary widely. The frequency of variation from normal was notably higher in tolvaptan, but the rate of potentially clinically significant variation was not. While there is no consistent association with any particular disease etiology, time frame, dose, or other indicator of drug effect, the association between tolvaptan use and occurrence of hyperglycemia cannot be excluded.

4.2.2.7 Uric Acid-related Events

Plasma uric acid concentrations are low in patients SIADH. This has been attributed to increased clearance of uric acid in the kidney, possibly mediated by the vasopressin V_{1a} receptor or its action on fluid homeostasis. Therefore potential effects on uric acid concentrations were considered for further analysis.^{118,119,120,121,122}

In analysis of TEAE incidence rates by exposure categories in the two tolvaptan studies with treatment durations greater than 54 weeks (156-03-236, 156-01-232), gout was observed more frequently in tolvaptan patients in the longer-term exposure categories. This, combined with reports of increased uric acid concentrations in tolvaptan patients, prompted further analysis of gout and hyperuricemia in the larger safety dataset. In the primary safety population, the aggregate incidence for hyperuricemia/gout was 14.8% for

tolvaptan versus 13.8% placebo. In the hyponatremia population, the rates were lower and differed by less than 1% between treatment groups: 10.5% tolvaptan versus 11.2 % placebo. Both hyperuricemia and gout were reported less frequently in tolvaptan groups compared to placebo for the hyponatremia population: hyperuricemia incidence was 3.0% in tolvaptan patients compared to 4.1% in placebo patients, and the incidence of gout was 1.5% versus 2.7%. All events were considered mild to moderate in severity.

4.2.3 Other Relevant Safety Analyses

4.2.3.1 Clinically-relevant Drug-drug Interactions

P-glycoprotein-mediated

At steady state, co-administration of tolvaptan with digoxin resulted in a 30% increase in peak digoxin plasma concentrations and a 20% increase in AUC. Tolvaptan plasma concentrations were not significantly changed.

CYP3A4-mediated

Co-administration of a potent CYP3A4 inhibitor, ie, ketoconazole, with tolvaptan increased tolvaptan peak plasma concentrations (C_{max}) by about 3.5-fold and AUC by 5.4-fold. Grapefruit juice increased tolvaptan C_{max} and AUC by 1.9- and 1.6-fold, respectively. As plasma tolvaptan concentrations increase above those achieved with 60 mg doses, the duration of pharmacological effect (increased urinary excretion) increases but the magnitude of the response does not increase.

Chronic administration of rifampin, a potent CYP3A4 inducer, reduced the peak plasma concentrations and AUC of a single dose of tolvaptan by 85%. When tolvaptan is administered with CYP3A4 inducers, additional dose increases should be considered based on clinical evaluation.

Tolvaptan had no clinically relevant interactions with other CYP3A4 substrates, ie, lovastatin, amiodarone. Tolvaptan is neither an inducer nor inhibitor of CYP3A4, unlike conivaptan.

4.2.3.2 Effects on Electrocardiographic Parameters

Twelve-lead electrocardiogram (ECG) data were collected in all phase 1 and phase 2/3 clinical trials with tolvaptan, except a single dose hemodynamic trial. As part of the phase 1 program, a thorough QTc trial was performed. ECG data collected in all phase 3 tolvaptan trials and the thorough QTc trial were read by a centralized ECG vendor.

Prior to the start of the placebo-controlled phase 3 heart failure trial (156-03-236), the sponsor undertook an extensive, retrospective analysis of ECG data from 26 phase 1 and phase 2 trials in healthy subjects and patients to evaluate the effects of tolvaptan on cardiac safety.¹²³ This analysis included data from 258 patients on placebo and 726 on tolvaptan; doses of 5 to 120 mg were explored. Overall, there was no evidence of any signal of effect on heart rate, cardiac conduction as manifested by the PR and QRS interval duration, or cardiac repolarization as manifested by changes in QTcF interval (ie, QT corrected using Fridericia's formula) durations. No new morphological changes were observed on tolvaptan compared to placebo.

Cardiac repolarization studies for tolvaptan

The effect of tolvaptan cellular repolarization was evaluated on the human ether-a-go-go related gene (hERG) channel current in vitro. Tolvaptan did not affect the hERG channel current when tested up to the maximal solubility limit.

In a tissue model, there was no effect of tolvaptan on action potential in guinea-pig ventricular papillary muscle when tested up to 30 μ M.

The effects of tolvaptan on cardiac repolarization were then evaluated in a thorough QTc trial. This was a single center, parallel-arm, double-blind, placebo- and positive-controlled, multiple dose trial of the typical dose of tolvaptan (30 mg and 300 mg) and moxifloxacin (400 mg, the positive control) in healthy subjects aged 18 to 45 years. The 30 mg tolvaptan dose was chosen as it was a typical dose used in clinical trials. The 300 mg tolvaptan dose was chosen as the supramaximal dose because higher doses did not produce higher peak plasma concentrations than those achieved with a 300 mg dose.

An analysis was conducted on the largest time-matched mean difference in the individually-corrected QT interval (QTcI) between the drug and placebo on Day 1 and Day 5. Time-matched differences were derived by subtracting Day 0 placebo data from Day 1 and Day 5 data for each QTc sampling time point for each patient; the means of the differences were calculated for each treatment group by sampling time point and day. The largest means (and the 95% one-sided upper CIs) within each day were reported for each treatment group for Day 1 and Day 5. This analysis was done for all subjects as well as for males and females; and was also performed using QT correction by Fridericia's formula and Bazett's formula (QTcB).

A summary of the largest time-matched mean difference in QTcI between the drug and placebo on Day 1 and Day 5 is presented in [Table 4.2.3.2-1](#) (all subjects). There were no

significant increases in maximum mean change in QTcI from Day 0 (placebo) following single (Day 1) or multiple QD doses (Day 5) for either tolvaptan 30 mg or 300 mg. The upper limits of the one-sided 95% CIs for all days and all doses of tolvaptan were less than 8.0 msec. There were significant increases following single and multiple QD oral doses of 400 mg moxifloxacin (positive control). The mean differences and upper limits for each day of moxifloxacin were greater than 8.0 msec. When analyzed by sex the QTcI results for tolvaptan were similar.

Table 4.2.3.2-1 Largest Time-matched Mean Difference in QTcI and the Upper Limit of the One-sided Confidence Interval on Day 1 and Day 5 (All Subjects) in the Tolvaptan Thorough QTc Trial						
Visit Treatment Group	Time Postdose (h)	N	Maximum Mean (SD) Change msec	Median	Range	95% One- Sided CI Upper Limit
Day 1						
TLV 30 mg	2	42	-1.48 (10.13)	-1.00	-24.0 - 14.0	1.15
TLV 300 mg	2	42	0.62 (11.85)	1.50	-36.0 - 29.0	3.70
MOXI 400 mg	2	42	10.07 (9.98)	7.50	-6.0 - 34.0	12.66
Placebo	24	43	2.28 (9.92)	2.00	-24.0 - 24.0	4.82
Day 5						
TLV 30 mg	5	40	0.60 (11.36)	0.50	-22.0 - 25.0	3.63
TLV 300 mg	3	40	2.68 (15.28)	2.00	-24.0 - 45.0	6.75
MOXI 400 mg	1	41	15.78 (13.58)	15.00	-12.0 - 52.0	19.35
Placebo	12	41	1.34 (9.46)	1.00	-18.0 - 18.0	3.83

Study 156-03-245.

CI = confidence interval; MOXI = moxifloxacin; QTcI = individually-corrected QT interval;

SD = standard deviation; TLV = tolvaptan.

Baseline = Day 0 (placebo). Day 1 = after single dose. Day 5 = after QD dosing on Days 1 to 5.

Additionally, an analysis of AEs related to arrhythmia revealed no treatment differences (Table 4.2.3.2-2). Therefore, there is no evidence that tolvaptan poses any risk in terms of cardiac safety as defined by its effects on the 12-lead ECG.

Table 4.2.3.2-2 Adverse Events of Arrhythmia Greater Than or Equal to 1% Incidence in Any Treatment Group in All Heart Failure and Hyponatremia Patients From Multiple-dose Placebo-controlled Studies of Tolvaptan				
Parameter	Primary Safety Population		All Hyponatremia Patients	
	Tolvaptan/ Any Dose (N=3294) n (%)	Placebo (N=2738) n (%)	Tolvaptan/ Any Dose (N=607) n (%)	Placebo (N=518) n (%)
Any Atrial Arrhythmia	208 (6.3)	172 (6.3)	30 (4.9)	30 (5.8)
Any Ventricular Arrhythmia	420 (12.8)	357 (13.0)	69 (11.4)	50 (9.7)
Any Arrhythmia-MedDRA SMQ	734 (22.3)	658 (24.0)	118 (19.4)	101 (19.5)

SMQ=Standardized MedDRA Query.

Primary safety population: studies 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.

Dose group assignment in study 156-97-204 is based on the patients' maintenance dose.

All hyponatremia patients: same as above, excluding 156-03-001. Hyponatremia patients from heart failure studies have baseline serum sodium < 135 mEq/L.

Incidence rates for potentially clinically significant vital sign and ECG abnormalities (Table 4.2.3.2-3) demonstrated some statistically significant differences between the treatment groups. Interpretations of results from these analyses were limited in some cases due to small sample sizes. No vital sign or ECG abnormalities were assessed as clinically relevant upon medical review.

Table 4.2.3.2-3 Analysis of Incidences of Potentially Clinically Significant Vital Sign or ECG Category Change Abnormalities by Fishers Exact Test (p < 0.05) in Heart Failure or Hyponatremia Patients from Phase 2 and Phase 3 Placebo-controlled Studies of Tolvaptan						
Vital Sign or ECG Parameter	Treatment Group - N		Treatment Group - n (%)		p-value ^a	Final Clinical Interpretation / Rationale
	Tolvaptan N	Placebo N	Tolvaptan n(%)	Placebo n(%)		
Heart Failure and Hyponatremia - Vital Signs						
Weight (kg) - Increase of ≥ 7% in Body Weight	3253	2704	461 (14.2)	440 (16.3)	0.0267	Effect favors tolvaptan
Heart Failure and Hyponatremia – ECG Category Changes						
PR Outliers - Notable Change	1811	1530	105 (5.8)	121 (7.9)	0.0186	Effect favors tolvaptan
QRS Outliers - Notable Change	3068	2588	312 (10.2)	310 (12.0)	0.0329	Effect favors tolvaptan
QTcB - New Onset (> 500 msec)	2975	2558	431 (14.5)	424 (16.6)	0.0335	Effect favors tolvaptan
QTcF- New Onset (> 500 msec)	2975	2558	251 (8.4)	276 (10.8)	0.0033	Effect favors tolvaptan
QTcF - > 60 msec	2975	2558	263 (8.8)	272 (10.6)	0.0254	Effect favors tolvaptan
Hyponatremia - Vital Signs						
Standing systolic blood pressure (mmHg)- ≤ 90 mmHg + decrease of ≥ 20 mmHg	133	65	24 (18.0)	20 (30.8)	0.0475	Effect favors tolvaptan. Small sample size.
Hyponatremia – ECG Category Changes						
Ventricular Outliers – Notable Change	551	472	91 (16.5)	56 (11.9)	0.0396	No difference in overall comparison of mean ventricular rates, or the analysis of minimum rates. Analysis of maximum rates demonstrated a difference of 2.6 beats/minute. In tolvaptan, the overall pattern was not felt to be clinical relevant.

^a Fishers Exact Test.

4.3 Safety Overall Conclusions and Risk Management Plan

Thorough assessment of the safety profile of tolvaptan revealed no significant risks found to be associated with the use of tolvaptan in hyponatremia patients and suggested that the benefits of treatment with tolvaptan outweigh the risks.

The following activities will contribute to the management of patient safety:

- The proposed label includes all the information necessary to protect the well-being of the patients treated with tolvaptan.
- Routine company practices for monitoring and assessment of the product profile will be ongoing utilizing post-marketing surveillance tools.

These activities will facilitate assessment and communication on any issues of product profile change and will determine implementation of any risk mitigation actions.

Therefore, a Risk Management Action Plan apart from the above regarding the use of tolvaptan after approval was deemed not necessary at this time.

5 Summary and Conclusions

Inappropriate vasopressin activity is the unifying underlying feature of hypervolemic and euvolemic hyponatremia. Tolvaptan is the first orally-administered vasopressin V₂ antagonist treatment shown to increase serum sodium concentrations by removal of free water. This briefing document and data from the tolvaptan program support the following:

- **There is medical utility for treating hyponatremia:** Hyponatremia is the most common serum electrolyte abnormality that physicians may encounter. The symptoms of hyponatremia can often be subtle and are usually associated with impaired neurological and mental functioning. However, if left untreated, these symptoms may progress to serious sequelae such as seizure, coma, respiratory arrest, and/or death. Improvement of hyponatremia can reverse these symptoms, thereby suggesting a causal relationship.
- **Treatment options for hyponatremia are currently suboptimal:** There are no approved pharmacotherapies in the US for the treatment of hyponatremia in the outpatient setting. Fluid restriction, the most commonly-prescribed intervention in these patients, is poorly effective and patients are often uncompliant. The unmet medical need in hyponatremia today is for a therapy that targets hyponatremia and can be used in both the inpatient and outpatient settings.
- **The common underlying pathophysiology of hypervolemic and euvolemic hyponatremia is excessive vasopressin activity:** Direct and specific blockade of AVP V₂ receptor stimulation has been hypothesized as the ideal therapeutic target to address the unmet medical need in hyponatremia. Tolvaptan is a selective V₂ receptor antagonist and an appropriate therapy for treating hypervolemic and euvolemic hyponatremia.
- **Tolvaptan increases serum sodium concentration:**
 - Increases in serum sodium evident following administration of tolvaptan were both statistically and clinically significant regardless of baseline severity (serum sodium <130 mEq/L or 130-134 mEq/L) or underlying illness (SIADH, cirrhosis, or CHF). These increases were sustained during continued open-label tolvaptan administration for at least 2 years.
 - Following discontinuation of tolvaptan, serum sodium concentrations decreased to <135 mEq/L; following reinitiation of tolvaptan therapy, serum sodium levels were restored to the normal range. These data demonstrate the need for continued tolvaptan therapy in order to maintain the effects on serum sodium.
 - Tolvaptan prevented decreases in serum sodium that could potentially lead to increasingly serious negative clinical outcomes.

- **Tolvaptan improves mental functioning in hyponatremia patients as assessed by health-related patient-reported outcome measures:**
 - Tolvaptan led to consistent, clinically meaningful improvements in mental functioning as evidenced by improved SF-12 Mental Component Summary (MCS) Scores in all patients and regardless of etiology (SIADH, cirrhosis, CHF) or baseline severity (serum sodium <130 mEq/L, 130-134 mEq/L).
 - Improvement in MCS Scores were correlated with improvements in serum sodium in response to tolvaptan therapy.
 - The degree of improvement was consistent with restoration of near normal mental functioning and well-being as compared with the general US population.
 - Results of SF-12 were validated by the Hyponatremia Disease-specific Survey which was specifically designed to quantify the symptoms of hyponatremia.
- **Tolvaptan improves clinical outcomes in hypervolemic hyponatremia associated with the patient's underlying disease:**
 - In hyponatremic patients with CHF or cirrhosis, tolvaptan treatment resulted in statistically significant improvements in signs and symptoms of patients' underlying disease, including body weight, fatigue and dyspnea in CHF, and body weight and fatigue in cirrhosis.
 - In the long-term CHF study with tolvaptan, there was evidence for a delay in time until first incidence of cardiovascular mortality/cardiovascular morbidity in patients with baseline serum sodium concentration < 130 mEq/L ($p = 0.038$; post hoc analysis) and in patients with baseline serum sodium concentration < 135 mEq/L ($p = 0.16$).
- **Tolvaptan has a favorable, readily-manageable safety profile:**
 - The most common adverse events observed such as thirst, dry mouth, and pollakiuria were consistent with the underlying mechanism of action of the drug.
 - Thorough assessment of the safety profile of tolvaptan revealed no significant risks found to be associated with the use of tolvaptan in hyponatremia patients and suggested that the benefits of treatment with tolvaptan outweigh the risks.

Tolvaptan is uniquely suited to address the clear unmet medical need for the correction of serum sodium and prevention of hyponatremia and its symptoms by targeting the basic underlying pathophysiological mechanism leading to euvolemic and hypervolemic hyponatremia. Tolvaptan represents the first orally-administered V_2 selective antagonist to be considered for approval for this indication by the US FDA.

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Appendix 1: Supportive Information

Table 1 KCCQ Effects in Patients with Hyponatremia and Heart Failure in the Phase 3 Study of Tolvaptan in Worsening Heart Failure (LOCF-ITT)													
KCCQ Domain	Time - point	Overall Population				Baseline Sodium <135 mEq/L				Baseline Sodium <130 mEq/L			
		Mean Score		Treat-ment Effect	p-value	Mean Score		Treat-ment Effect	p-value	Mean Score		Treat-ment Effect	p-value
		TLV	PLC			TLV n=102	PLC n=101			TLV n=10	PLC n=23		
Overall Score	BSL	30.03	30.69	-		28.12	27.42	-		19.58	25.6	-	
	W1	50.08	49.44	0.76	.34	50.74	46.10	3.83	.23	40.45	39.32	6.39	.48
	W24	52.92	52.13	1.09	.22	52.14	49.65	2.03	.59	49.88	42.31	13.39	.24
	EOT	56.24	54.52	2.16	.04	53.33	48.34	4.49	.26	47.94	41.99	8.23	.49
Clinical Summary Score	BSL	29.15	29.76	-		31.09	30.07	-		20.61	29.26	-	
	W1	50.45	50.13	0.36	.66	54.82	51.49	1.78	.58	48.72	46.54	8.04	.33
	W24	52.19	52.12	0.32	.73	54.74	53.43	0.35	.92	55.31	48.17	14.75	.17
	EOT	55.50	54.78	1.13	.29	54.82	52.32	1.23	.75	50.95	51.46	3.60	.74
Quality of Life	BSL	29.23	29.64	-		25.58	26.24	-		21.67	23.91	-	
	W1	50.39	49.35	1.14	.28	47.57	42.10	6.87	.06	37.50	38.89	3.59	.73
	W24	55.39	53.39	2.07	.07	50.82	48.29	3.52	.42	54.63	43.89	17.31	.17
	EOT	58.81	56.60	2.47	.07	52.68	49.38	4.09	.35	52.78	46.88	7.78	.54
Social Limitation Score	BSL	32.58	33.54	-		26.15	24.18	-		15.42	22.72	-	
	W1	49.00	48.29	0.89	.43	46.61	42.10	2.56	.56	31.25	39.58	4.19	.80
	W24	51.75	51.00	1.38	.22	49.89	45.03	3.58	.47	44.68	39.58	18.72	.29
	EOT	55.03	51.86	3.71	<0.01	52.08	45.16	6.25	.20	46.99	47.12	16.79	.22
Physical Limitation Score	BSL	30.54	31.47	-		33.63	33.37	-		21.75	35.60	-	
	W1	45.30	44.65	0.74	.42	51.82	46.09	3.41	.35	41.30	39.72	10.66	.24
	W24	45.63	45.32	.68	.47	48.98	48.58	-1.06	.79	49.38	43.39	15.61	.17
	EOT	48.39	47.18	1.61	.15	49.76	45.76	2.42	.56	44.75	46.72	2.95	.80

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EOT=End of Treatment, PLC=Placebo, TLV=Tolvaptan 30 mg, W=Outpatient Week.

Table 2 Analysis of Change from Baseline in Dyspnea by Visit - Randomized Patients with CHF Etiology in the Phase 3 Study of Tolvaptan in Worsening Heart Failure (OC)

Analysis of Change from Baseline in Dyspnea by Visit - Randomized Patients with CHF Etiology (OC)																			
Visit	Treatment Group	# of Points in Change from Baseline														Chance to Be Better than PLC ¹		95% CI ¹	P-value ²
		N		-3		-2		-1		0		1		2		3			
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%		
Baseline	TLV 15-60mg	66	100.0																
	Placebo	60	100.0																
Day 2	TLV 15-60mg	64	100.0	0	0.00	3	4.69	12	18.75	44	68.75	4	6.25	1	1.56	0	0.00	0.5350	0.3774
	Placebo	54	100.0	0	0.00	1	1.85	7	12.96	43	79.63	2	3.70	1	1.85	0	0.00	(0.454, 0.616)	
Day 3	TLV 15-60mg	64	100.0	1	1.56	3	4.69	17	26.56	38	59.38	4	6.25	0	0.00	1	1.56	0.5409	0.3699
	Placebo	52	100.0	0	0.00	2	3.85	10	19.23	37	71.15	3	5.77	0	0.00	0	0.00	(0.451, 0.631)	
Day 4	TLV 15-60mg	60	100.0	2	3.33	3	5.00	18	30.00	32	53.33	4	6.67	1	1.67	0	0.00	0.6003	0.0396
	Placebo	52	100.0	0	0.00	1	1.92	11	21.15	32	61.54	4	7.69	3	5.77	1	1.92	(0.504, 0.696)	
Week 1	TLV 15-60mg	57	100.0	1	1.75	4	7.02	15	26.32	30	52.63	4	7.02	2	3.51	1	1.75	0.5142	0.7796
	Placebo	51	100.0	0	0.00	1	1.96	17	33.33	26	50.98	5	9.80	2	3.92	0	0.00	(0.414, 0.615)	
Week 2	TLV 15-60mg	58	100.0	2	3.45	0	0.00	16	27.59	31	53.45	5	8.62	1	1.72	3	5.17	0.4839	0.7803
	Placebo	46	100.0	0	0.00	1	2.17	15	32.61	23	50.00	5	10.87	2	4.35	0	0.00	(0.381, 0.587)	
Week 3	TLV 15-60mg	51	100.0	1	1.96	2	3.92	16	31.37	25	49.02	5	9.80	2	3.92	0	0.00	0.5184	0.7527
	Placebo	42	100.0	0	0.00	0	0.00	15	35.71	21	50.00	5	11.90	1	2.38	0	0.00	(0.409, 0.628)	
Day 30	TLV 15-60mg	48	100.0	0	0.00	3	6.25	13	27.08	24	50.00	7	14.58	1	2.08	0	0.00	0.5616	0.2857
	Placebo	40	100.0	0	0.00	2	5.00	9	22.50	19	47.50	8	20.00	2	5.00	0	0.00	(0.448, 0.675)	
7 Day F/U	TLV 15-60mg	48	100.0	0	0.00	2	4.17	14	29.17	23	47.92	8	16.67	1	2.08	0	0.00	0.5250	0.7139
	Placebo	43	100.0	1	2.33	2	4.65	10	23.26	20	46.51	9	20.93	1	2.33	0	0.00	(0.413, 0.637)	

¹ Based on Section 6.1.2 of Joseph Fleiss' 1999 book of Design and Analysis of Clinical Experiments. A value > 0.5 favors tolvaptan.

² Derived from CMH mean score test with modified ridit score (van Elteren test), stratified by protocol.

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Table 3 Analysis of Change from Baseline in Orthopnea by Visit - Randomized Patients with CHF Etiology in the Phase 3 Study of Tolvaptan in Worsening Heart Failure (OC)

Analysis of Change from Baseline in Orthopnea by Visit - Randomized Patients with CHF Etiology (OC)

Visit	Treatment Group	# of Points in Change from Baseline														Chance to Be Better than PLC ¹		P-value ²
		N		-3		-2		-1		0		1		2		3		
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	
Baseline	TLV 15-60mg	66	100.0															
	Placebo	60	100.0															
Day 2	TLV 15-60mg	64	100.0	1	1.56	3	4.69	7	10.94	50	78.13	3	4.69	0	0.00	0	0.00	0.5751 (0.501, 0.649) 0.0472
	Placebo	54	100.0	0	0.00	1	1.85	3	5.56	44	81.48	5	9.26	1	1.85	0	0.00	
Day 3	TLV 15-60mg	64	100.0	0	0.00	2	3.13	17	26.56	41	64.06	3	4.69	1	1.56	0	0.00	0.5760 (0.489, 0.663) 0.0866
	Placebo	52	100.0	0	0.00	2	3.85	6	11.54	39	75.00	4	7.69	1	1.92	0	0.00	
Day 4	TLV 15-60mg	60	100.0	2	3.33	1	1.67	14	23.33	40	66.67	3	5.00	0	0.00	0	0.00	0.5555 (0.468, 0.643) 0.2144
	Placebo	51	100.0	1	1.96	3	5.88	5	9.80	38	74.51	3	5.88	1	1.96	0	0.00	
Week 1	TLV 15-60mg	57	100.0	3	5.26	5	8.77	10	17.54	31	54.39	5	8.77	3	5.26	0	0.00	0.5342 (0.438, 0.630) 0.5502
	Placebo	51	100.0	1	1.96	2	3.92	8	15.69	35	68.63	2	3.92	3	5.88	0	0.00	
Week 2	TLV 15-60mg	58	100.0	2	3.45	1	1.72	13	22.41	32	55.17	4	6.90	4	6.90	2	3.45	0.4756 (0.376, 0.575) 0.5953
	Placebo	46	100.0	1	2.17	2	4.35	9	19.57	29	63.04	3	6.52	2	4.35	0	0.00	
Week 3	TLV 15-60mg	51	100.0	1	1.96	1	1.96	10	19.61	33	64.71	3	5.88	3	5.88	0	0.00	0.4699 (0.370, 0.569) 0.6106
	Placebo	42	100.0	0	0.00	3	7.14	8	19.05	28	66.67	2	4.76	1	2.38	0	0.00	
Day 30	TLV 15-60mg	48	100.0	0	0.00	2	4.17	13	27.08	26	54.17	5	10.42	2	4.17	0	0.00	0.5237 (0.417, 0.631) 0.6208
	Placebo	40	100.0	0	0.00	2	5.00	7	17.50	27	67.50	4	10.00	0	0.00	0	0.00	
7 Day F/U	TLV 15-60mg	50	100.0	0	0.00	4	8.00	9	18.00	27	54.00	9	18.00	1	2.00	0	0.00	0.5000 (0.395, 0.605) 0.9738
	Placebo	43	100.0	0	0.00	1	2.33	9	20.93	27	62.79	5	11.63	1	2.33	0	0.00	

¹ Based on Section 6.1.2 of Joseph Fleiss' 1999 book of Design and Analysis of Clinical Experiments. A value > 0.5 favors tolvaptan.

² Derived from CMH mean score test with modified ridit score (van Elteren test), stratified by protocol.

Table 4 Analysis of Change from Baseline in JVP by Visit - Randomized Patients with CHF Etiology in the Phase 3 Study of Tolvaptan in Worsening Heart Failure (OC)

Analysis of Change from Baseline in JVP by Visit - Randomized Patients with CHF Etiology (OC)

Visit	Treatment Group	# of Points in Change from Baseline														Chance to Be Better than PLC ¹	95% CI ¹	P-value ²
		N		-3		-2		-1		0		1		2		3		
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	
Baseline	TLV 15-60mg	62	100.0															
	Placebo	58	100.0															
Day 2	TLV 15-60mg	59	100.0	0	0.00	2	3.39	7	11.86	45	76.27	5	8.47	0	0.00	0	0.00	0.5074 (0.433, 0.582) 0.8624
	Placebo	52	100.0	0	0.00	0	0.00	6	11.54	44	84.62	2	3.85	0	0.00	0	0.00	
Day 3	TLV 15-60mg	60	100.0	0	0.00	6	10.00	7	11.67	42	70.00	5	8.33	0	0.00	0	0.00	0.5662 (0.483, 0.650) 0.1191
	Placebo	50	100.0	0	0.00	0	0.00	6	12.00	39	78.00	4	8.00	1	2.00	0	0.00	
Day 4	TLV 15-60mg	56	100.0	1	1.79	3	5.36	8	14.29	41	73.21	3	5.36	0	0.00	0	0.00	0.5965 (0.516, 0.677) 0.0184
	Placebo	49	100.0	0	0.00	0	0.00	3	6.12	41	83.67	4	8.16	1	2.04	0	0.00	
Week 1	TLV 15-60mg	53	100.0	0	0.00	2	3.77	6	11.32	43	81.13	1	1.89	1	1.89	0	0.00	0.4762 (0.392, 0.561) 0.5821
	Placebo	49	100.0	0	0.00	1	2.04	10	20.41	35	71.43	1	2.04	2	4.08	0	0.00	
Week 2	TLV 15-60mg	54	100.0	1	1.85	3	5.56	7	12.96	41	75.93	1	1.85	1	1.85	0	0.00	0.5364 (0.448, 0.624) 0.4194
	Placebo	45	100.0	0	0.00	0	0.00	8	17.78	33	73.33	3	6.67	1	2.22	0	0.00	
Week 3	TLV 15-60mg	47	100.0	1	2.13	3	6.38	7	14.89	33	70.21	3	6.38	0	0.00	0	0.00	0.5624 (0.467, 0.658) 0.1984
	Placebo	39	100.0	0	0.00	0	0.00	5	12.82	31	79.49	3	7.69	0	0.00	0	0.00	
Day 30	TLV 15-60mg	45	100.0	1	2.22	3	6.67	6	13.33	31	68.89	3	6.67	1	2.22	0	0.00	0.5493 (0.451, 0.648) 0.3196
	Placebo	37	100.0	0	0.00	0	0.00	4	10.81	30	81.08	3	8.11	0	0.00	0	0.00	
7 Day F/U	TLV 15-60mg	46	100.0	1	2.17	3	6.52	5	10.87	31	67.39	5	10.87	1	2.17	0	0.00	0.5239 (0.425, 0.623) 0.5919
	Placebo	40	100.0	0	0.00	0	0.00	6	15.00	30	75.00	3	7.50	0	0.00	1	2.50	

¹ Based on Section 6.1.2 of Joseph Fleiss' 1999 book of Design and Analysis of Clinical Experiments. A value > 0.5 favors tolvaptan.

² Derived from CMH mean score test with modified ridit score (van Elteren test), stratified by protocol

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Table 5 Analysis of Change from Baseline in NYHA Class by Visit - Randomized Patients with CHF Etiology in the Phase 3 Study of Tolvaptan in Worsening Heart Failure (OC)

Analysis of Change from Baseline in NYHA Class by Visit - Randomized Patients with CHF Etiology (OC)

Visit	Treatment Group	N		-3		# of Points in Change from Baseline		-2		-1		0		1		2		3		Chance to Be Better than PLC ¹	95% CI ¹	P-value ²
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%			
Baseline	TLV 15-60mg	65	100.0																			
	Placebo	59	100.0																			
Day 2	TLV 15-60mg	63	100.0	0	0.00	0	0.00	10	15.87	52	82.54	1	1.59	0	0.00	0	0.00	0.5591	(0.496, 0.623)	0.0697		
	Placebo	53	100.0	0	0.00	0	0.00	3	5.66	48	90.57	2	3.77	0	0.00	0	0.00					
Day 3	TLV 15-60mg	64	100.0	0	0.00	1	1.56	12	18.75	47	73.44	3	4.69	1	1.56	0	0.00	0.5541	(0.474, 0.634)	0.1878		
	Placebo	51	100.0	0	0.00	0	0.00	6	11.76	40	78.43	5	9.80	0	0.00	0	0.00					
Day 4	TLV 15-60mg	60	100.0	0	0.00	1	1.67	8	13.33	50	83.33	1	1.67	0	0.00	0	0.00	0.5044	(0.426, 0.583)	0.9187		
	Placebo	50	100.0	0	0.00	0	0.00	10	20.00	36	72.00	3	6.00	1	2.00	0	0.00					
Week 1	TLV 15-60mg	58	100.0	0	0.00	1	1.72	12	20.69	39	67.24	6	10.34	0	0.00	0	0.00	0.4982	(0.408, 0.588)	0.9786		
	Placebo	49	100.0	1	2.04	0	0.00	9	18.37	35	71.43	4	8.16	0	0.00	0	0.00					
Week 2	TLV 15-60mg	57	100.0	0	0.00	1	1.75	12	21.05	35	61.40	8	14.04	1	1.75	0	0.00	0.4650	(0.370, 0.560)	0.4838		
	Placebo	46	100.0	1	2.17	1	2.17	8	17.39	33	71.74	3	6.52	0	0.00	0	0.00					
Week 3	TLV 15-60mg	51	100.0	0	0.00	2	3.92	11	21.57	32	62.75	6	11.76	0	0.00	0	0.00	0.4911	(0.389, 0.593)	0.8432		
	Placebo	42	100.0	0	0.00	1	2.38	10	23.81	27	64.29	4	9.52	0	0.00	0	0.00					
Day 30	TLV 15-60mg	47	100.0	0	0.00	2	4.26	8	17.02	32	68.09	5	10.64	0	0.00	0	0.00	0.5029	(0.400, 0.606)	0.9654		
	Placebo	40	100.0	0	0.00	1	2.50	8	20.00	26	65.00	5	12.50	0	0.00	0	0.00					
7 Day F/U	TLV 15-60mg	49	100.0	0	0.00	0	0.00	13	26.53	31	63.27	5	10.20	0	0.00	0	0.00	0.5203	(0.419, 0.622)	0.6994		
	Placebo	43	100.0	0	0.00	1	2.33	9	20.93	28	65.12	4	9.30	1	2.33	0	0.00					

¹ Based on Section 6.1.2 of Joseph Fleiss' 1999 book of Design and Analysis of Clinical Experiments. A value > 0.5 favors tolvaptan.

² Derived from CMH mean score test with modified ridit score (van Elteren test), stratified by protocol.

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Table 6 Demographic and Baseline Characteristics: Primary Safety Population - Tolvaptan						
Characteristic	Statistic	Tolvaptan < 15 mg (N = 24)	Tolvaptan 15-60 mg (N = 3181)	Tolvaptan > 60 mg (N = 89)	Any Tolvaptan Oral Dose (N = 3294)	Placebo/ Other (N = 2738)
Age	Mean (SD), years	58 (14.7)	65.2 (12.3)	62.6 (12.3)	65 (12.3)	64.8 (12.4)
	Median	58	66	64	66	66
	Range	32-86	18-94	28-88	18-94	18-100
	< 65 years, n (%)	15 (62.5)	1426 (44.8)	46 (51.7)	1487 (45.1)	1242 (45.4)
	≥ 65 years, n (%)	9 (37.5)	1755 (55.2)	43 (48.3)	1807 (54.9)	1496 (54.6)
Gender	Male, n (%)	15 (62.5)	2247 (70.6)	68 (76.4)	2330 (70.7)	2031 (74.2)
	Female, n (%)	9 (37.5)	934 (29.4)	21 (23.6)	964 (29.3)	707 (25.8)
Race	Caucasian, n (%)	18 (75.0)	2518 (79.2)	45 (50.6)	2581 (78.4)	2274 (83.1)
	Black, n (%)	1 (4.2)	319 (10.0)	21 (23.6)	341 (10.4)	227 (8.3)
	Hispanic, n (%)	5 (20.8)	196 (6.2)	20 (22.5)	221 (6.7)	150 (5.5)
	Asian, n (%)	0 (0.0)	100 (3.1)	1 (1.1)	101 (3.1)	39 (1.4)
	Other, n (%)	0 (0.0)	47 (1.5)	2 (2.2)	49 (1.5)	48 (1.8)
	Not available, n(%)	0 (0.0)	1 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)

Studies 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. Dose group assignment in Study 156-97-204 is based on the patients' maintenance dose.

Table 7 Demographic and Baseline Characteristics: All Hyponatremia Patients From Placebo-controlled, Multiple-dose Hyponatremia and Heart Failure Studies - Tolvaptan					
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)
Hyponatremia Severity	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 Origin	Cirrhosis, n (%)	12 (4.4)	63 (28.3)	100 (16.5)	83 (16.0)
	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 Status	Euvolemic	1 (0.4)	124 (55.6)	131 (21.6)	129 (24.9)
	Hypervolemic	274 (99.6)	99 (44.4)	476 (78.4)	389 (75.1)

Studies 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, and 156-03-238. Hyponatremia patients from heart failure studies with baseline serum sodium < 135 mEq/L. Dose group assignment in study 156-97-204 was based on the patient's maintenance dose. Tolvaptan 15-60 mg dose group includes only patients from studies 156-02-235 and 156-03-238.

Table 8 Extent of Exposure in All Patients From Tolvaptan Phase 1 to 3 Studies														
Dura- tion (Days)	Tolvaptan < 15 mg (N = 68) n (%)		Tolvaptan 15-60 mg (N = 4122) n (%)		Tolvaptan > 60 mg (N = 306) n (%)		Tolvaptan 1 mg IV (N = 14) n (%)		Any Tolvaptan Oral Dose (N = 4423) n (%)		Placebo/other (N = 3099) n (%)		Blinded^a (N = 128) n (%)	
	Period^b	Cumul- ative^c	Period^b	Cumul- ative^c	Period^b	Cumul- ative^c	Period^b	Cumul- ative^c	Period^b	Cumul- ative^c	Period^b	Cumul- ative^c	Period^b	Cumul- ative^c
1 to 30	68 (100.0)	68 (100.0)	1619 (39.3)	4122 (100.0)	229 (74.8)	306 (100.0)	14 (100.0)	14 (100.0)	1843 (41.7)	4423 (100.0)	923 (29.8)	3099 (100.0)	64 (50.0)	128 (100.0)
31 to 60	0 (0.0)	0 (0.0)	277 (6.7)	2503 (60.7)	49 (16.0)	77 (25.2)	0 (0.0)	0 (0.0)	326 (7.4)	2580 (58.3)	237 (7.6)	2176 (70.2)	15 (11.7)	64 (50.0)
61 to 90	0 (0.0)	0 (0.0)	132 (3.2)	2226 (54.0)	3 (1.0)	28 (9.2)	0 (0.0)	0 (0.0)	135 (3.1)	2254 (51.0)	112 (3.6)	1939 (62.6)	13 (10.2)	49 (38.3)
91 to 180	0 (0.0)	0 (0.0)	600 (14.6)	2094 (50.8)	2 (0.7)	25 (8.2)	0 (0.0)	0 (0.0)	602 (13.6)	2119 (47.9)	427 (13.8)	1827 (59.0)	32 (25.0)	36 (28.1)
181 to 360	0 (0.0)	0 (0.0)	578 (14.0)	1494 (36.2)	0 (0.0)	23 (7.5)	0 (0.0)	0 (0.0)	578 (13.1)	1517 (34.3)	602 (19.4)	1400 (45.2)	4 (3.1)	4 (3.1)
361 to 720	0 (0.0)	0 (0.0)	796 (19.3)	916 (22.2)	23 (7.5)	23 (7.5)	0 (0.0)	0 (0.0)	819 (18.5)	939 (21.2)	704 (22.7)	798 (25.8)	0 (0.0)	0 (0.0)
> 720	0 (0.0)	0 (0.0)	120 (2.9)	120 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	120 (2.7)	120 (2.7)	94 (3.0)	94 (3.0)	0 (0.0)	0 (0.0)

Studies 156-03-236, 156-97-251, 156-97-252, 156-98-213, 156-00-220, 156-00-222, 156-01-232, 156-02-235, 156-03-238, 156-96-201, 156-96-203, 156-97-204, 156-03-244, 156-96-205, 156-98-201, 156-01-223, 156-01-225, 156-01-226, 156-01-233, 156-01-234, 156-03-239, 156-03-240, 156-96-301, 156-98-202, 156-98-210, 156-00-001, 156-00-002, 156-00-003, 156-01-229, 156-03-242, 156-03-245, 156-05-001, 156-05-003, 156-05-252, 156-05-254, 156-05-256, 156-00-221, 156-01-231, 156-04-247, 156-04-248, 156-04-249, 156-04-001, 156-94-001, 156-94-002, 156-95-301, 156-95-302, 156-95-303, 156-95-304, 156-95-305, 156-97-202, 156-05-004, 156-05-253, 156-04-250, 156-03-001, 156-03-002, 156-04-246, 156-06-801-01, 156-06-260, 156-07-262, 156-04-251, 156-05-002, 156-06-002, and 156-06-005.

Exposure data are cumulative for tolvaptan patients enrolled in parent double-blind studies (156-02-235 and 156-03-238; 156-04-248 and 156-04-249; or 156-04-001) who rolled over into open-label extension studies (156-03-244; 156-04-250; and 156-05-002, respectively). Placebo patients from these studies may be counted toward placebo exposure in the parent studies and tolvaptan exposure in the extension studies.

^aBlinded studies are 156-04-246 and 156-04-251 (data cutoff, 01 Oct 2007) and 156-06-002 and 156-06-005 (data cutoff, 01 Sep 2007).

^bPatients are counted once in the category representing their greatest period of exposure.

^cPatients are counted in each category for which they had exposure.

Table 9 Extent of Exposure of All Hyponatremia Patients From Placebo-controlled, Multiple-dose Hyponatremia and Heart Failure Tolvaptan Studies												
Days of Exposure	Any Tolvaptan						Placebo					
	Mild (≥ 130 mEq/L) (N = 418) n (%)		Severe (< 130 mEq/L) (N = 189) n (%)		Total (N = 607) n (%)		Mild (≥ 130 mEq/L) (N = 340) n (%)		Severe (< 130 mEq/L) (N = 178) n (%)		Total (N = 518) n (%)	
	Period^a	Cumula- b tive	Period^a	Cumula- b tive	Period^a	Cumula- b tive	Period^a	Cumula- b tive	Period^a	Cumula- b tive	Period^a	Cumula- b tive
1 to 30	179 (42.8)	418 (100.0)	117 (61.9)	189 (100.0)	296 (48.8)	607 (100.0)	145 (42.6)	340 (100.0)	108 (60.7)	178 (100.0)	253 (48.8)	518 (100.0)
31 to 60	69 (16.5)	239 (57.2)	43 (22.8)	72 (38.1)	112 (18.5)	311 (51.2)	53 (15.6)	195 (57.4)	37 (20.8)	70 (39.3)	90 (17.4)	265 (51.2)
61 to 90	12 (12.9)	170 (40.7)	0 (0.0)	29 (15.3)	12 (2.0)	199 (32.8)	11 (3.2)	142 (41.8)	4 (2.2)	33 (18.5)	15 (2.9)	175 (33.8)
91 to 180	47 (11.2)	158 (37.8)	8 (4.2)	29 (15.3)	55 (9.1)	187 (30.8)	28 (8.2)	131 (38.5)	7 (3.9)	29 (16.3)	35 (6.8)	160 (30.9)
181 to 360	55 (13.2)	111 (26.6)	8 (4.2)	21 (11.1)	63 (10.4)	132 (21.7)	47 (13.8)	103 (30.3)	9 (5.1)	22 (12.4)	56 (10.8)	125 (24.1)
361 - 720	51 (12.2)	56 (13.4)	12 (6.3)	13 (6.9)	63 (10.4)	69 (11.4)	48 (14.1)	56 (16.5)	11 (6.2)	13 (7.3)	59 (11.4)	69 (13.3)
> 720	5 (1.2)	5 (1.2)	1 (0.5)	1 (0.5)	6 (1.0)	6 (1.0)	8 (2.4)	8 (2.4)	2 (1.1)	2 (1.1)	10 (1.9)	10 (1.9)

Studies 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, and 156-03-238. Hyponatremia patients from heart failure studies with baseline serum sodium < 135 mEq/L. Dose group assignment in study 156-97-204 was based on the patient's maintenance dose. Tolvaptan 15-60 mg dose group includes only patients from studies 156-02-235 and 156-03-238.

^aPatients were counted once in the category representing their greatest period of exposure.

^bPatients were counted in each category for which they had exposure.

Table 10 Incidence of Deaths (Regardless of Causality) in All Hyponatremia Patients From Placebo-controlled, Multiple-dose Hyponatremia and Heart Failure Tolvaptan Studies		
System Organ Class MedDRA Preferred Term	Any Tolvaptan Dose (N = 607) n (%)	Placebo (N = 518) n (%)
Any TEAE leading to death	131 (21.6)	108 (20.8)
Cardiac Disorders		
Cardiac failure	31 (5.1)	23 (4.4)
Cardiac failure congestive	23 (3.8)	16 (3.1)
Cardiac arrest	11 (1.8)	4 (0.8)
Cardiogenic shock	6 (1.0)	5 (1.0)
Cardiac failure chronic	5 (0.8)	3 (0.6)
Cardio-respiratory arrest	4 (0.7)	3 (0.6)
Ventricular fibrillation	2 (0.3)	1 (0.2)
Acute myocardial infarction	1 (0.2)	1 (0.2)
Myocardial infarction	1 (0.2)	1 (0.2)
Cardiac failure acute	1 (0.2)	0 (0.0)
Low cardiac output syndrome	1 (0.2)	0 (0.0)
Ventricular tachycardia	1 (0.2)	0 (0.0)
Cardiomyopathy	0 (0.0)	3 (0.6)
Cor pulmonale	0 (0.0)	1 (0.2)
Gastrointestinal Disorders		
Gastrointestinal haemorrhage	1 (0.2)	2 (0.4)
Intestinal ischemia	0 (0.0)	1 (0.2)
General Disorders and Administration Site Conditions		
Sudden death	10 (1.6)	8 (1.5)
Sudden cardiac death	8 (1.3)	5 (1.0)
Death	2 (0.3)	3 (0.6)
Multi-organ failure	1 (0.2)	5 (1.0)
General physical health deterioration	0 (0.0)	1 (0.2)
Hepatobiliary Disorders		
Hepatic failure	1 (0.2)	2 (0.4)
Cholestasis	1 (0.2)	0 (0.0)
Hepatorenal syndrome	0 (0.0)	1 (0.2)
Immune System Disorders		
Transplant rejection	0 (0.0)	1 (0.2)
Infections and Infestations		
Sepsis	2 (0.3)	2 (0.4)
Septic shock	1 (0.2)	1 (0.2)
Peritonitis bacterial	1 (0.2)	0 (0.0)
Respiratory tract infection	1 (0.2)	0 (0.0)
Pneumonia	0 (0.0)	2 (0.4)
Bacteraemia	0 (0.0)	1 (0.2)
Pulmonary sepsis	0 (0.0)	1 (0.2)
Injury, Poisoning and Procedural Complications		
Cervical vertebral fracture	1 (0.2)	0 (0.0)
Subdural haematoma	1 (0.2)	0 (0.0)
Injury	0 (0.0)	1 (0.2)

Table 10 Incidence of Deaths (Regardless of Causality) in All Hyponatremia Patients From Placebo-controlled, Multiple-dose Hyponatremia and Heart Failure Tolvaptan Studies		
System Organ Class MedDRA Preferred Term	Any Tolvaptan Dose (N = 607) n (%)	Placebo (N = 518) n (%)
Neoplasms benign, Malignant and Unspecified (Including Cysts and Polyps)		
Lung neoplasm malignant	1 (0.2)	0 (0.0)
Non-Hodgkin's lymphoma	1 (0.2)	0 (0.0)
Lung adenocarcinoma metastatic	0 (0.0)	1 (0.2)
Nervous System Disorders		
Cerebral ischaemia	1 (0.2)	0 (0.0)
Encephalopathy	1 (0.2)	0 (0.0)
Hepatic encephalopathy	1 (0.2)	0 (0.0)
Cerebral haemorrhage	0 (0.0)	1 (0.2)
Renal and Urinary Disorders		
Renal failure acute	1 (0.2)	1 (0.2)
Renal failure	1 (0.2)	0 (0.0)
Renal failure chronic	0 (0.0)	1 (0.2)
Respiratory, Thoracic, and Mediastinal Disorders		
Respiratory failure	2 (0.3)	0 (0.0)
Chronic obstructive pulmonary disease	1 (0.2)	0 (0.0)
Pulmonary embolism	1 (0.2)	0 (0.0)
Respiratory arrest	1 (0.2)	0 (0.0)
Pneumonia aspiration	0 (0.0)	1 (0.2)
Pulmonary oedema	0 (0.0)	1 (0.2)
Respiratory distress	0 (0.0)	1 (0.2)
Vascular Disorders		
Cardiovascular insufficiency	1 (0.2)	0 (0.0)
Hypotension	0 (0.0)	2 (0.4)
Arteriosclerosis	0 (0.0)	1 (0.2)

Studies 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, and 156-03-238. Hyponatremia patients from heart failure studies with baseline serum sodium < 135 mEq/L. Dose group assignment in study 156-97-204 was based on the patient's maintenance dose. Tolvaptan 15-60 mg dose group includes only patients from studies 156-02-235 and 156-03-238.