DEPARTMENT OF HEALTH AND HUMAN SERVICES
UNITED STATES FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Cardiovascular and Renal Drugs

Advisory Committee Meeting

Wednesday, June 25, 2008

8:00 a.m.

Hilton Hotel--Silver Spring
8727 Colesville Road
Silver Spring, MD

PAPER MILL REPORTING
(301) 495-5831

C O N T E N T S

C O N T E N T S (Continued)

P A R T I C I P A N T S

William R. Hiatt, M.D., Chair
Elaine Ferguson, B.S. Pharm., R.Ph.

Cardiovascular and Renal Drugs Advisory Committee Members (Voting)

John M. Flack, M.D., MPH
Robert A. Harrington, M.D.
Frederick J. Kaskel, M.D., Ph.D.
A. Michael Lincoff, M.D., FACC
James D. Neaton, Ph.D.
Emil P. Paganini, M.D., FACP, FRCP
Lynne L. Warner Stevenson, M.D.

Temporary Voting Members

Alan G. Robinson, M.D.
Sidney M. Wolfe, M.D. (Consumer Representative)
Paul H. Zanetti, M.D., (Patient Representative)

Industry Representative (Non-Voting)

Jonathan C. Fox, M.D., Ph.D., FACC

FDA (Non-Voting)

Robert Temple, M.D.
Norman Stockbridge, M.D.

P R O C E E D I N G S

Call to Order

DR. HIATT: My name is William Hiatt. I would like to welcome you to the Cardiovascular and Renal Drugs Advisory Committee. I am from the University of Colorado, Denver School of Medicine, the section of vascular medicine. This is my last day to chair this committee so, hopefully, it will be another interesting meeting.

I would like to go around the room and have the members of the committee introduce themselves. I think, Norman, maybe we could start with you and work around the room.

Introduction of the Committee

DR. STOCKBRIDGE: Good morning. I am Norman Stockbridge. I am the Director of the Division of Cardiovascular and Renal Products.

DR. HARRINGTON: Bob Harrington. I am an interventional cardiologist at duke University.

DR. ZANETTI: Paul Zanetti, patient representative.

DR. PAGANINI: Emil Paganini, adult nephrology, Cleveland.

DR. ROBINSON: Alan Robinson, Executive Associate

Dean and endocrinologist at UCLA.

MS. FERGUSON: Elaine Ferguson, designated federal official.

DR. FLACK: John Flack, Chairman of Medicine and cardiovascular epidemiologist at Wayne State.

DR. NEATON: Jim Neaton, biostatistician from the University of Minnesota.

DR. LINCOFF: Mike Lincoff, an interventional cardiologist from the Cleveland Clinic.

DR. WARNER STEVENSON: Lynn Warner Stevenson, Brigham and Women=s Hospital in Boston, heart failure and transplant cardiology.

DR. KASKEL: Fred Kaskel, pediatric nephrologist, Albert Einstein College of Medicine.

DR. FOX: Jonathan Fox, industry representative.

DR. WOLFE: Sid Wolfe, Director of the Health Research Group of Public Citizen, consumer representative.

DR. HIATT: We will go on to the conflict of interest statement.

Conflict of Interest Statement

MS. FERGUSON: First I would like to identify the FDA press contact. His name is Chris Kelly. If you are

present, can you please stand? Thank you.

The food and Drug Administration is convening today=s meeting of the Cardiovascular and Renal Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, the members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of the committee=s compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. 208 and 712 of the Federal Food, Drug and Cosmetic Act is being provided to participants in today=s meeting and to the public.

FDA has determined that the members and temporary voting members of the committee are in compliance with the federal ethics and conflict of interest laws. Under 18 U.S.C 208, Congress has authorized FDA to grant waivers to special government employees who have potential financial conflicts when it is determined that the agency=s need for a

particular individual=s services outweighs his or her potential financial conflict of interest.

Under 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular government employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussions of today=s meeting, members and temporary voting members of this committee who are special government employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

Today=s agenda involves discussing the new drug application, NDA 22-275, tolvaptan, proposed name SAMSKA, Otsuka Pharmaceutical Development and Commercialization, Inc., for the proposed indication of treatment of hypervolemic and euvolemic hyponatremia.

The committee will hear presentations from the FDA and the sponsor specifically regarding change in sodium level as the basis for drug approval. This issue is characterized as a particular matter involving specific parties.

Based on the agenda for today=s meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

Additionally, we would like to disclose that Jonathan Fox, M.D. is serving as the non-voting industry representative, acting on behalf of all regulated industry. Dr. Fox is an employee of AstraZeneca.

We would like to remind the members and temporary voting members of the committee that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have with any firms at issue. Thank you.

DR. HIATT: Thank you very much. We are going to begin with Dr. Stockbridge providing some opening remarks.

FDA Opening Remarks

DR. STOCKBRIDGE: Good morning. I would like to begin by acknowledging four retiring members of the committee. Elaine, here, has a plaque to commemorate the occasion for each of you. The four retiring members are John Teerlink, who is not here this morning; Lynn Warner Stevenson; Fred Kaskel; and our Chairman, Bill Hiatt.

On behalf of the Cardiorenal Division and FDA, I want to thank all of you for your years of service on the committee and I hope everybody here joins me in thanking you.

[Applause]

DR. STOCKBRIDGE: Today=s meeting continues a theme. In October of 2007 we discussed pre-dialysis use of phosphate binders and the advisory committee was asked at that time what level of phosphate was so clearly associated with adverse outcomes that it necessarily necessitated immediate treatment. The committee believed that such a level existed but was unable to name it and we did not in this session come up with a plan for determining such a

level. There that matter sits to this very day.

Today we are considering tolvaptan for hyponatremia, and I will mention that there is a development program for heart failure but we are not asking you any questions that relate to it.

The sponsor was told during development that affective serum sodium was a reasonable basis for approval for hyponatremia, but late in the development program a different review division has called that basis for approval into question.

Now Bob Temple, on my left here, may have to consider the implications of sort of changing the standard at this point in the game, but I don't want that to be part of the committee=s consideration. What we would like from the committee is for you to address the scientific basis that is appropriate for approval.

In building their case, the sponsor has been encouraged to provide to you all of the evidence it can bring to bear on the clinical benefits associated with increasing serum sodium in general and based on their own development program regardless of whether those particular analyses and arguments have undergone FDA review. So, that

is a little unusual.

If you conclude that there is a plausible case for approval of tolvaptan in some population that you will name, then we will review the basis of that claim if we have not already done so.

If you conclude that a population has not been identified where tolvaptan should be approved the committee is requested to describe how one might go about getting such a claim. Thank you.

DR. HIATT: Thank you, Norman. For the next couple of hours there is a series of sponsor presentations. I would like to ask you all to stay on time. I think the committee will have lots of questions based on your presentations. We have a bit of time towards the end of the morning to ask those questions. We may have to extent those into the afternoon. But why don't we begin with the introduction. Dr. McQuade?

Sponsor Presentations

Otsuka Pharmaceutical Development & Commercialization, Inc.

Introduction

DR. McQUADE: Mr. Chairman, members of the advisory committee, representatives of the FDA and guests, good

morning.

[Slide]

My name is Robert McQuade and I am Vice President of Global Medical Affairs at Otsuka Pharmaceutical Development & Commercialization. Otsuka welcomes the opportunity this morning to meet with you to discuss tolvaptan and the medical utility of treating hyponatremia.

[Slide]

Otsuka has made a couple of changes to the agenda. The first is a minor reordering of the presentations. The second is that due to illness, Dr. William Carson will present the safety presentation. I will actually begin by reviewing the regulatory history for tolvaptan. In addition, I will provide the committee with a brief overview of the tolvaptan clinical development program.

In response to requests from FDA, the sponsor has invited experts to give testimony on the medical utility of treating hyponatremia and its relationships to the underlying illnesses associated with it.

Dr. Verbalis, from Georgetown University, will begin with a broader overview of hyponatremia. Following that presentation, Dr. Czerwiec, from Otsuka, will present

the efficacy data for the pivotal Phase 3 studies of tolvaptan in hyponatremia.

[Slide]

Next, Dr. Udelson, from Tufts University, will discuss the impact of hyponatremia in heart failure, following which Dr. Zimmer will discuss supportive data for the treatment of hyponatremia from our large study in patients with worsening heart failure.

Dr. Carson will present the safety profile for tolvaptan. Dr. Schrier, from the University of Colorado, will then summarize the presentations and comment, from the clinician perspective, on the benefits of tolvaptan in treating hyponatremia. Finally, I will come back to present some closing comments from the sponsor. In addition, the slides you have received are in the correct order in which they will be presented this morning.

[Slide]

In terms of the regulatory history for tolvaptan, let me briefly review with you those activities that have taken place prior to today=s meeting.

The original discussions with FDA for the development program for tolvaptan as a treatment for

hyponatremia were with the Division of Metabolic and Endocrine Drug Products, and they continued to be the primary contact through the Phase 3 development program.

A special protocol assessment, or SPA, was requested from FDA in 2003. Discussions between the agency and the sponsor resulted in the following consensus agreement regarding pivotal Phase 3 trials in hyponatremia. The indication being sought was agreed to be the treatment of hypervolemic and euvolemic hyponatremia. The patient populations would include all potential patients with hyponatremia, as defined by serum sodium concentrations less than 135 mEq/L regardless of their underlying disease. It was agreed with FDA that no one underlying illness would constitute more than 50 percent of the entire database.

An agreement was reached with FDA to stratify those patients into two separate groups, those patients with more severe hyponatremia at baseline, mainly serum sodium levels of less than 130 mEq/L, and those patients with serum sodium levels between 130-134 mEq/L.

It is important to note, and this is an issue that will be revisited throughout this morning=s presentations, that FDA has consistently advised us to gather as many

patients as possible in the population less than 130 mEq/L. In fact, patients with baseline serum sodium concentrations of less than 130 constitute more than 50 percent of our clinical trial database in the pivotal Phase 3 studies.

[Slide]

The primary endpoints were agreed upon with FDA and were specified as change in the average daily AUC, or area under the curve, for serum sodium from baseline to day 4 and from baseline to day 30, representing both a short term and a sustained measure of impacting serum sodium levels.

While there were a number of prespecified secondary endpoints, those that are most relevant for today=s discussion are the prespecified analyses of the mental and physical component summary scores of the SF-12.

In 2003, when these studies were initiated, because of the broad symptoms and the varied underlying etiologies associated with hyponatremia, there was no clear understanding of what scale would be most appropriate for determining impact on clinical outcomes. As such, Otsuka chose a broadly applicable generic patient-reported outcome scale as the tool for determining the effects of correcting

hyponatremia.

The SF-12 scale has been used in many clinical studies in patients with a wide variety of clinical conditions. It was not validated specifically for the hyponatremic population a priori but, because of its broad applicability, it was hypothesized to be an appropriate secondary endpoint to begin the process of understanding the outcomes of correcting hyponatremia.

Before we move on, Otsuka would like to stress to the committee that these studies were designed, in collaboration with FDA, primarily to investigate the effects of tolvaptan on serum sodium levels. The studies were not designed to demonstrate the benefits of improving sodium levels on clinical outcome measures.

[Slide]

In April, 2007, as Dr. Stockbridge noted, Otsuka was notified by the FDA that the NDA for hyponatremia was going to be transferred to the Division of Cardiovascular and Renal Drug Products and they would be reviewing both NDAs for heart failure and hyponatremia.

At the time of our pre-NDA meeting in May, 2007 the Cardiovascular and Renal Division acknowledged the

previous development agreements with Metabolic Endocrine. The Cardiorenal Division, like the Metabolic Endocrine Division, encouraged us to have as many patients as possible with baseline serum sodium levels of less than 130 mEq/L at baseline where, as quoted from the official FDA minutes, the usefulness of treatment is not in doubt.

In addition, there were requests for information regarding validation of the scales used to quantify improvements in mental function. A formal validation dossier has been submitted to the FDA on May 30th of this year.

[Slide]

The NDA for hyponatremia and worsening heart failure was submitted simultaneously in October, 2007 to the Cardiorenal Division. The proposed indication in the hyponatremia NDA was for the treatment of euvolemic and hypervolemic hyponatremia including patients with heart failure, cirrhosis, SIADH and others, and for the prevention of worsening hyponatremia.

The first part of this indication is consistent with that of the special protocol assessment discussed on the previous slides while the second part, regarding

prevention of worsening hyponatremia, was added based on data that emerged from the pivotal studies.

That being said, however, FDA has clearly said on numerous occasions that any indication in hyponatremia might need to be specific to those patients with more severe levels of hyponatremia at baseline, as supported by the stratification of patients with serum sodium less than 130. The 130 threshold was used in the development program for conivaptan, the only approved V2 antagonist.

In recognition of this feedback, Otsuka would be willing to discuss with the agency an alternative indication for the treatment of persistent euvolemic and hypervolemic hyponatremia in patients with baseline serum sodium less than 130 mEq/L including patients with heart failure, cirrhosis, SIADH and others, and prevention of worsening.

[Slide]

Before delving into the data it might be helpful to have a high level overview of the clinical development program for tolvaptan and hyponatremia. As mentioned previously, there were, in fact, two parallel Phase 3 development programs, one for the treatment of euvolemic and hypervolemic hyponatremia which we are here to discuss

today, and a separate program for the treatment of worsening heart failure.

In terms of total human exposure, over 4,300 subjects have been treated with tolvaptan in the global development program, including nearly 900 patients who received tolvaptan for at least one year. In terms of patients with hyponatremia, over 600 received tolvaptan, including 150 exposed for at least one year.

[Slide]

The primary efficacy data for the effects of tolvaptan on serum sodium levels are derived from the Phase 3 pivotal placebo-controlled studies in hyponatremia. These studies have been published in The New England Journal of Medicine and have been referred to by the acronyms of SALT-1 and SALT-2. The key data derived from these studies include the change in serum sodium concentrations and the percent of patients who achieved normalization in their sodium levels.

In addition, these studies uncovered very interesting effects on the prevention of worsening hyponatremia. The importance of the clinical observation on worsening warranted their inclusion in our NDA submission.

As mentioned earlier, the only attempt to quantify

the benefits of improving hyponatremia in these clinical studies were measured using specific patient-reported outcomes such as the SF-12 scale, and demonstrated improvements in mental functioning that are correlated with improvements with serum sodium levels. These measurements were prespecified secondary endpoints but were not envisioned to support definitive claims of improved outcome. Again, the primary purpose of these studies was to demonstrate improvement in serum sodium.

Additional long-term safety data in hyponatremic patients who completed the SALT studies were collected in a Phase 3 open-label, long-term extension study that has been referred to as SALTWATER. While the study was designed primarily to gather additional long-term safety data, serum sodium levels were monitored to determine if the effects of tolvaptan on increasing serum sodium concentrations could be maintained with long-term therapy.

Finally, supportive data for the hyponatremia indication come from the hyponatremic subset of the EVEREST study. EVEREST was a large, long-term study in patients with worsening heart failure. It has been published in JAMA.

In addition to supportive data documenting the improvement in serum sodium levels and the prevention of worsening of hyponatremia, which are consistent with the findings of the SALT studies, data were collected which document the improvement in the signs and symptoms of worsening heart failure and the effects on long-term clinical outcomes in these patients.

[Slide]

Otsuka hopes that by the end of today=s meeting the medical utility for the treatment of hyponatremia, especially in those patients with baseline serum sodium levels of less than 130 mEq/L, has been established for you by the expert testimony of Drs. Verbalis, Udelson and Schrier.

Otsuka believes that the data presented today will clearly demonstrate the unmet medical need for treatment of hyponatremia, especially in those patients with baseline serum sodium levels less than 130.

The literature supports that the criteria for determining the appropriate patients for treatment are not solely a function of the absolute serum sodium levels. Factors including the rate of change, the presence of

symptoms, even milder subtle symptoms, and the risk of allowing the hyponatremia to worsen all contribute to the clinician=s decision of which patients to treat. The inadequacy of current therapy will also be discussed and will demonstrate that these therapies have significant toxicities and patient compliance issues that severely limit their effectiveness.

Finally, we will discuss the fact that vasopressin antagonists represent the first class of therapies that directly target the primary underlying pathophysiology of hyponatremia, namely the excess activity of vasopressin.

[Slide]

Otsuka believes that the data presented today support the clinical benefits of tolvaptan in the treatment for hyponatremia. The data will clearly demonstrate that tolvaptan increases serum sodium levels regardless of baseline severity or underlying illness.

The data will also show that tolvaptan prevents worsening of hyponatremia and may, therefore, help to prevent more severe symptoms in patients whose serum sodium concentrations will continue to fall in the absence of therapy.

Tolvaptan produces improvements in mental functioning as measured by patient-reported outcomes. These improvements are, in fact, correlated with improvements with serum sodium levels. In addition, tolvaptan has demonstrated the ability to improve the signs and symptoms of worsening heart failure, especially with regards to weight and dyspnea. Finally, Otsuka believes that the data will support that tolvaptan has a favorable safety profile. Based on these data, Otsuka believes that the benefit/risk ratio for tolvaptan in the treatment of hyponatremia is worthy of approval.

Thank you very much. With that, I will turn the microphone to Dr. Verbalis, from Georgetown University, to discuss the medical utility of treating hyponatremia.

Unmet Medical Need in Hyponatremia

DR. VERBALIS: Good morning.

[Slide]

My name is Joe Verbalis. I am professor of medicine and physiology across town, at Georgetown University.

Over the next 25 minutes I would like to summarize the importance of hyponatremia from the perspective of a

physician scientist who has been studying, treating patients and teaching about hyponatremia for the last 30 years.

[Slide]

In the course of the talk I am going to try to cover all of these areas. But given question number 1 addressed to this advisory committee by the FDA, I am going to concentrate mostly on the symptomatology of hyponatremia and try to explain what we do know about the symptomatology and its response to correction of hyponatremia.

[Slide]

Firstly, it is important to recognize that hyponatremia demands our attention, if not solely, importantly because of the high incidence and prevalence of this disease.

[Slide]

It is very clear from studies done over the last four decades that hyponatremia is, indeed, the most common electrolyte disorder of hospitalized patients throughout the world. The prevalence varies with the level of serum sodium used to define hyponatremia. For all hyponatremia serum sodium less than 135 there is a very high incidence and prevalence, between 13-18 percent. For those more severe

forms of hyponatremia, typically accompanied by the symptomatology that we will discuss, incidence and prevalence rates are significantly lower, in the range of 2-4 percent of hospitalized patients, but still quite substantial.

[Slide]

This is documented in this recent study of over 120,000 patients followed for a year, showing that for all hyponatremia inpatient incidences were 28 percent; outpatient between 7-21 percent but, again, the more severe forms, in this case serum sodiums less than 126, much lower prevalences but still substantial in terms of the overall population.

[Slide]

To understand this high incidence of hyponatremia it is important that you first understand the underlying pathophysiology.

[Slide]

As depicted in this slide which shows a simplified human body as a beaker which is two-thirds full of water, which reflects our total body content, divided between the intracellular compartment or potassium as the major solute,

the extracellular compartment where sodium is the major solute and, under normal circumstances there is a balance of fluid coming into the body and fluid leaving the body via the kidney.

Using this very simplified reduction, this model, there are really only two ways to develop hyponatremia. If there is a depletion of body solute, and particularly sodium, either through the GI tract and the skin as sweat or the kidney as salt wasting, then there is a deficiency of sodium and typically volume contraction, and we call that a depletional hyponatremia. In contrast, if the spigot is turned too tight and the kidney is unable to maximally excrete free water and the water keeps coming into the body there is a buildup of excess water, shown here by the blue bar, which then dilutes the sodium in the extracellular compartment as well as the potassium in the intracellular compartment, and we call this a dilutional hyponatremia.

Importantly, although the sodium levels may be the same between these two states, this is the state of overall volume depletion in the body; this is the state of water excess. Today we will predominantly be talking about dilutional hyponatremias caused by an excess of body water.

[Slide]

We know the major cause of that excess body water, which is inappropriate secretion of the pituitary hormone arginine vasopressin. This shows a series of patients with inappropriate ADH secretion, which is the quintessential disease of dilutional hyponatremia.

What you see on the slide here are individual patients and AVP levels relative to their plasma osmolality. The normal range for you and I is here. Normally, when our plasma osmolality falls below 280 AVPs are suppressed to unmeasurable levels, which is that yellow dotted line. In these patients they are not suppressed and that constitutes an inappropriate secretion of this hormone which, in turn, causes the water retention and subsequently a dilutional hyponatremia.

I could show you similar slides documenting exactly the same pathophysiology for congestive heart failure and cirrhosis, but in view of time I won=t do that.

[Slide]

Let=s turn to symptomatology. In assessing the symptomatology of hyponatremia it is crucial to differentiate symptoms associated with acute hyponatremia

versus those associated with chronic hyponatremia because this impacts greatly upon our treatment decisions for this disease.

[Slide]

In studies going back several decades now it has been well documented that the majority of symptomatology of hyponatremia is neurological and pertains to brain function. As the serum sodium level decreases patients go from being alert to confused, stuporous, comatose and having seizures and, at this point, with the potential for death from respiratory arrest due to cerebral edema.

It has been well documented that this inverse relationship between how low the sodium level is and the severity of the symptoms exists. However, this slide in itself shows that in addition to this it has been well recognized that there is great individual variability in the level of serum sodium at which these symptoms present, such that you have patients with serum sodiums of 120 or less who are alert and without overt neurological symptoms and other patients at the same or higher serum sodium levels that are comatose, stuporous and seizing. This is now known, that this individual variability is mostly a function of whether

the hyponatremia is acute or chronic.

[Slide]

So, with acute hyponatremia we know that it can cause seizures. It can cause coma. It can cause respiratory arrest. And, these often progress very quickly with relatively little warning. There can also be an accompanying neurogenic pulmonary edema which causes further increased brain swelling due to hypoxia, and death, if it results, resulting from cerebral edema with herniation, and it has particularly been noted to be common in young children and women.

[Slide]

Just to show you the extent of what can happen with acute hyponatremia, this is a CT scan of a brain of an acutely hyponatremic patient compared to a normal CT scan. You can see the severe degree of brain edema with obliteration of ventricular space and the sulci between the cortex. In fact, the brain only has an 8 percent capacity to swell before it reaches the limits of the boundaries of the skull, resulting in herniation downward with compression of the respiratory centers and respiratory arrest.

[Slide]

To graphically illustrate this process from a historical perspective I would like to show you this slide, which is from the 1930s, and it represents a diagnostic test that was done back then. Of course, we weren't around then, most of us weren't, but this is important to understand what we can and can't do in terms of experimental studies in hyponatremia in which patients who were thought to have an underlying seizure disorder were given vasopressin, shown here as the extract pitressin, and were water-loaded, in this case about 6 liters over a day and a half.

In response to that, you can see that, in fact, they were able to induce seizures in virtually all patients that were given this test. Even though it was not done at the time because this was before the era of measurement of serum sodium by fluorophotometry, if you calculate out the weight gain, which is about 11 percent, this test reliably would have dropped the serum sodium concentration about 10-15 mEq/L, in this case down to about 125 mEq/L.

Now, importantly, we don't do this test anymore, nor do we do similar procedures. They have been abandoned because of the recognition that this induced EEG changes and seizures in virtually all patients given the test. More

importantly, patient deaths were reported as a result of this test.

[Slide]

And, that is important to understand because it relates to the degree that we have evidence-based randomized, controlled trials in hyponatremia. In fact, we do not have that many of that type of trial because of the potential for severe neurological complications, including death, that have made us feel that such kinds of studies have been unsafe and are unsafe, and we have known that since the 1940s.

As a result, most of the knowledge in such patients with hyponatremia is derived from retrospective reviews of outcomes with different treatment strategies rather than randomized, controlled trials of treatment versus non-treatment of hyponatremia.

[Slide]

With chronic hyponatremia, as opposed to what I showed you with acute hyponatremia, symptoms are known to be markedly less. In this single hospital study stupor or coma occurred in only 6 percent. I apologize, the column seems to have been moved a little bitB-6 percent with chronic

hyponatremia compared to 100 percent with acute. For seizures, only 4 percent chronic compared to 30 percent acute. The mortality, only 6 percent in chronic hyponatremia compared to 50 percent with acute, and none of those was viewed to be attributable to the hyponatremia.

[Slide]

The reason for this profound difference between the symptoms of chronic hyponatremia and acute hyponatremia can best be understood by the process of brain volume regulation. I am going to walk you through this because it is crucial that you understand this to understand this difference in symptomatology.

As the extracellular sodium concentration decreases outside the brain, regardless of whether that is because of a decrease in sodium or an increase in water, there is an obligate movement of water into the brain across osmotic gradients. That causes brain edema, shown by the dotted line which I also showed you on the CT scan of the hyponatremic patient. As I stated, there is only 8 percent room to expand in the brain and once that is exceeded, then death occurs because of herniation of the brain through the tentorium and the foramen magnum.

However, if the patient survives that initial episode of hyponatremia, particularly if it is a chronically slow developing hyponatremia, then a very important regulatory process occurs in which solute is lost from the brain. Electrolytes, sodium, potassium chlorate, as well as a series of small organic molecules called organic osmolytes.

As the brain loses solute it is able to lose the excess water and come into an adapted state in which brain edema is very little, in some cases actually absent by MRI and CT, and, correspondingly, most of the symptoms of acute hyponatremia that I showed you are absent because most of the brain edema is gone. However, it would be a mistake to think that this adapted state of chronic hyponatremia really represents a normal state of a normal brain.

[Slide]

The reason for that is that the cost that is paid for adapting the brain to hyponatremia is loss of solute from the brain. In experimental studies done in my lab in rats all of these compounds are lost significantly with adaptation of hyponatremia. Normal animals are shown in the black bars and the hyponatremic in the white bars.

Importantly, this includes glutamate, the most important excitatory neurotransmitter in the brain which essentially controls all motor activity including speech. This is decreased 30 percent in this model. So, the brains of adapted patients, and this has been shown and replicated in patients using NMR spectroscopy to document that these findings in animals are, in fact, valid in humans--the brains of adapted hyponatremic patients are markedly decreased in solute including important neurotransmitters.

[Slide]

But because of this adaptation process chronic hyponatremia is arguably a condition that clinicians may not need to be as concerned about, and in some papers it has been called asymptomatic hyponatremia.

This report documents that chronic hyponatremia is not really that asymptomatic. This is 223 patients with hyponatremia due to thiazide ingestion with sodium ranging from 98-129. You can see from this list of symptoms that these patients, despite having chronic hyponatremia for weeks, were in fact quite symptomatic. Though some symptoms such as dizzy spells could be attributable to the volume depletion caused by the thiazides, others such as confusion,

obtundation, falls, headache and seizures are much more likely to be consistent with the symptomatology we know of hyponatremia.

The reason I am showing you this study, which is thiazide-induced hyponatremia, is because there aren't that many hyponatremias that we can actually correct easily and see whether symptoms resolve. With thiazides it is relatively simple. We simply stop the diuretic. We give back the patient sodium chlorate and we can restore that sodium back to normal in a relatively short period of time. So, if you want to ask are these symptoms really due to hyponatremia, the fact is that in this study they all resolved with the therapy that I have shown you and correction of the hyponatremia. So, we can reliably say that, in fact, the symptoms in these 223 patients were, in fact, secondary to their hyponatremia because they reversed with correction of the hyponatremia.

[Slide]

So in summary, if you look at all of the symptoms that have been attributable to hyponatremia you can divide them into two major categories, those that are life-threatening, stupor/coma, convulsions and respiratory

arrest, and they usually occur with acute hyponatremia of less than 48 hours duration. Then, we have those which are symptomatic but patients are less impaired, and they run the gamut from headache all the way to disorientation and they are generally seen with chronic hyponatremia.

[Slide]

In addition to these neurological symptoms of both acute and chronic hyponatremia there has been a long-standing association with hyponatremia with adverse outcomes across a variety of different diseases.

[Slide]

Perhaps the best study is the relationship to heart failure in which patients with a lower serum sodium level, less than 130 and heart failure, clearly have worse outcomes in terms of morbidity and mortality in terms of survival compared to patients with higher serum sodiums. That will be discussed in greater detail by my colleague, Jim Udelson, in a subsequent presentation.

[Slide]

More recently hyponatremia has also been found to be an independent predictor of mortality in liver failure. The MELD score is used to prioritize patients for liver

transplantation and takes into account multiple parameters that dictate how sick that patient is, and how likely they are to die imminently without a liver transplant.

Notably, at every MELD score, if patients are hyponatremic, shown in the grey bars, compared to normal, shown in the black bars, the mortality rate is significantly increased. This is perhaps the best example, showing that even controlling for severity of underlying disease, in this case by the MELD score, hyponatremia confers an independent risk of mortality in patients with cirrhosis.

[Slide]

Given the frequency and symptoms of hyponatremia, it is important now to consider the medical need for treatment of hyponatremia.

[Slide]

Clinicians, including myself, have used all the therapies in this list depicted in this table over the last 40-50 years, and we use them because they all work in specific circumstances but none of them are ideal and they all have significant limitations that are summarized in this table.

But perhaps most importantly, none except

demeclocycline and vasopressin receptor antagonists actually target the underlying pathophysiology of hyponatremia which, I have shown you, is inappropriate elevations of AVP levels. Demeclocycline, however, is not FDA approved. We use it for the toxicity of the drug and not the effect of the drug itself, and it also has significant nephrotoxicity.

In the next few slides I will summarize the major drawbacks of the three treatments we use most often, hypertonic saline, fluid restriction and the AVP antagonist conivaptan.

[Slide]

Hypertonic saline is life-saving with acute hyponatremia. It has now been well documented that over-rapid correction of hyponatremia which can occur with hypertonic saline, can cause massive demyelination of descending motor neurons in the ponsB-these are several brains from humans at autopsy showing this--leading to quadriparesis and locked-in syndrome.

The important part about this is that even though this doesn't occur that frequently, it has made physicians, my colleagues, very reluctant to use hypertonic saline today in any except the most life-threatening circumstances of

hyponatremia.

[Slide]

Fluid restriction, arguably a very cheap form of treating hyponatremia simply by restricting fluids, does, indeed, work and has been the mainstay of treating chronic hyponatremia for many years. But its major drawback has been known since these studies in 1957, which were the studies by Schwartz and Barter which actually described the disease by the syndrome of inappropriate antidiuretic hormone secretion.

In this patient you can see that even with the fluid restriction that is quite severe less than 500 cc per day and, in fact at some point zero cc per day, there is, indeed, a correction of the serum sodium, in this case from 115 up to 135, but you also see how long it takes. It takes about 7 days in order to do that, and that is a rate of correction that we know, with fluid restriction, is about 1-2 mEq/L per day. So, in a symptomatic patient this would take days to get your patient to a level where symptoms are resolved.

In addition, because the patient is actually volume depleted at that point, this therapy is very poorly

tolerated due to increased thirst and compliance is quite poor.

[Slide]

Although we certainly thank the FDA for approval of the vasopressin receptor antagonist conivaptan, which I and my colleagues are using very effectively for treatment of inpatients with acute hyponatremia, even this therapy has significant limitations, including CYP3A4 interactions which limit its use to only 4 days of inpatient therapy; combined V1a and V2 antagonism which potentially could be dangerous in patients with portal hypertension and has not been studied; an attenuated aquaresis after 4 days of infusion, which limits long-term effectiveness; and a high incidence of infusion site reactions.

[Slide]

As a result, those in our field have come to the conclusion that all existing therapies, while they do work sometimes, are suboptimal for many different reasons, including variable efficacy, slow responses, intolerable side effects, and dangerous toxicities. Furthermore, and I think very importantly, other than demeclocycline which antagonizes the AVP and the kidney at a post receptor level,

none of these therapies, other than conivaptan, directly targets the underlying cause of most all dilutional hyponatremias, namely inappropriate elevated AVP levels.

[Slide]

So, before getting to discussion of therapeutic indications, let me just show you the rationale for using aquaretic therapies in hyponatremic patients, which can best be appreciated by an analysis of the determinants of the serum sodium concentration.

[Slide]

It has been known since the 1950s classic studies of Dr. Edelman and his colleagues that serum sodium is very simply the balance between the exchangeable sodium and the exchangeable potassium in the body and the total body water. Since there are only two sides to this ratio, one can correct hyponatremia by adding to the numerator, namely giving back sodium and this is what we do when we infuse isotonic or hypertonic saline. It is the treatment of choice for depletional hyponatremia when these levels are low.

[Slide]

However, we know that most of the patients we

treat in the hospital today are not depletional. Only about 20 percent are. In fact, 60, 70 percent are dilutional hyponatremias, SIADH, heart failure and cirrhosis being the major forms of this disease.

[Slide]

In these disorders it makes much more sense pathophysiologically to work on the denominator by getting rid of body water, and antagonists to the vasopressin V2 receptor are designed to do this, and do this as documented in the briefing document supplied by Otsuka to the FDA advisory committee, and which you will hear more about later.

[Slide]

So, let me close with what I think are treatment indications for treating hyponatremia. Note that these are based on current standards of clinical practice that I think amply support what I am going to propose as these indications.

[Slide]

First, it is clear that correction of hyponatremia is associated with marked improved neurological outcomes in patients with severe symptomatic hyponatremia. In this

retrospective study by Ayus and Arieff of patients who presented with hyponatremia and serum sodium levels under 130, prompt therapy with hypertonic saline resulted in the correction in the range of 20 mEq/L and all of those patients recovered from their symptomatology.

In contrast, patients presenting with the same average sodium level and the same type of symptoms who were treated by fluid restriction alone had a very small correction in serum sodium, about 3 mEq/L, in the first 24-72 hours of correction, typical of what I have shown you in the slide from Schwartz and Barter and, importantly, virtually all those patients either died or had a permanent disability and a vegetative state.

[Slide]

Consequently, acute hyponatremia presenting with these life-threatening symptoms requires therapy with hypertonic saline. It is doubtful that tolvaptan can increase the serum sodium concentrations as quickly as hypertonic saline. However, that leaves these patients with symptoms that are less impairing and less life-threatening in whom physicians are reluctant to use hypertonic saline because of the osmotic demyelination I have shown you, and

those patients with more chronic hyponatremia, with lesser but still important neurological symptoms are, in fact, the ideal target population that would benefit from employment of an AVP receptor antagonist to normalize their symptomatology.

[Slide]

What about patients who really don't have much in the way of symptomatology? Well, even in those patients there are indications for treatment of their hyponatremia. In this case, studies done at the University of Virginia showed that the single factor that best predicted patients who were admitted to the hospital with symptomatic hyponatremia, shown here, is the preexistence of asymptomatic hyponatremia, 71 percent.

So, in their hospital, 71 percent of patients who had an admission for symptomatic hyponatremia, for the symptoms I have shown you, had a preexisting asymptomatic hyponatremia. Thus, treatment with tolvaptan to maintain normonatremia could potentially prevent hospital admissions for more severe hyponatremia in these selected patients with recurrent episodes of admission for hyponatremia.

[Slide]

Finally, patients with hyponatremia have been shown and demonstrated to have significant gait instability. In this study from Belgium 12 patients were asked to walk a tandem gait, shown here on the X axis, but on a computerized platform that measures the center of gravity on the ball of their foot this slide illustrates the Gait Test in 2 of the 12 patients. I will show you the full data set on the next slide. You can see that in the hyponatremic state, 124 and 130, these patients wandered significantly off the tandem line in terms of their center of gravity. You can quantitate this simply by summing up the length of this line over a specified length of tandem walk. With correction of their hyponatremia to 139 and 135 their gait normalized in terms of center of gravity.

[Slide]

To show you the data set of all 12 patients, the total traveled way was significantly lengthened in those patients with hyponatremia to this degree. After correction of the hyponatremia this normalized to that seen in 25 normal controls. Importantly, this was significantly greater in terms of gait instability even in normal subjects who ingested alcohol to a blood alcohol level of 0.06.

[Slide]

What is the functional significance of this? In another study from Belgium 122 patients who presented to an emergency room over a one-year period with serum sodiums that were less than 130 but were judged to be asymptomatic, with no severe neurological symptoms, were compared to 244 age matched, sex matched, disease matched controls. And, the simple question asked was, why did you come to the emergency room? The asymptomatic hyponatremic patients came because of a recent fall, with a 21 percent incidence, whereas normonatremic controls only 5 percent, resulted in an adjusted odds ratio of 67 for presenting to the emergency room because of a fall if a patient was hyponatremic.

[Slide]

The real clinical significance of this is that falls in our elderly population cause increased morbidity and mortality because of fractures. In a recent study just reported this year, in 533 new fractures, compared to age and sex matched controls, the incidence of hyponatremia in the fracture group was 13 percent as opposed to 4-5 percent in the controls. Thus, the true clinical significance of hyponatremia in the elderly may be increased morbidity and

mortality associated with fractures in this group.

[Slide]

So, based on all the available data that I showed you, and there is obviously more than I have been able to show you, this slide represents a summary of what I think are reasonable treatment indications for hyponatremia, which is based predominantly on the severity of presenting symptomatology regardless of what the actual serum sodium level is, and I will describe this for those patients with euvolemic hyponatremia such as SIADH. Dr. Udelson will show you how this could be related to patients with hypervolemic hyponatremia from heart failure in his presentation.

First, at the most severe level of threat, level 3, where symptoms are severe including vomiting, seizures, obtundation, respiratory distress and coma, we know that is life-threatening and, because of that, the treatment, as I have already stated, should be hypertonic saline, followed by fluid restriction or possibly a vaptan to maintain the hyponatremia in such patients who are already proven to present with life-threatening complications of hyponatremia.

Those patients with more moderate symptoms, level 2 threat level, who have nausea, confusion, disorientation

and altered mental status, obviously are very impaired by their symptoms and need to be treated but, as I have mentioned, physicians are reluctant to use hypertonic saline for fear of inducing osmotic demyelination. Those patients are ideal candidates for treatment with a vasopressin receptor antagonists, with or without fluid restriction as required for correction of hyponatremia.

What about those patients with either no symptoms or very minimal symptomatology, headache irritability, inability to concentrate, altered mood or depression? Well, I feel that fluid restriction is still the most reasonable choice for those patients, but there are selected circumstances even in that case without symptoms where a vaptan would be indicated.

First is a therapeutic trial to see the symptoms, because even though they are mild, they do impair our patients= ability to function maximally and normally. If the sodium level is very low, and we can argue what that level should be, certainly any patient under 125, regardless of symptomatology I feel should be treated.

Others might feel that 130 is a more appropriate level to do this in any patient with recurrent symptomatic

hyponatremia because maintaining them at a normal level will prevent admissions and potential harm. Patients with unstable gait or high fracture risk because of the data I showed you on gait instability. And, inability to tolerate fluid restriction or failure of fluid restriction. Finally, in some patients the need to increase the serum sodium concentration to a normal range to allow surgical or other procedures.

[Slide]

In summary, what I have told you in the last half hour is that hyponatremia causes a full spectrum of neurological symptoms. Acute hyponatremia causes severe neurological dysfunction as a result of cerebral edema. Chronic hyponatremia is better tolerated by virtue of brain volume regulation but, nonetheless, is accompanied by neurocognitive changes and gait disturbances, possibly as a result of brain solute and neurotransmitter losses, and an increased incidence of falls and possibly fractures.

Secondly, the degree of symptomatology in any given patient depends more on the degree of brain volume regulation that has occurred than it does on the actual serum sodium level accounting for the large individual

variability in the presenting symptoms and is the reason why you simply can't use the absolute level of sodium as a marker, an indicator of who should be treated and who shouldn't.

[Slide]

Thirdly, current therapies for hyponatremia are clearly suboptimal and, with the exception of demeclocycline and conivaptan, they do not target the underlying pathophysiology which is AVP elevation. In contrast, drugs that block vasopressin activation of the renal V2 receptor cause increased free water excretion called aquaresis, and this represents unquestionably the ideal method to increase the sodium concentration in dilutional hyponatremias.

Finally, treatment indications for hyponatremia should be categorized by the symptomatology associated with hyponatremia. In most cases, this will be with serum sodium levels less than 130 mEq/L when such symptoms are more likely to occur, although carefully selected patients with levels even above this range may benefit from therapy as well in selected circumstances.

Thank you and I would like to turn the podium over to Dr. Frank Czerwiec, from Otsuka, who will describe the

tolvaptan hyponatremia development program.

Tolvaptan Hyponatremia Phase 3 Program:

Efficacy and Clinical Benefits

DR. CZERWIEC: Good morning. My name is Frank Czerwiec. I am Senior Director of Global Clinical Development with Otsuka.

[Slide]

This presentation will help to address FDA questions 1, 2 and 3. The focus will be on the primary efficacy data acquired in the Phase 3 hyponatremia program. The answer to question 2, change in serum sodium, will be addressed first. Next we will discuss patient reported outcomes. The subject of FDA=s question 3. We will also discuss the validation of these outcome tools and their correlation to serum sodium and the correction of the disease burden, which will be useful in answering question 1. These data will show that the program=s primary goal of hyponatremia correction was achieved.

[Slide]

Beginning with program design--

[Slide]

B-the SALT studies were unique in their use of

titration to achieve a gradual correction of hyponatremia. In this regard they mimic the approach accepted in clinical practice.

This schematic represents the typical progress of subjects through the SALT trials. Eligible patients were randomized to either tolvaptan or placebo in a 1:1 ratio, with stratification based on hyponatremia strategy and etiology.

On day 1 subjects were titrated from 15 to as much as 60 mg per day of study drug, with the goal of elevating serum sodium concentration to the lower limit of normal in a prompt but controlled manner. Doses could be adjusted upward if by the next day the subject was still in the hyponatremic range and the rate of change was no greater than 4 mEq/L per day.

Subjects spent the first day in hospital so that we could monitor their serum sodium, body weight and fluid balance. After 30 days of continued therapy study drug was discontinued and sodium was again reassessed 7 days later.

[Slide]

The study inclusion and exclusion criteria had three general goals, first, to identify typical patients

with persistent dilutional hyponatremia; second, to permit standard of care medications but limit medications which might confound efficacy; and, third, to enlist patients whose underlying morbidity would not unduly affect safety or efficacy evaluations.

For example, patients could have serum sodium concentrations less than 120 mEq/L but only if their mental faculties were not impaired and would not prevent obtaining informed consent.

[Slide]

As mentioned previously, the primary endpoints were the correction of serum sodium assessed as the average daily area under the curve, or AUC, for change in serum sodium from baseline to day 4 or from baseline to day 30. The FDA recommended that these be co-primary so we could assess both short-term and sustained efficacy, and accepted the Hochberg procedure to avoid multiplicity. FDA required that patients with serum sodium concentrations below 130 also demonstrate a trend towards efficacy.

[Slide]

The protocols made clear that the secondary endpoints were only meant to support the primary endpoints

or, in the case of SF-12 to assess their clinical relevance. Therefore, the secondary endpoints were not corrected for multiplicity and there were no recommendations or requirements for multiplicity adjustment given during the SPA discussions.

[Slide]

The secondary endpoints relate to sodium change, to aquaretic effects and, importantly, to patient-reported outcomes.

The items shown in white were all found to be significant in at least one of the two studies. In response to FDA=s questions today, a major emphasis will be placed on the results of the SF-12 mental components summary score and a prespecified exploratory tool, the Hyponatremia Disease-Specific Survey which was developed to help support the validation of SF-12.

[Slide]

Now, the SALT program represents the largest prospective interventional study of hyponatremia. The disposition in the SALT studies was equitable between treatment groups, with over 70 percent of patients completing the 30-day evaluation.

Typical demographic characteristics were also well balanced between treatment groups for age, gender and race, and were representative of the underlying etiologies and of the locations where the trials were conducted.

Stratification goals were also met. Over 50 percent of subjects had a serum sodium concentration at baseline below 130 mEq/L in each treatment group. The three principle etiologies of hyponatremia were also equally represented between treatment arms.

[Slide]

Now, unless otherwise noted, the efficacy results shown in the following slides are based on prespecified analyses. The primary endpoints, the average daily area under the curve for day 0-4 and 0-30 were both positive for each study. The blue bars represent tolvaptan response while the grey bars that for placebo.

The response effect averaged 3-4 mEq/L in the short term and was sustained at an average of 6 mEq/L over the full 30 days of therapy. Therefore, the efficacy criteria set forth for approval were met, the finding of meaningful efficacy in replicable studies. But, recall, the FDA also stated that this endpoint would only be acceptable

for approval if the subgroup of subjects with serum sodium concentrations less than 130 also demonstrated at least a trend.

[Slide]

In fact, this important subgroup=s results are even greater, averaging 4-5 mEq/L in the short term and 7-8 mEq/L over 30 days. The findings were again significant for each study and for each time point. This demonstrates tolvaptan=s efficacy in correcting even the more severe forms of hyponatremia.

[Slide]

So, tolvaptan works in general and for severe hyponatremia. The question was also asked whether tolvaptan worked for all of the AVP-mediated etiologies, and it does. Shown here, in this example, the endpoint was significant for all etiologies with meaningful effect sizes. As noted for other vasopressin antagonists, the degree of sodium correction was highest for SIADH and lowest for cirrhosis.

[Slide]

This time course of effect represents the mean serum sodium concentrations for each of the two SALT studies. The diamonds in the upper lines are tolvaptan-

treated patients. The circles in the lower lines are placebo-treated subjects. Statistically significant differences were observed for all post baseline time points, beginning at 8 hours after the first dose and extending through 30 days of therapy. The overall proportion of subjects reaching normal concentrations of serum sodium at day 4 and at day 30 were also significant, with an almost 5-fold and 2-fold advantage for tolvaptan in each case.

At day 30 the study therapy was withdrawn. This had little effect on the placebo-treated patients but for those who were previously given tolvaptan this resulted in a fall from above to below the normal range for these patients. This provided further empirical evidence that tolvaptan=s efficacy continued for the full 30 days of therapy but in patients with chronic or persistent hyponatremia could dissipate with drug removal.

[Slide]

Now turning to worsening hyponatremia, prespecified categorical analyses suggested that placebo subjects worsened during the trial. We confirm this finding in these post hoc analyses shown here. The bars represent the percentage of subjects in each treatment group whose

serum sodium concentration crossed from above to below the 130 mEq/L threshold or who experienced a 3 mEq/L decline from baseline in their serum sodium.

The solid bars indicate worsening at any time point during the study. The patterned bars represent anyone who had a sustained decline over successive visits during the study. You can note that the risk for any worsening was roughly 3 times higher for placebo and the risk for sustained worsening approximately 5-fold for placebo over tolvaptan.

[Slide]

Now, in question 2 FDA asks whether the effects of tolvaptan could be sustained. The SALTWATER study demonstrated that the benefits of tolvaptan could be sustained longer than 30 days. In fact, it supports efficacy for nearly four years. It also replicated the real-world use of tolvaptan in that hospitalization was not required when the drug was introduced and titration could be more gradual.

The response during the double-blind, placebo-controlled studies is shown on the left and on the right-hand graph you see the response for 111 patients who

enlisted in this open-label extension study. Note that between studies and while subjects were again treated using the standard of care their mean serum sodium concentration had returned on average to a subnormal range. Once placed on tolvaptan, the average sodium concentrations improved and remained in the normal range for up to four years. Those who discontinued therapy during this part of the trial saw their serum sodium concentrations return again to below normal levels.

[Slide]

Now, data on hyponatremia-related outcomes were collected to evaluate the clinical relevance of the primary endpoints. Our strategy to test this and the implementation is discussed in the next slides.

[Slide]

The hypothesis that sodium correction can affect health status by impacting the neurological and cognitive symptoms associated with hyponatremia was tested using patient-reported outcomes. Since many symptoms of hyponatremia are internal to the patient only they can assess the burden of their disease and the impact on treatment.

We have already demonstrated the effects of tolvaptan on sodium, the defining feature of hyponatremia, and a tool for measuring outcomes in hyponatremia was needed and we chose the SF-12 12-item short form health survey.

The SF-12 survey is an abbreviated and cross-validated form of the widely used SF-36 instrument which has been used to evaluate general health functions in thousands of subjects in hundreds of studies and in dozens of disease states. As the FDA PRO guidelines were evolving, we also recognized the need to draw a link between this general tool and the very specific neurological complaints often reported in hyponatremia.

We, therefore, developed a collaboration with the experts in the field of hyponatremia and PRO instrument development, a new tool which we called the Hyponatremia Disease-Specific Survey.

[Slide]

Now, the SF-12's questions are purposefully broad, making it a useful tool among the widest possible spectrum of clinical disorders, and each of these are rated to mental and physical function summary measures. Dr. John Ware is one of the developers of the tool and he is with us today.

And, given the questions before you, I would like to invite him to the podium to say a bit more about this tool and its use in hyponatremia.

DR. WARE: Good morning. I am John Ware. I am a research professor in the Department of Medicine at Tufts University, and I am CEO at QualityMetric, Inc.

As you can see on this slide, the SF-12 uses 1 or 2 items to represent each of the 8 health domains of the SF-36 health survey. Those 8 domains, in turn, were sampled from 40 distinct domains of health and well being that were the outcomes in the medical outcomes study, and there is an entire book written about the development of those domains.

Four of the 8 domains receive high positive weights in estimating the mental component summary score and 4 of the 8 domains receive high positive weights in estimating the physical component summary score. Despite the brevity of the reduced respondent burden of the SF-12 it is a shorter form of the SF-36 that estimates the physical and mental component summaries with about 90 percent accuracy. That reproduction has been independently verified in numerous chronic disease populations and in numerous developed countries throughout the world.

I probably don't have to tell this committee that these short forms are sufficiently reliable and valid to detect outcomes in group level comparisons such as these clinical trials because that has been shown now in more than 1,000 published randomized, controlled trials.

What you may not know is that over the years the peer-reviewed literature about these forms has grown to more than 14,000 published articles, including more than 1,000 studies in cardiovascular disease alone. This is the basis for my confidence that this is an appropriate choice for the generic health outcome assessment in the SALT trials.

Because the SF-12 is one of the most content valid generic health surveys, representing 8 of the most frequently measured generic health domains, it is particularly appropriate for the SALT trials because of the comorbidities that nearly all of these patients suffer from.

In response to questions about content validity, I would argue actually that it is a strength of the SF-12 health survey that it is not confounded with items measuring specific symptoms of hyponatremia or specific symptoms of other chronic diseases. It is a generic tool that allows us to compare and to understand the functional implications of

those symptoms.

In the comparison that Dr. Czerwiec is going to show you in a moment, comparing the well population to patients with chronic conditions with or without hyponatremia, it would not be possible to make those comparisons using a tool measuring symptoms that are specific to those conditions.

Of course, there is more to validity than content validity. Measures and results also have to make sense clinically, and I would argue that the total pattern of empirical results that we are going to see linking treatment to changes in serum sodium within treatment groups, linking changes in serum sodium to changes in the mental component summary, provides a very strong basis for us being confident when we see a significant outcome favoring treatment in the combined analysis in the mental component summary measure.

Given the symptoms that have been attributed to hyponatremia in the published literature and that were observed in these clinical trials--headaches, dizziness, confusion, irritability, mental slowing--we should not be surprised that it is the mental component summary and not the physical component summary that responded to treatment

in these trials.

Finally, because the sponsor used the standard published scoring for these outcomes and used the standard criteria for detecting change on these measures and the magnitude of differences that were observed between a fourth to a half of the standard deviation on average, I can say with confidence that average outcomes or differences in change score distributions of the size observed are clinically important. They are economically important and they are socially important in patients= everyday lives.

Dr. Czerwiec is now going to describe the other measures that were used in the trial and the sponsor=s results.

[Slide]

DR. CZERWIEC: Turning now to the hyponatremia disease-specific survey, this consisted of 1 physician and 12 patient questions. Like the SF-12, 8 of these questions are specifically focused on cognitive or physical symptom concepts and, in this case, tied to some of the more commonly seen symptoms in hyponatremia patients.

For example, questions relating to cognitive function such as concentration or calculating ability were

asked in the context of everyday activities, such as the ability to be able to focus on a conversation or calculate change. Data and analyses supporting the validity of both of these instruments for specific use in hyponatremia have only recently been provided to FDA.

[Slide]

In question 3 FDA asks about clinical relevance. Shown on this slide are 2 definitions of clinical relevance for the SF-12. Tolvaptan improved the SF-12 MCS score by greater than 5 points. This change represents nearly twice the minimally important difference defined by the clinical, economic and social improvements that John Ware just described.

Another non-specific criteria, published by Cohen and widely used in behavioral science testing, is based on the proportions of the standard deviation. Using these criteria, the 5-point difference observed in the MCS represents a moderate effect size.

[Slide]

The normative data are also useful in clarifying clinical relevance and relative disease burden on mental function. Data have been collected for the SF instruments

for patients with similar underlying etiologies to those studied in our trials in over 400 studies in heart disease and over 100 studies in liver disease.

For the MCS scoring algorithm we used questions producing a mean score for the average adult of 50, with a standard deviation of 10. The average well adult scored a bit higher at 55. The mental function for heart failure and liver patients in general based on normative data falls near that of the average adult. But if these heart failure and cirrhosis subjects had hyponatremia, as in the SALT studies or SIADH, they scored worse.

The convergence of all three etiologies between one-half and three-quarters of the deviation below this average supports a direct and clinically relevant impact of hyponatremia on mental function through the MCS, as would be expected with disorders associated chiefly with neurological symptoms.

[Slide]

The effects of tolvaptan on treatment of the mental component summary score were statistically significant in one trial and numerically favorable in the other. The effect sizes were similar between trials, such

that a post hoc pooled analysis was also significant.

Shown on the right, again, are the relative effect sizes and the minimally important difference thresholds. Based on these data, the tolvaptan group changes for MCS can be assessed as being in the clinically relevant range.

[Slide]

Now, the degree of change seen with tolvaptan treatment brought patients back from near the threshold for clinical depression to near that of the average adult. This potentially translates to improved work performance and less risk of healthcare utilization.

[Slide]

In contrast, the effects of the treatment on the physical component score were neutral, being neither statistically significant nor or a clinically relevant effect size.

[Slide]

In the prespecified pooled subgroup analyses the changes in mental component summary score were favorable regardless of the starting level of serum sodium, and statistically significant for the group beginning below 130 mEq/L. Once again, the PCS score was neutral for both

levels of starting sodium.

[Slide]

In another prespecified pooled subgroup analysis, this time by etiology, the changes in the mental component summary score were equally favorable for all etiologies, and statistically significant for the cirrhosis subgroup using the LOCF analysis, and for the SIADH subgroup. If you look at the observed case data set this suggests a robust benefit independent of the underlying pathology leading to hyponatremia. Again, the PCS scores were neutral for nearly all etiologies. This pattern is consistent and robust, arguing for a true and meaningful effect of tolvaptan on mental function in hyponatremia.

[Slide]

To better understand whether drug treatment itself or serum correction is responsible for these benefits, the correlation between serum sodium shifts, regardless of treatment, and patient-reported outcomes of the MCS were also explored.

[Slide]

In the literature there are few correlative studies of cognition and serum sodium concentration. Vieweg

et al. used the Mini-Mental State Questionnaire in a small number of subjects prone to hyponatremia and found a correlation between serum sodium levels and their score on this test. The SF-12 MCS data, including all data regardless of treatment, were also found to be moderately but significantly correlated with the change in serum sodium.

Now, this correlation held and in some cases was even better when you compared only tolvaptan or only placebo-treated subjects. The correlations also held when assessing those with only mild, greater than 130, or more severe forms of hyponatremia at baseline.

[Slide]

This figure represents another look at the data, clinical response based analysis of the correlation. Again, the data include all subjects in both the tolvaptan and placebo populations. On the horizontal axis there are three clinically relevant categories of serum sodium change noted. The right-most represents the better group and the left-most the worst group. The vertical axis represents the change in MCS scores. This analysis again demonstrates that subjects with the greatest improvements in serum sodium had

the greatest improvements in mental component summary score.

[Slide]

The correlation was even more significant for subjects beginning with a lower serum sodium. As seen on the left side of this figure, worsening serum sodium concentration was also associated with a decrement in the MCS score, while improvements with serum sodium on the right side were associated with improved mental function.

In summary, these data demonstrate a statistically and potentially clinically relevant impact of sodium correction using tolvaptan on mental outcomes which can be detected with this instrument.

[Slide]

Switching now to the Hyponatremia Disease-Specific Survey, similar results were observed. The MCS scores, and this is post hoc pooling, were significant for both the total population and for the more severe population of patients. While the physical component scores were consistently numerically favorable, the changes were again small and not statistically significant. This pattern replicated that seen for the SF-12 MCS and PCS. Even though

fewer subjects provided data for this instrument, the HDS MCS score was more significantly correlated with changes in serum sodium than SF-12.

Importantly, the HDS findings were also consistent with the SF-12 mental component summary data and correlated well, supporting each instrument=s validity in assessing mental function in hyponatremia.

[Slide]

A validation dossier for SF-12 and its use in hyponatremia had been recently submitted to FDA. This provides further analyses which document the psychometric properties of the SF-12 in hyponatremic patients. The SF-12 was judged by us to be successfully implemented in the SALT studies as assessed by tests of its psychometric performance. Important to the questions before you, the clinical validity of this tool has also been documented and illustrated for you in this presentation.

With respect to hyponatremia, the SF-12 MCS is sensitive to the disease burden. It is responsive to its correction and it is specific in finding the anticipated changes in mental functioning without finding changes in physical function. Importantly, another more disease-

specific tool implemented in some of the same patients had similar results.

[Slide]

Now, in questions 1 and 3 FDA asks about symptoms and tools used to assess hyponatremia. This figure illustrates the relationship of the SF-12 in hyponatremia disease-specific questions to the mental and physical health component summaries and illustrates which questions were most sensitive to hyponatremia correction.

Those questions highlighted in blue or green either trended or significantly improved with correction of hyponatremia in the less than 130 mEq/L subpopulation. You will note that no single question but several related questions were responsible for the changes in MCS and its significance. Few physical component questions showed any movement. Again, this demonstrates that both instruments independently and specifically detect the hypothesized mental function effects in hyponatremia.

[Slide]

In summary, the primary and nearly all of the secondary endpoints were met for the tolvaptan hyponatremia Phase 3 program. Based on these data, the following

conclusions can be drawn: Tolvaptan improves hyponatremia. Tolvaptan can prevent worsening of hyponatremia. Tolvaptan improves mental function in hyponatremia and the improvements in hyponatremia seem to correlate with improvements in patient-reported cognitive outcomes.

[Slide]

I would next like to invite Dr. James Udelson, of Tuft New England Medical Center, to the podium. Dr. Udelson will speak to the challenge of managing hyponatremia in heart failure.

Treatment of Hyponatremia in Heart Failure

DR. UDELSON: Thank you. I am James Udelson, a cardiologist at Tufts Medical Center in Boston, involved in the care and treatment of heart failure patients.

[Slide]

In the next few minutes what I would like to do, I have been asked to frame some of the issues regarding treatment of patients with heart failure who also have hyponatremia.

A typical patient might look like this, hospitalized for worsening heart failure Class III symptoms; significant left ventricular dysfunction; moderate dyspnea;

substantial volume overload, edema and orthopnea; background history of an MI; diabetes; some degree of chronic kidney disease; taking evidence-based therapies and a modest dose of furosemide as an outpatient; sodium concentration 129 mEq/L; moderate renal dysfunction on initial labs.

Now, to frame the treatment goals, of course, for patients like this, they are to relieve symptoms and to relieve congestion, but to do so without making the hyponatremia worse, and that is the challenge which I will try to address. The other potential treatment complications include, of course, worsening renal function and creating a more severe state of hyponatremia.

[Slide]

So, what I would like to outline in the next few minutes is to try and build the case that hyponatremia is a complication of the underlying pathophysiologic state of heart failure and left ventricular dysfunction; that it is a frequent problem in hospitalized patients; perhaps most importantly, that it is a practical challenge to the standard of treatment of decompensated heart failure and it is a consistent predictor of a poor prognosis and, thus, might be an appropriate target in these patients for

treatment with the agent that we are discussing today.

[Slide]

So first, the underlying pathophysiology. The initial descriptions of inappropriate elevation of vasopressin actually began in the 1960s from a report out of Japan.

[Slide]

But the modern era began with the publication of this paper 25 years ago from Goldsmith and colleagues in a group of about 30 heart failure patients, advanced heart failure, withdrawn from medications for 2 days, compared to age matched normal controls, showing that arginine vasopressin levels were elevated in the heart failure patients compared to the age matched controls, and this was by radioimmunoassay methods. This has been shown over and over again since this seminal publication 25 years ago.

[Slide]

Now, the elevated levels of vasopressin exert effects through stimulation of vasopressin V2 receptor in the kidney, as Dr. Verbalis mentioned, causing free water retention and dilutional hyponatremia, as you have heard earlier. However, in the setting of patients with heart

failure and left ventricular dysfunction vasopressin action at the V2 receptor also contributes to volume expansion, manifested as signs and symptoms of heart failure such as congestion and edema.

[Slide]

The central role of vasopressin, and particularly its action at the V2 receptor in the kidney and contributing to both hyponatremia and congestion in these heart failure patients make a class of agents such as the vaptans, which directly target the underlying pathophysiology, conceptually attractive.

[Slide]

So, hyponatremia due to the inappropriately elevated vasopressin levels does seem to be a complication of the underlying pathophysiology and part and parcel of the generalized activation of neurohormonal systems in patients with heart failure.

[Slide]

Hyponatremia is also a fairly frequent problem in hospitalized heart failure patients, and this has been seen many times in both clinical trials and registries, some of which are shown here, with the percent of patients in these

trials who are hyponatremic defined as serum sodium less than 135 mEq/L in this slide, in the Uptime clinical trial of miltirone, the active Phase 2 trial of tolvaptan, the optimized registry, the ESCAPE trial and the EVEREST trial which we will hear more about the prevalence of hyponatremia ranging from 11 percent up to 27 percent and in the 20 percent range on average.

So, this is a relatively frequent problem, and I think a somewhat less appreciated problem is that hyponatremia can also develop in the hospital as a complication of therapy in decompensated heart failure patients.

[Slide]

These are some data from a large administrative database, where yellow is the serum sodium level on admission at various cut points, here on the X axis, and purple are patients who either had hyponatremia at baseline or became hyponatremic in the hospital after being normonatremic initially. You can see at each level of serum sodium, from mild to more moderate and severe, less so down here, that hyponatremia developed in the hospital in a minority, but a significant minority of patients, likely as

a complication of treatment.

[Slide]

Thus, hyponatremia is, indeed, a frequent problem in hospitalized patients and can occur as a complication of treatment.

[Slide]

I think most importantly though, the presence of hyponatremia creates a real practical challenge to the standard treatment of decompensated heart failure.

[Slide]

This has to do in part with the mechanism of action of loop diuretics which, of course, are the mainstay of therapy in decompensated heart failure patients. Loop diuretics are associated with an isotonic urine and, thus, in the absence of highly effective fluid restriction, which is challenging as we will discuss in a moment, loop diuretic use may result in little change in hyponatremia and could worsen hyponatremia if free water intake is not adequately restricted.

[Slide]

To illustrate some of these points, I would like to show some unpublished data from the EVEREST trial. You

will hear a lot more about this in the subsequent talk by Dr. Zimmer. The EVEREST tolvaptan Phase 3 trial involved over 4,000 patients with decompensated heart failure at several hundred sites around the world who were enrolled and then randomized to tolvaptan or placebo on top of standard therapy for decompensated heart failure.

[Slide]

But I would like to use data from the placebo group, in other words standard therapy of decompensated heart failure, to illustrate some of these points.

[Slide]

First is that hyponatremia is not corrected in the majority of patients who are hospitalized with heart failure and hyponatremia during standard therapy. There are over 200 patients in the placebo arm of EVEREST receiving standard therapy. By day 1 only about 30 percent had normalized serum sodium and by day 7 or the time of discharge only about a third of patients had normalized their serum sodium.

[Slide]

Similar to what I showed you before, hyponatremia also developed in patients who initially came in with normal

serum sodium. Those patients, almost 1,800 of those patients, are shown here in the yellow. The data from the previous slide are again shown in purple. So, 11 percent of the EVEREST patients randomized to placebo, in other words standard therapy, were hyponatremic at baseline but by the time of discharge 17 percent were hyponatremic because about 11 percent of people became hyponatremic, initially coming in with normal sodium, as a consequence of standard therapy.

[Slide]

Moreover, patients with hyponatremia in the placebo arm of EVEREST had a blunted response to therapy. These are data, and you will see more about this in the next presentation, of self-assessed dyspnea score of the patients in the trial. They were asked whether they were markedly, moderately or minimally better, unchanged or worse. In yellow are the normonatremic patients. In purple are the hyponatremic patients.

As you can see, fewer patients with hyponatremia reported themselves as moderately or minimally better; more patients were unchanged and more patients were worse. The difference in proportions here was significant. This suggests that patients with hyponatremia have a less

favorable response to standard therapy as regards changes in dyspnea, which is the main symptom they come in with, of course.

[Slide]

Now, it is also of interest to look at the diuretic dosing in these patients. Shown here on the Y axis is the mean daily IV furosemide dose among patients who received any dose of intravenous furosemide during their hospitalization at multiple time points. On the X axis, yellow is the hyponatremic patients; purple is the normonatremic patients.

As you can see, at each time point, and in fact growing a bit during the course of the trial, the patients with hyponatremia were more aggressively diuresed, higher doses of IV furosemide and, thus, these blunted responses, or the less favorable response, to dyspnea happened despite higher diuretic dosing, suggesting these patients are diuretic-resistant, very difficult to treat and have a less favorable response to therapy.

[Slide]

So, it is, indeed, a practical challenge to the standard treatment, and I think people who take care of

these patients, particularly with severe hyponatremia, have all had the challenging experience of trying to institute fluid restriction, turning off the water in the room, etc. It is, indeed, very difficult.

Of course, many studies, and Dr. Verbalis showed some of this, demonstrate that hyponatremia is a consistent predictor of a poor prognosis. There are many studies. I will just showed you data from EVEREST, very contemporary data.

[Slide]

This is in-hospital mortality on the You axis; admission serum sodium on the X axis. Among those with severe hyponatremia there was a substantial increase in in-hospital mortality, again, shown in many other papers for further time points out from the hospitalization.

[Slide]

Thus, it is, indeed, a consistent predictor of a poor prognosis.

[Slide]

I would like to finish by going back to the treatment algorithm that Dr. Verbalis showed you for euvolemic hyponatremia with fluid restriction, the potential

role of vaptans, hypertonic saline for severe symptoms, and try to extrapolate this to the patients with hypervolemic hyponatremia, the heart failure patients.

[Slide]

Just to demonstrate that our repertoire of approaches for patients like this for their management is, indeed, quite limited. Fluid restriction is very difficult, as everyone knows. These patients are thirsty. They are on diuretics. Instituting and managing effective fluid restriction is very difficult and, of course, hypertonic saline would be essentially contraindicated in these patients. So, our repertoire of approaches to these patients is, indeed, very limited and it is a very challenging group of patients to treat.

[Slide]

So, I would like to turn the podium over to Dr. Zimmer, who will discuss some of the treatment effects of tolvaptan. Thank you.

Supportive Data from the Tolvaptan Phase 3 Heart Failure Program for the Treatment of Hyponatremia

DR. ZIMMER: Good morning, everyone. The information that I am about to share with you, the

information contained in this presentation, will respond to question number 4 in the list of FDA=s questions to the panel. Question number 4 relates to any other benefits of treating hyponatremia that have been shown in the sponsor=s development program.

As you heard earlier, the development program for tolvaptan consisted of two pathways. There was a pathway for the treatment of hyponatremia and, separately, a pathway for the treatment of worsening heart failure. The pivotal Phase 3 safety and efficacy trials in hyponatremia, the SALT trials, enrolled significant proportions of patients with heart failure. Conversely, the pivotal Phase 3 safety and efficacy trials in heart failure, the EVEREST trial, enrolled a significant proportion of patients with hyponatremia.

This presentation focuses on that subgroup of patients, patients with hyponatremia from the Phase 3 heart failure development program. Why? Because the supportive data that arise from looking at this subgroup of patients will help complete the story from a clinical patient management perspective.

[Slide]

What is that patient management story? Well, the case that I would like to build is that correction of low serum sodium and improvement in fluid balance are linked. They are intertwined in patients with hypervolemic dilutional hyponatremia. In other words, the aquaretic effects of vasopressin antagonists such as tolvaptan would be expected to not only correct serum sodium but also directly improve congestive signs and symptoms in heart failure.

There is a twist. As Dr. Udelson discussed earlier, the foundation for the management of congestion is conventional loop diuretic therapy. The challenge is that the presence of low serum sodium in certain patients with heart failure may cause physicians to pause before using diuretics for fear of worsening the hyponatremia.

So, one indirect benefit of correcting hyponatremia in certain patients may be a sense among clinicians that these therapies can be used more safely, which would also potentially lead to improvement in signs, symptoms or clinical outcomes.

The reason I am showing you these pathways is because whether they are convergent as I have shown here, or

independent, these pathways form the underlying basis for understanding the data, understanding the effects of managing hyponatremia on associated congestive symptoms in patients with heart failure.

[Slide]

Now, it is important to be clear. The data I am showing you come from a subgroup of patients from the EVEREST trial. So, I am going to begin by laying a brief foundation, sharing with you the study design, providing a brief overview of the primary results, followed by the supportive results relating to the effects in patients with hyponatremia and heart failure.

Dr. Udelson focused earlier on the practical treatment challenge, for example, how do you prevent worsening of hyponatremia when the drugs that you need to use to manage congestion do just that, worsen hyponatremia? What I am going to share with you is that in fluid overloaded heart failure patients= serum sodium and body weight can be improved.

We will also discuss an analysis of dyspnea and these fluid overloaded hyponatremic heart failure patients which shows a greater treatment effect. Finally, the data

relating to the effect of tolvaptan on clinical outcomes, especially in patients with heart failure and severe hyponatremia, will also be presented.

[Slide]

You have seen this before, a schematic of the EVEREST outcomes trial. Patients were randomized within 48 hours of hospitalization, then entered a treatment period, finally completing a 14-day post treatment followup period.

All patients were randomized to either standard medical therapy plus placebo or standard medical therapy plus tolvaptan. The thing that is important to note is that no medications were withheld. The median duration of treatment was about 10 months, and the trial was designed to continue until 1,065 deaths had occurred.

Over 4,100 patients were randomized and all 4,100 patients were assessed for the dual primary endpoints of time to all-cause mortality and, separately, the composite of cardiovascular death or heart failure hospitalization. Every mortality event, every cardiovascular or hospitalization was adjudicated by an independent committee to consistently evaluate events across the entire population. It is also important to note that this trial

was specifically designed to rule out excess mortality in a severe heart failure population.

[Slide]

So, what was the profile of the average EVEREST patient? As I mentioned, patients were randomized within 48 hours of hospitalization. All patients had systolic heart failure with ejection fractions less than or equal to 40 percent. All patients demonstrated signs of fluid overload. The exclusion for renal impairment permitted a wider range of renal function than typically seen in clinical trials. The creatinine exclusion was greater than 3.5.

[Slide]

Now, in the EVEREST trial there were no specific inclusion or exclusion criteria relating to serum sodium which permitted a broader distribution of baseline sodium levels. In fact, 11.5 percent of patients were hyponatremic with serum sodium levels less than 135. Of these patients, 383 had serum sodium levels between 130-134; 92 had serum sodium levels less than 130.

[Slide]

Focusing on these 475 hyponatremic patients for a moment, what was the profile of this subgroup relative to

the overall population? In general the hyponatremic subgroup, as highlighted in the box on the right, mirrored the overall population, and the overall population was typical for a clinical trial in worsening heart failure. In terms of cardiac function, the average ejection fraction was about 27 percent. About 40-50 percent of patients were in NYHA functional Class IV. Approximately 40 percent of patients had diabetes, and a quarter of patients had renal insufficiency.

[Slide]

The overall EVEREST population and the subgroup of patients with hyponatremia, both were well treated. Large proportions of patients received diuretics, ACE inhibitors, beta blockers, aldosterone receptor antagonists both at baseline and throughout the trial. With respect to the profile of congestion, at baseline approximately 90 percent of patients had dyspnea; 80 percent had edema.

[Slide]

Let=s take a look at outcomes in the overall population. What you see here, on the left, is the Kaplan-Meier analysis of all-cause mortality and, on the right, the composite of cardiovascular mortality and heart failure

hospitalization.

Now, as I mentioned a moment ago, both of these primary endpoints were based on independently adjudicated outcomes. The analysis plan permitted excess mortality to be ruled out with an upper bound of 1.11. So, in the overall population, therefore, there was no difference, neither improvement nor worsening, associated with tolvaptan treatment.

With respect to other outcome secondary endpoints, for example the composite of cardiovascular mortality and morbidity, the incidence of cardiovascular mortality, the incidence of worsening heart failure, none of those differed between the two treatment groups.

[Slide]

However, for the prespecified secondary endpoints relating to signs and symptoms, statistically significant improvements were seen in dyspnea, in body weight, in edema which were evaluated in large numbers of patients, and also in serum sodium. No significant changes were observed at outpatient week 1 for the Kansas City Cardiomyopathy Questionnaire, a heart failure specific quality of life questionnaire.

[Slide]

So, within the subgroup of heart failure patients with hyponatremia, all of the primary and secondary endpoints that I just described were evaluated, sodium correction, body weight outcomes. What I am going to share with you are the post hoc analyses using the specific cutoffs of sodium of 135 and sodium of 130 that were used in the SALT trials. Beginning with sodium, what about the practical challenge of trying to correct hyponatremia in a fluid overloaded heart failure patient receiving diuretic therapy?

[Slide]

The data from the EVEREST trial shows that tolvaptan produced consistent and lasting increases in serum sodium in fluid overloaded heart failure patients with hyponatremia. Looking for a moment at the X axis, inpatient days are shown on the left; outpatient visits on the right. Looking at the Y axis, serum sodium, beginning with a baseline of about 131 mEq/L is shown, demonstrating statistically significant improvements that occurred early and lasted throughout the treatment period in patients receiving tolvaptan.

The key message here is that the long-term placebo-controlled data that derives from the EVEREST trial provides evidence for efficacy of tolvaptan relative to standard of care well beyond the 30-day treatment period examined in the SALT trials. But simply improving low serum sodium isn't the only thing that is important to a clinician. Achieving normalization, preventing worsening, preventing new onset of hyponatremia, all of those things factor into the ultimate treatment objective.

[Slide]

And, we observe that among patients with hyponatremia in the EVEREST trial. Significantly greater proportions of patients did achieve normal serum sodium during their hospitalization. Here day 1 is shown on the left. Discharge is shown on the right. The Y axis represents the percent of patients with serum sodium greater than 135.

This data responds directly to one of the challenges that Dr. Udelson discussed earlier, the challenge of improving hyponatremia with standard medical care. Here we see that standard of care is only associated with about 29 percent normalization, while normalization was observed

in 64 percent of patients using tolvaptan by the time of discharge. Beyond normalizing serum sodium, use of tolvaptan was associated with less frequent worsening of hyponatremia. Here, among those patients already with hyponatremia, those that worsened to below 130 was significantly smaller among tolvaptan-treated patients.

[Slide]

Dr. Udelson also spoke earlier about the difficulty posed by the relatively frequent development of hyponatremia among patients with normal serum sodiums during their course of hospitalization. These were patients who were not hyponatremic at baseline. Among those patients with normal serum sodiums in the EVEREST trial, significantly smaller proportions of patients receiving tolvaptan developed hyponatremia any time during the study falling below the cutoffs of 135, shown on the left, and 130, shown on the right.

[Slide]

So, pulling all of this together for a moment, we have seen that tolvaptan therapy results in improvements in serum sodium. We have seen that it results in lower rates of new onset hyponatremia. We have seen that it can

decrease the incidence of worsening of hyponatremia. But does that translate into anything further? It does.

[Slide]

We know that with respect to signs and symptoms the literature from multiple trials suggests that dyspnea is the most frequent symptom in patients hospitalized with worsening heart failure. It is a symptom that causes tremendous fear and anxiety among patients. The sensation has been likened to a sense of impending death. For clinicians it represents an urgent treatment priority in patients hospitalized with worsening heart failure.

In EVEREST patient-assessed dyspnea on day 1 was measured using a 7-point scale. Patients were asked to self-rate their breathing relative to the initiation of study drug therapy. This was the same scale, by the way, that was used in the VMAC study of nasiritide.

The relative proportions of patients who assessed themselves by each category are shown in the current slide. The three worsening categories have been merged because on top of standard therapy very few patients worsened. What you see is that there was broad consistency in each category, with each of the categories of improvement showing

an advantage associated with tolvaptan treatment.

[Slide]

If we compile all of the categories of improvement and all of the categories of worsening into a typical responder type analysis, the proportion of patients reporting an improvement in their self-assessed dyspnea was amplified. It was more than doubled in patients with heart failure and hyponatremia compared with the overall population where the incremental improvement was approximately 6 percent.

To respond to the point that Dr. Udelson made earlier, part of what you may be observing is less effective standard medical therapy in the placebo group. But to close the loop on a point that we started out with originally, whether it is the direct effect of aquaresis or the indirect effect of greater use or efficacy of standard medical therapy, it appears that patients with heart failure and hyponatremia do better with respect to the symptom of dyspnea.

[Slide]

And, these improvements in dyspnea occurred in the context of statistically greater body weight reduction in

patients hospitalized with heart failure and hyponatremia. Orienting for a moment to this slide, the magnitude of body weight loss in the hyponatremic subgroup is shown on the left on day 1 and then on the right on day 7 or discharge. Use of tolvaptan was associated with a similar incremental, maintained loss in body weight from day 1 to day 7 of about 0.75 kg or about 1.6 lbs relative to standard of care.

Now, for the clinician routinely involved in managing fluid overloaded heart failure patients with hyponatremia, body weight remains a clinically important guide to fluid management therapy. But what is the relevance of this additional 0.7 kg, 1.6 lbs loss in fluid weight in one day?

[Slide]

Here, to our knowledge for the first time is a statistically significant association between improvement in dyspnea and mean reduction in body weight. Those patients reporting the greatest improvement in dyspnea had the greatest decreases in body weight.

Now, this analysis which was conducted in the overall population illustrates the length between fluid management using body weight in the congested patient and an

important symptom in heart failure. But it also helps answer the question what exactly is the clinical relevance of the incremental loss of 0.7 kg of additional fluid weight that we saw earlier. This correlation suggests that if subjects lost 0.7 kg they would move from no change in their dyspnea to moderately better in the self-assessed dyspnea.

[Slide]

Finally, and most importantly with respect to outcomes, we know that no studies, including EVEREST, conducted thus far have been powered to adequately detect an effect of treating serum sodium on outcomes in patients with hyponatremia. You saw earlier in the overall population that there was no difference, neither improvement nor worsening, associated with tolvaptan treatment. And, in a prespecified non-inferiority analysis of all-cause mortality tolvaptan was demonstrated to be non-inferior to placebo, ruling out the risk of excess mortality with therapy.

However, in a post hoc subgroup analysis of patients with hyponatremia using the sodium cutoff of 130, which many in the field identify as a group worthy of treatment, and focusing on these endpoints--all-cause mortality, cardiovascular death, heart failure

hospitalization and the combined endpoint of cardiovascular death and cardiovascular morbidity--in each case the point estimate favored tolvaptan, and in the final endpoint of cardiovascular death and cardiovascular morbidity, this reassuring trend reached a nominal p value of p less than 0.05, albeit in small numbers of patients.

[Slide]

Now, when we looked more closely at this last endpoint, the endpoint of cardiovascular death and cardiovascular morbidity, using Kaplan-Meier analysis, we observed essentially no separation in the curves in the subgroup of patients greater than 130, shown here on the left, but separation that occurred as early as 2 months in the subgroup of patients with sodium less than 130.

To be clear, this is a non-prespecified post hoc analysis designed to explore potentially supportive data. It provides further indication for the safety of tolvaptan in this important subgroup of patients.

[Slide]

In summary, we believe that we have addressed the issues raised in question number 4, and have demonstrated with these supportive post hoc analyses that treatment with

tolvaptan was associated with improvements in serum sodium and reduced worsening of hyponatremia; greater improvements in patient-assessed dyspnea; increased fluid removal as evidenced by decreases in body weight; and a reassuring cardiovascular safety profile.

[Slide]

I would like now to introduce Dr. William Carson to review the broader safety profile of tolvaptan.

Questions from the Committee

DR. HIATT: Thank you very much. I wonder if we could just pause for a second here. We are coming up within a few minutes of a break and I know your presentations were scheduled for after the break. I hope it would be all right if we could maybe just take ten minutes, because we have heard a lot of material, and have the committee ask some clarifying questions and then come to your safety presentation after the break.

We have ten minutes or so. I guess I would like to ask the committee to try to clarify anything they have heard today. I guess I would like to take the prerogative to ask the first question.

We are going to be asked to deliberate the value