randomized sample we didn't know exactly what was in it. But it turned out that we had 7 people treated with tolvaptan and 12 on placebo; 4 males on tolvaptan, 11 males in the placebo group, a total of 19 subjects.

Here are the curves. You have seen lots of them. I am not going to go into too much detail but the bottom line there is that they started out at around 130. We had 12 of those 19 subjects. When we looked at our data and Goldman=s data and a couple of other subjects from other sites, those above 130 and those below 130 were about split 50/50. But you can see up there that both groups, the tolvaptan group and the placebo group, started at a mean of about 130.

We had a rather dramatic separation in serum sodium 8 hours after the first dose that morning. That number is not statistically significant but it did reach a 0.08 level. By the next morning we had 0.05 in terms of differences in values.

The endpoints that Otsuka was looking at, as reported, mostly have been day 4 out here and day 30 out here. But I just took the liberty of putting all the data points up there so you can see them. The size of that

effect in this sample was 0.7, a small sample but a huge effect. You also notice that when the drug was stopped at day 30 serum sodiums went back down to where they started.

So, is hyponatremia important to this population? It is a critical issue. It is an unmet need. As I say, most of the conversation today is not in schizophrenia at all, but I just raise it as something that I hope in your deliberations you consider as something that is critical for this population and their families.

In terms of our fellow here, at least to my knowledge, this is the longest person being treated with a vaptan. He started out in the conivaptan project and then went...

DR. HIATT: Can someone get the mike back on?

DR. JOSIASSEN: Like most of these folks, they don't get to be discharged from these institutions because the community is terrified of having folks in their programs that have seizures or they are going to die so they wind up staying in state hospitals.

He has been now out in the community for more than four years. He has had no seizures since he started conivaptan. Instead of being sort of this mute little guy

in the corner, it turns out John actually speaks three languages and has begun to utilize all of them, is a bit more engaged socially in the day programs and in his living arrangement out in the community.

So, my plea to you all is to think about schizophrenia and the importance of it as you discuss tolvaptan and hyponatremia. Thanks.

DR. HIATT: Thank you very much for your perspective. Are there any other speakers for the open public hearing? I know only one was registered. Are there any others? If not, then we are going to close this part of the session and we will now move back to the sponsor to address questions that were raised in the morning session.

Questions from the Committee (continued)

DR. McQUADE: Thank you, Mr. Chairman. We will start with some of the more specific questions and move to some of the more theoretical and conceptual questions as we go through our discussion.

I forget who asked the specific questions so my apologies to those people. In terms of what sites were included in the SALT studies, I would like to ask Dr. Czerwiec to address where the sites were; what kind of

quality they were in response to that.

DR. CZERWIEC: Thank you. Can I have the slide on, please?

[Slide]

I am going to speak specifically to the two SALT studies. The SALT-1 study was conducted in the United States. There were 42 investigative sites participating in this. Of those, the vast majority of them, I would have to say, were nephrology physicians or physicians specializing in nephrology.

As the study evolved there were also investigators who were cirrhosis experts or hepatologists. There were very few oncologists. I don't believe any of those participated; and some generalists and some endocrinologists. Could I have the next slide?

[Slide]

The SALT-2 study was conducted in North America and in Europe. Again, this is the distribution of sites between the different countries. The types of investigators was very similar amongst these populations as well.

DR. HIATT: Thank you.

DR. McQUADE: Thank you. The next question that we

were asked to discuss was the adverse event of thirst. I think Dr. Stevenson asked this question. Again, Dr. Czerwiec will address this in terms of what we observed in our clinical studies and the design of those studies. Frank?

DR. CZERWIEC: Yes, I will begin and then I will ask Dr. Berl to give a clinician=s perspective. Thirst was very important, as was indicated by Dr. Warner. In terms of helping our patients to manage the level of water that their body needed, we actually require that patients have an intact sensation of thirst, and I believe that is also going to be reflected in our label as a requirement for patients being treated with this drug.

It is a very effective mechanism of managing that. Nevertheless, thirst was also reported as an adverse event in our studies in a higher proportion of patients with tolvaptan than in placebo. I would like to show one piece of data that we collected using the Hyponatremia Disease-Specific Questionnaire as well. If I could have the slide up, please?

[Slide]

During the use of tolvaptan--on tolvaptan in the

purple or the lighter bars, and placeboB-patients were asked the question whether or not they felt thirsty or how thirsty they felt. As you can see, very many patients reported a level of thirst that was relatively high. But the differences were significant between the treatment groups, probably most significant at day 18.

Now, this is somewhat different from the adverse event data that you have seen in our AE tables where a much larger number of patients on tolvaptan reported thirst. We have to keep in mind that thirst is a very cyclical type of event. The person will sense thirst only when they are relatively volume depleted or their sodium concentrations become elevated relative to where they were previously and respond to that with drinking behavior and then satiety, and then the cycle will go around again over the course of the day.

So, thirst probably occurred many times during the day in our patients, probably was recognized more by the patients as this being something different perhaps but, in a sense, really it is less of an adverse event and more of a physiological and a protective response, as was described. I will ask Dr. Berl to stand up and speak to that as well.

DR. BERL: Tom Berl, University of Colorado. I want to echo this. I was repeatedly impressed by the patients complaining of thirst and puzzled by the fact that it occurred at levels of serum sodium well below what we would consider normal, suggesting that it is the trait of change perhaps of serum sodium that triggers the thirst.

But I want to turn what is reported as an adverse effect to some protective effect that mitigates against unduly large changes in serum sodium. You may recall that from the 7 patients that Dr. Czerwiec described as having a large change in serum sodium, more than half of them had been water restricted. So, I would view the stimulation of thirst as protective and mitigating against what would be an undesirable increase in serum sodium.

DR. LINCOFF: In connection with that then, in the extension study was thirst in excess? The rates, were they high as well? Because one would assume that once they have reachedB-I understand there was not a comparative group but once one has reached a stable level of sodium one would have expected those levels to be sort of historical controls.

DR. CZERWIEC: Dr. Berl just mentioned in passing that the patients that he has in that study aren't really

complaining of thirst that much but, again, it is something that was probably sensed as being somewhat different by the patients and they acclimate more to it. So, I mean, it is more of a difference in routine perhaps than an actual problem that the patients are experiencing.

DR. WARNER STEVENSON: I wonder if maybe Dr. Schrier could comment on the thirst. I was quite impressed by the consistency with which thirst was an AE. Up to about 20 percent of patients, you know, 5-8 times that in the placebo group and, certainly, when we are talking about symptoms thirst is quite a prominent one for many patients with heart failure in general. It is not necessarily a pleasant sensation at all.

DR. SCHRIER: Well, patients with heart failure do have arterial under-filling secondary to their decrease in cardiac output and that is the nonosmotic barrier receptor stimulation of vasopressin. But I am sure, though the data is less compelling, the same nonosmotic pathway barrier receptor mediated is stimulating thirst. So, these patients in general have thirst.

Now, your question about why would tolvaptan make them thirstier, I think we don't know because it certainly

is not in the range where the osmotic stimulation of thirst would explain it. It is too low. But there is some data suggesting that change in osmolality could explain that. And, maybe there is some psychological effect. When you urinate more you think you are supposed to drink more. So, I don't think we have hard data but, to me, it is not surprising that patients with heart failure who are thirsty become a little more thirsty, some of them become a little more thirsty when they are having diuresis secondary to tolvaptan.

DR. WARNER STEVENSON: Except, as I understand it, in chronic therapy with tolvaptan the major change is relatively early on in terms of the weight, fluid and sodium and then it stays fairly stable. Yet, it looks as though thirst continues to be an issue.

DR. SCHRIER: Well, they probably stabilize because of thirst, and I think that is a defensive mechanism that Dr. Berl was talking about. So, the osmolality doesn't change even though the urine output is higher because they drink more.

DR. HIATT: Thank you. There were a couple of other residual questions. One was the confidence intervals

around the hyponatremia population mortality rate, and the other one that Lynn asked for is separating that group of patients between 130 and 135 and looking at their outcomes differently.

DR. ZIMMER: Hi, Dr. Hiatt and Dr. Stevenson. The figure that I am going to show you is from page 81 of the briefing package and actually shows the subgroups of all-cause mortality and the other two endpoints, cardiovascular mortality and heart failure hospitalization, cardiovascular mortality and cardiovascular morbidity, using the cutoffs of 135 and 130. Just for clarity, you are interested in looking at that subgroup of patients between 130 and 135.

We have a series of Kaplan-Meier analyses for each of these three endpoints so I just show you these to help orient you based on what is in the briefing package.

[Slide]

This is the Kaplan-Meier analysis for the first of the three endpoints, all-cause mortality for that subgroup of patients with sodiums between 130 and 134. You will see that the confidence interval includes 1, a slightly higher upper bound so slightly less confidence here but a p value of 0.15.

[Slide]

The next analysis looks at the second of the three endpoints, the composite of cardiovascular mortality and heart failure hospitalization, also in the same subgroup. So, going down the series of three endpoints, this is the second in the series, confidence interval narrower with an upper bound of 1.32, p value of 0.7459.

DR. HIATT: Remind us once again which population you are drawing this from. Go back to the one before.

DR. CZERWIEC: This is the ITT population from the EVEREST trial. So, all patients randomized irrespective of whether they received treatment; all patients randomized irrespective of whether they received treatment and EVEREST trial patients worsening with heart failure. The cut of patients with sodium between 130 and 134.

Then just marching down the three endpoints, this is the first one, all-cause mortality.

[Slide]

The second one, cardiovascular mortality and heart failure hospitalization. I will just let you look at this for a moment. Upper bound, 1.3, p value 0.745.

[Slide]

Then the third endpoint which was the one that had a nominal p value and sodium less than 130, cardiovascular mortality and cardiovascular morbidity.

Does that help a little bit, Dr. Stevenson, jut to round out the picture?

DR. McQUADE: Thank you. And, the confidence interval for the hyponatremia safety set?

[Slide]

DR. ZIMMER: I think, Dr. McQuade, you were going to talk to this one for the analysis that was asked about earlier, relating to some of the differences between the FDA=s analysis and our analysis.

DR. McQUADE: I believe what was asked for in the question was for the confidence intervals in the safety set, the all-hyponatremia safety set. Here are the 95 percent confidence intervals that we calculated over lunch.

DR. HIATT: All right. Let=s have the committee look at that. What I would expect, with a few less events but not wildly different than the overall heart failure population. Comments on that to make sure we digest that information?

DR. TEMPLE: Is this the less than 130? Which

group is this?

DR. McQUADE: This is the all-hyponatremia safety set, so all patients in the Phase 2/3 controlled studies. That was the one that was specifically asked for, the all-hyponatremia less than 130 is the next line down. These are the confidence intervals. The all-hyponatremic heart failure here. The EVEREST hyponatremic heart failure here. The EVEREST hyponatremia patients excluding the post treatment period and, finally, the EVEREST patients less than 130.

DR. HIATT: Could you hold that up for a moment and just let the committee go through that? The question was asked earlier whether non-hyponatremic heart failure patients would provide a suitable safety database for an indication where you would exclude those patients from this therapy. So, let=s just look at these numbers and see if we are convinced that that is, in fact, the case.

[Inaudible question]

DR. McQUADE: No, the first one is not. The first one is the primary safety database for all patients, and these are the confidence intervals, again, a slightly lower rate with tolvaptan. This is the hyponatremia safety set, a

slightly lower rate with placebo with the corresponding confidence intervals. These are the hyponatremic patient with less than 130, a slightly lower rate with tolvaptan and the confidence intervals.

DR. HIATT: Just to clarify what we are seeing, if you take everybody the upper limit of the confidence interval is below 1.0. So, that is a really good thing. But if you then go to the populations of interest, all-hyponatremia, the confidence intervals go to 1.4. It is obvious why these things happen.

DR. McQUADE: Right, they are smaller patient populations.

DR. HIATT: Sure.

DR. LINCOFF: But it leaves out the intent-to-treat analysis.

DR. McQUADE: This is not the intent-to-treat analysis. This is treatment emergent adverse events leading to fatalities as described in the protocol.

DR. LINCOFF: So, if a patient dies the day after you stop the drug they are not on this.

DR. McQUADE: Chris, would you comment to that, please?

DR. ZIMMER: They would be included in this.

DR. LINCOFF: What is the window? The table 7.3.1-1 of the FDA packet actually has a numerically higher rate of mortality with tolvaptan. Now, granted, that was the complete intent-to-treat which I understand in the big heart failure trial was forever for the duration of the trial and, obviously, somewhere in between may be worthwhile. But what was your window here? If a patient had an event and stopped the drug and then died a couple of days later from an event, was that also included?

DR. HIATT: Yes, because ITT for efficacy is the most conservative but it is on treatment for safety that is the most conservative. So, the question is critical. Are we counting events that might not reflect the exposure or not?

DR. ZIMMER: I am actually going to read from the FDA=s own briefing package to give the definition. It is on page 68. For Phase 3 the sponsor used the definition beginning more than 7 days after the end of treatment period, so adverse events beginning more than 7 days after the treatment period were excluded. What was the treatment period? The treatment period was defined as the latter of

the study drug end date or the date when the decision was made to permanently discontinue drug.

DR. McQUADE: So, the adverse event had to occur during treatment or within 7 days.

DR. HIATT: Any comments on that? Lynn has got me interested in the 130-134. If we had the point estimate for the 130-134 the odds ratio is obviously greater than 1.0 and obviously with very broad confidence intervals. So, this gets to something that Bob Temple asked us, are we comforted by a safety database that looks in total pretty good for mortality unless there is something different about the hyponatremic patients.

So, now you have the hyponatremic patients who were less than 130 where the point estimate is in favor of the drug but the greater than 130 is where the point estimate is on the other side. Now, obviously, these confidence intervals all overlap but it is not as though, Bob, the point estimates all nicely line up on the same side. There is some divergence and I fully understand uncertainty and confidence intervals, but they are not all nicely lined up.

DR. TEMPLE: It may be but it is a little funny.

They oscillate in somewhat unexpected ways. Right?

DR. HARRINGTON: Unexpected if you think you know what everything does.

DR. TEMPLE: Well, whatever I think I know, the less than 130, which is the more extreme deviation, looks okay. The less deviation is slightly the other side. That is why we invite you guys here so you can explain things like that.

DR. HARRINGTON: But you are the one that always tells us that we don't necessarily go into this with the belief that we understand all the physiology, and I would just accept the data for what it is, that the point estimate falls on one side for one group, falls on the other side for the other. And, I don't have enough knowledge. I could create a hypothesis, I am sure. It is the old Ashow us the data, we'll come up with the hypothesis.@

DR. TEMPLE: My initial reaction to things like this is that the confidence intervals are very broad and you don't know--

DR. HARRINGTON: That is the key phrase, we don't know.

DR. TEMPLE: What does Jim think?

DR. NEATON: One of the problems in interpreting this is you have all these overlapping groups so there are three mutually exclusive subgroups. You know, greater than 135, 130-134 and less than 130. What is the evidence that those odds ratios are different from one another? My guess is that there is no evidence that they differ. But that should be quantified.

DR. LINCOFF: I would also point out, I mean, we would like to see them lining up on the same side but here the overall for hyponatremia is almost exactly 1.0. So, you know, the likelihood by randomness that if you picked different groups they are going to be on either side a little bit to average to 1.0 is higher than it would be if the odds ratio were, say, 0.8 or something like that.

DR. HARRINGTON: Correct, but my only point, Mike, is that we are uncertain.

DR. HIATT: Right, but we do have some upper boundary on that certainty so let=s make sure that is registered too. I mean, it may be as much as a 40 percent increase that can be excluded. Of course, then it gets down to what is the benefit relative to that level of risk excluded.

DR. HARRINGTON: If you show that Kaplan-Meier, did I get it correct that for the 130-134 the lower boundary was about 0.9 and the upper boundary was 1.4? Was that correct? So, most of the data is on the other side. So, I am just pointing out that we don't know. There is not a lot of information with the number of patients.

DR. HIATT: Right, but we can say, across all these subgroups, that you are excluding a certain amount of risk. You know, it is not a 50 percent risk. The boundaries are tighter than that no matter how you cut it. They haven=t shown us anything that is worse than around 40 percent.

DR. McQUADE: Dr. Koch, would you like to comment?

DR. KOCH: Yes.

[Slide]

Again, let=s look at the three displays again, the Kaplan-Meier curves, the XU-1, which is basically the mortality one.

[Slide]

Then look at the next one.

[Slide]

And then look at the third one. Basically, what is going on here is your are essentially seeing random

variation about 1.0, as your colleague said. If you keep drawing random samples from a population for which the hazard ratio is 1.0 some of them will be bigger than 1.0, some of them will be less than 1.0.

The sponsor presented results for less than 135 because that is the population they studied in the SALT study. They presented results less than 130 because that was a population that had been identified as of particular interest in the SALT study. The results pretty much fit together across the different criteria that you would look at and across the different populations.

DR. WARNER STEVENSON: I am comfortable with this, you know, in terms of the variation. I just thought it was important because it is a much larger group than the less than 130. So, if we are going to look at the hyponatremic I wanted to make sure we were looking at the higher group.

DR. NEATON: I don't know whether we are going to pass this. I have four relatively brief design questions and I don't know whether to ask them now.

DR. HIATT: Were there any more on your list that you wanted to get to?

DR. McQUADE: Somebody asked for additional

information about cirrhotic hemorrhaging and we were prepared to address that question. There were also some comments around the small data set size that we had discussed this morning that we were prepared to make additional comments to as well. But I leave it to the discretion of the Chair.

DR. HIATT: The goal here is to get through these residual questions, go to the FDA presentation, then perhaps go through a final round of questions. So, why don't you go ahead and complete issues raised this morning, if you could?

DR. McQUADE: Fine. Then I will ask Dr. Carson to address some of the questions that came up about the cirrhotic bleeds.

[Slide]

DR. CARSON: This slide presents a summary of all of the cirrhotic patients. These are from the SALT-1 and SALT-2 trials. There were 63 patients on tolvaptan, 57 on placebo. I presented the percentages of a history of varices. As you can see, 23 of the tolvaptan patients, or 36.5 percent, had a history of varices versus 13 of 57 of the placebo patients, leading to a percentage of 22.8.

With regards to the concomitant medications for

this patient population, you see the data here. For warfarin you had 3 patients on placebo; a similar number of patients for heparin; and 2 for aspirin; and 4 for placebo.

[Slide]

This was the slide that you saw during the presentation. This is the summary of the cirrhotic patients with bleeds so the numbers are the same that you just saw. For the tolvaptan patients you had 63 patients. That is the denominator. And, 57 patients for placebo. You had 6 bleeds for the tolvaptan-treated patients versus 1.

We would like to point out that with regard to the patient GI bleeds, one of those patients had a rectal GI bleed with a known history of hemorrhoids, and these are the concomitant medications for that population.

Dr. Robinson had asked a question about the V2--

DR. LINCOFF: I am sorry, can you go back to the previous slide, please?

[Slide]

This is obviously very different, now recognizing that those 5 were of those who bled.

DR. CARSON: Yes.

DR. LINCOFF: So, there were 23 patients in the

tolvaptan group who had varices and 5 bled so that is about 20 percent. There were 13 patients in the placebo group who had varices and only one bled, so that isB-what?--8 percent. So, that is sort of a difference. If you have a varice, at least numerically you have a higher risk of bleeding in the tolvaptan group than the placebo group, which is sort of a different impression than we got I think.

DR. HARRINGTON: And is this all the bleeding data you had? I didn't realize it was 15 out of 63. Did you collect bleeding information in other trials?

DR. CARSON: With regards to cirrhotic patients, this is the information we have.

DR. HARRINGTON: These drugs have antiplatelet activity. Did you not, as part of the overall SALT population, collect bleeding? Then, I would be interested in the EVEREST trial which is heart failure. A large percentage of those must be patients with ischemic heart failure who likely are on aspirin. Do we have bleeding data in the EVEREST trial?

DR. CARSON: Just one second.

DR. HARRINGTON: Okay.

DR. HIATT: Then maybe we can wrap up with this

level of questions.

DR. CARSON: Slide up, please.

[Slide]

This is a presentation of the SMQ analysis of the adverse events of hemorrhage and this excludes the laboratory terms. This shows the populations so you have the primary safety population, and this would be warfarin use. So, what you are seeing are the patients who are taking warfarin in each of these populations, as well as the terms of hemorrhage for those particular populations.

So, in the primary safety population you had 161 of the 893, so 18 percent, versus similar number or 21 percent in the placebo population. For hyponatremia, this is the concomitant warfarin use so 118 patients took warfarin and 31 had an adverse event term of hemorrhage versus 32 in 117 in placebo.

DR. McQUADE: Then the numbers on the bottom reflect the patients who did not have concomitant warfarin. Therefore, if you add up the first line you get to the primary safety database of over 6,000. The second line gives you the hyponatremic safety database of over 1,100.

DR. HARRINGTON: So, this looks very reassuring

from a bleeding perspective, but just define for me hemorrhagic term and why excluding laboratory, and laboratory, I am assuming, means drop in hematocrit, hemoglobin, that sort of thing.

DR. CARSON: I am going to ask Dr. Zimmer to go through the SMQ for this particular term.

DR. ZIMMER: Hi, Dr. Harrington. Yes, you know, the MedDRA dictionary contains over 17,000 terms so we provide these prespecified lists of terms to help with signal identification. Hemorrhage contains literally dozens and dozens of terms relating to any type of hemorrhage from rectal bleeding to skin bruising, for example, and this particular category excludes all of the laboratory variations that would have related to bleeding. We have separate ones that include laboratory terms. Slide up.

[Slide]

For example, this variation on the SMQ analysis includes or is limited to the laboratory terms.

DR. HARRINGTON: Great. Thank you.

DR. HIATT: Any other residual questions from this morning?

DR. McQUADE: I think the only other thing we were

going to discuss was that Dr. Morgenroth was going to make some comments about the small safety data set to sort of extend the discussion that we were having this morning about that, and Dr. Verbalis was going to comment on the small set within the SIADH population.

DR. MORGENROTH: I will try to make this very brief. My name is Joel Morgenroth. I am a consulting cardiologist from Philadelphia.

I was impressed with the comment made by Dr. Wolfe regarding approximately 90 subjects in the database to infer tolvaptan safety for those with sodiums under 130. Of course, as we learned from all these presentations, if you actually look at all the patients that are under 130 it is really almost 189, I believe, that were studied on tolvaptan, I believe it is too small a database to be comfortable about safety.

The company has spent close to five years or over five years trying to acquire patients less than 130 and has obtained this number. It needed to go from the SALT trials where they only had 50 to cast a much wider net in EVEREST, looking for a different indication but, in so doing, added a lot more hyponatremic patients. They have had close to 500

sites around the world for five years.

So, I wonder if it is practical to get to thousands of patients with hyponatremia under 130 to get comfortable about safety. So, as Dr. Temple pointed out, the next best thing is obviously to pick a population where you use tolvaptan to see if there are any safety signals that would come out. I think his word was fragile. The fragile population I would think would be the one studied in EVEREST. The huge number of events I think attest to that. There, there appears to be no signal of harm.

Clearly, there is no basis from preclinical and electrocardiographic data to worry about proarrhythmic events. So, it is just a simple point that I am not sure that it is practical to do other than what the sponsor has done.

DR. WOLFE: A quick follow-up on that is that were this drug to be approved--and, again, it is for outpatient use; it is not pronolol like the predecessorB-it is not just likely, it is certain that there will be huge numbers of people with serum sodiums under 130 who would use it. We haven=t heard anything about that this should never be used by anyone under 130. So, the practical effect of an

approval would be to expose large numbers of people with sodiums under 130 to this drug for which, as you have just said, there is a very tiny database.

DR. MORGENROTH: So, one has to be comfortable that the surrogate of the huge heart failure population in up to 3,000 patients on tolvaptan without a signal is sufficient for approval. Then, obviously, Phase 4 surveillance to make sure that that was the right decision, assuming that is the decision. That would be the standard approach, would it not?

DR. WOLFE: In the FDA briefing and also the presentation they are going to give this afternoon they actually show an excess mortality in both subjects with hyponatremia in the Phase 2 heart trial and the subjects with heart failure enrolled in the hyponatremia trial. So, it isn't as though there isn't some worry there, and these are both point estimates that are above 1.0 and they don't provide the confidence intervals.

So, again, I am very concerned about approving a drug that will be used by tens, if not hundreds of thousands of people, many of who have serum sodiums under 130 who don't have heart failure and who are at risk not just for

whatever interaction there is between the disease that caused their low serum sodium, but the low serum sodium itself. We know that it is the ones under 130 at most risk for the over-rapid restoration of the serum sodium level and, again, this is going to be outpatients.

The study was done first day in the hospital and there are a number of things, including the inclusion/exclusion criteria, that make it very different than the real-world situation that would occur if this drug were approved.

DR. HIATT: I might suggest that this is a good segue to the FDA presentation.

DR. MORGENROTH: Just a quick comment. The final comment that I will make is, as I think was addressed by Dr. Koch, the point you are making. If you look at various subsets, clearly, you have one on one side of 1.0 as a confidence interval and others on the other side. The FDA pointed out the one on the bad side of 1.0. I am comfortable that the overall is 1.0 and that, in fact, when you look at the worst population under 130, you go on the opposite side. But, you are right, that is the decision of comfort you have to make.

DR. WOLFE: We have different levels of comfort.

DR. HIATT: Thank you very much. We will transition now to the FDA presentations.

FDA Presentation

Tolvaptan for the Treatment of Hyponatremia

DR. THOMPSON: My name is Aliza Thompson. I am a medical officer at FDA. Before I begin, I would like to point out that in the version of the slides that you got there are some errors. So, I would like you to pay attention to the slides that you are going to see up here today.

[Slide]

As you heard this morning, the goal of tolvaptan=s development program was to establish the product=s ability to raise serum sodium. The primary endpoint in the Phase 3 hyponatremia trials was a change in serum sodium. As you heard today and as this slide is meant to show, the Phase 3 trials successfully established tolvaptan=s ability to raise serum sodium.

That being said, a critical question remains, and that question, of course, is what is the clinical significance of this rise in serum sodium in the studied

population?

[Slide]

In addressing this issue today I would like to focus on three questions. One, who was studied in the tolvaptan development program? Two, is serum sodium a valid surrogate for benefit in this population? And, finally, three, how the benefits weigh against the potential risk of tolvaptan?

[Slide]

Who was targeted? Well, to address this question it is really best to begin by focusing on the inclusion and exclusion criteria. Notable inclusion criteria included hyponatremia and euvolemic or hypervolemic states. In this case, hyponatremia was defined as a serum sodium less than 135, made on one measurement prior to randomization. In terms of notable exclusion criteria, these included acute and transient hyponatremia associated with head trauma or postoperative state; low sodium levels, sodium less than 120 with associated neurologic impairment; and essentially subjects who, it was felt, would likely require IV saline.

In essence, if you think about these inclusion criteria, it meant that subjects essentially with mild

hyponatremia would be enrolled; essentially subjects with seemingly asymptomatic hyponatremia would be enrolled; and essentially subjects without a clear medical imperative for treatment.

In terms of the duration of hyponatremia, it is a little bit hard to know. Certainly, some subjects with acute and transient hyponatremia were excluded from these trials but it is possible that some who had other etiologies of acute and transient hyponatremia were enrolled.

[Slide]

Given these inclusion and exclusion criteria, it is perhaps not surprising that the mean serum sodium level in patients who enrolled in this trial and treated with tolvaptan was about 120 mEq/L and fewer than 30 subjects actually had serum sodiums less than 125.

[Slide]

Let=s move on to what we know about hyponatremia, its clinical significance. As you heard this morning, acute and severe drops in serum sodium are associated with cerebral edema potentially and also herniation. This can manifest with increasing lethargy, with eventually respiratory failure, death or permanent neurologic

disability.

This is what we see with acute and severe drops in serum sodium. But what about the population we are talking about, patients with relatively mild hyponatremia, patients with seemingly asymptomatic and possibly chronic hyponatremia?

[Slide]

What do we know about that population? Much of what we know comes from the published literature and comes from observational studies in the published literature. And, what you heard this morning was about things like falls in the elderly, essentially subjects with hyponatremia defined as a serum sodium of less than 133 mEq/L; that these subjects fall more than subjects with higher serum sodium levels; that in patients with heart failure with hyponatremia, defined variably, sometimes as a serum sodium less than 135, that these subjects are more likely to be rehospitalized; that these subjects are also more likely to die than those with higher serum sodium levels.

You also heard about data in subjects with cirrhosis. Again, that these patients are more likely to suffer from refractory ascites or hepatic encephalopathy

than, again, their counterparts with higher serum sodium levels.

But what do these observational studies really tell us? I would argue that what they tell is about association and not causation; that what they tell us is that low serum sodium levels are markers of sick patients. But they don't tell us whether or not raising serum sodium levels ultimately helps the patient to feel, function or live better.

[Slide]

As you heard, the primary endpoint in the Phase 3 hyponatremia trials was a change in serum sodium. This slide is meant to show the secondary endpoints studied and, as you can see, the vast majority of these 15 secondary endpoints also focused on changes in serum sodium. Only one of these secondary endpoints really looked at possible clinical benefit to raising serum sodium in this population and that is, of course, the SF-12. Though we heard that hyponatremia is associated with falls and hospitalization with neurocognitive deficits, we don't really see any of these listed as secondary endpoints for the Phase 3 hyponatremia trial.

It is because of this that we asked the sponsor to go back and look through their data and do post hoc analyses. These post hoc analyses looking for a clinical benefit to raising serum sodium are clearly very important. But that being said, as you consider these analyses we ask that you remember their limitations and it seems that you have done that.

[Slide]

You have already heard this morning about some of these patient-reported measures of quality of life, and you are certainly going to hear a lot more about them from Dr. Papadopoulos who will speak after me. I want to touch on them just briefly.

The SF-12, as you heard this morning, was a patient-reported measure of quality of life that was conducted in both of the Phase 3 trials. As you remember, in one of these trials but not the other, and for one of the scores, the mental component but not the physical, a statistically significant difference was seen between the two treatment arms.

What to make of this? You certainly raised a lot of important questions this morning about the results of

this, including concerns about the lack of specification for maintaining the alpha at 0.5; concerns about the amount of missing data.

But really the chief concern should be whether or not this instrument has content validity for this population; whether or not this instrument actually measures the signs of hyponatremia that we heard about today. Again, Dr. Papadopoulos will talk more about that shortly.

[Slide]

Another patient-reported outcome that you heard about this morning was the Hyponatremia Disease-Specific Survey. Again, this instrument was developed internally by the sponsor. It was conducted in one trial, or studied in one trial and, following the conduct of this trial, a post hoc decision was made to combine four of the questions to calculate a mental component. It was found that by combining these questions a statistically significant treatment effect was then seen between tolvaptan and placebo-treated subjects.

Again, what do we make of this instrument? I think, again, the same questions are raised, statistical questions. Are we concerned about the post hoc nature or

statistical analysis plan? Again, the key question again is whether or not this instrument ultimately has content validity for the population of interest.

[Slide]

In addition to these patient-reported outcome measures, other exploratory measures or analyses were conducted as part of the Phase 3 hyponatremia trials. In contrast to these patient-reported outcomes, these were actually direct assessments of what a patient=s neurologic function was. A neurologic exam was done in both Phase 3 hyponatremia trials and this neurologic exam included things like muscle strength, tone, tremor, ataxia and at least in one of the trials data was collected on most subjects on stance, gait and coordination.

Remember, you heard today that some of the observational data has suggested that mild hyponatremia is associated with changes in gait. This neurologic exam seems to have been measured maybe 6-7 times during the course of the study. So, it is an interesting question to ask what they found.

I would just like to point out that what they found during these multiple measurements was some slight

changes in reflexes in one trial; stance with eyes closed at week 2 in one trial; and ataxia, and I can't remember whether it is right finger to nose or left finger to nose, in the intent-to-treat analysis in trial 1560-3238. This actual difference was found after the subjects had been off treatment for 17 days. So, in essence, not strong evidence to support real clinical benefit to raising serum sodium in this population.

[Slide]

Now, what I have focused on to this point in the talk are really secondary endpoints and exploratory analyses that were conducted as part of the Phase 3 hyponatremia trials. But, as was pointed out, other studies were also done in patients and, specifically, tolvaptan was also developed for another indication, as treatment for worsening heart failure.

What I would like to do now is focus on the Phase 3 heart failure trial and some of the efficacy findings presented to you this morning in this subgroup of subjects, the subgroup of subjects enrolled in the Phase 3 heart failure trials who had hyponatremia.

[Slide]

What did you hear? Well, you heard that there was no difference in the Kansas City Cardiomyopathy Questionnaire, a patient-reported measurement to assess overall health. You heard that what there were changes in body weight at day 1 and in patient day 7, and changes in patient-assessed dyspnea at day 1.

[Slide]

What do these data tell us? What do they tell us about the clinical benefit of raising serum sodium in this population? What I would argue is they tell us very little about that. What they do tell us is about tolvaptan as a treatment for worsening heart failure, which is separate from tolvaptan as a treatment for serum sodium, again, using tolvaptan simply to treat a patient because their serum sodium is low.

[Slide]

With that, I would like to move on to the safety database. There has been a lot of discussion about the safety database already and what I would like to do is sort of go over again where the patients are coming from.

Over 3,000 subjects with heart failure or hyponatremia were treated in multiple dose placebo-

controlled trials. As the pie chart on the left is meant to show you, the vast majority of these subjects did not have hyponatremia.

If you look at the subset with hyponatremia, you can look to the pie chart on the right and you can see that about 40 percent of subjects with hyponatremia were enrolled in the Phase 3 hyponatremia trials and got the proposed dose of 15-60 mg of tolvaptan. About 40 percent of our safety database of hyponatremia subjects comes from the Phase 3 heart failure trial and got a set dose of 30 mg. Finally, an additional 20-25 percent were enrolled in either Phase 2 heart failure trials or Phase 2 hyponatremia trials.

[Slide]

Another way of looking at this population of hyponatremic subjects in the safety database is by serum sodium level and by underlying etiology of hyponatremia. As you can see in the pie chart on the left, only approximately 9 percent of enrolled subjects had serum sodiums less than 125 in the safety database and the vast majority of subjects with hyponatremia in the safety database had heart failure as an underlying etiology.

Now, why do we care? Why does this matter? Well,

it matters to the extent whether or not we can generalize findings from this larger, essentially normonatremic heart failure population to patients with lower levels of serum sodium to patients without heart failure. Again, if susceptibility to tolvaptan=s adverse effects are influenced at all by these underlying factors, then analyses of this larger safety data set will be a bit misleading.

[Slide]

With that, I would like to move on to some of the safety findings which have actually already been discussed in depth by the committee members. I would like to begin by focusing on mortality in subjects with heart failure and hyponatremia. If you look at mortality in the overall development program, mortality, as you saw, was similar in tolvaptan- and placebo-treated subjects.

But if you look in subjects who had hyponatremia, a much smaller data set, there was a numerically small difference between the treatment arms. And, if you looked for where this difference in mortality was being seen, it was primarily driven by subjects with heart failure with hyponatremia and enrolled in the Phase 3 heart failure study so, again, a subset of subjects.

[Slide]

What do we see? Now, there have been a lot of presentations already about mortality and I would like to point out that some of these presentations that you have seen this morning have focused on mortality within an intent-to-treat population. Though an intent-to-treat population is an appropriate analysis to run for an efficacy analysis, when you are thinking about safety what you actually want to know is whether or not you are looking at someone who actually got drug and when the adverse event actually occurred relative to the drug.

The Phase 3 heart failure trial allowed patients to go on and off the drug during the course of the trial. Moreover, you could discontinue from the drug and you would still continue to be followed for many months thereafter for the efficacy analysis.

If you look at all treated subjects within this Phase 3 heart failure trial you will see that mortality was, in essence, no different between the treatment arms. But if you look in the subgroup of subjects with hyponatremia and look at deaths on treatment or within 7 days of stopping the drug, you see again that numerically there is a difference

between the two treatment arms.

What to make of this? It is hard to know, but one thing one could do in trying to understand this better is to look at heart failure subjects with hyponatremia who were enrolled in other studies conducted as part of the tolvaptan program.

So, the yellow is meant to show you those subjects with heart failure and hyponatremia enrolled in the Phase 3 heart failure trial. And, now I would like to focus on subjects with heart failure and hyponatremia enrolled in these other studies.

[Slide]

And what do you see? Essentially, there are small numbers of subjects in these studies but, again, you see very small numerical differences essentially showing a worse outcome in tolvaptan-treated subjects with hyponatremia and heart failure.

[Slide]

Moving on then to another adverse event and another population, subjects with hyponatremia and cirrhosis, as you saw this morning and as you heard, GI bleeding was more common in subjects who received tolvaptan

and had cirrhosis than in subjects who received placebo.

Now, why look at bleeding in this population when overall in the total population bleeding was not more common in tolvaptan-treated subjects? The reason to do so is because, as many of you know, the V2 receptors are involved in von Willebrand Factor and Factor VIII release and these factors play an important role in hemostasis. Moreover, we know that patients with cirrhosis are at a particularly high risk of bleeding. So, I thought it was important to look at bleeding in this population.

In addition to looking at bleeding analyses, they also focused on ecchymosis, again, do we care about ecchymosis? Are these horrible adverse events? Perhaps not, but they are another indication of hemostasis and if you look at GI bleeding and you combine it with ecchymosis you see that there really is a dramatic difference in the two treatment arms.

Now, why is this? Is this because of differences in underlying risk for bleeding? It is possible. Is this because of an effect, a target effect that tolvaptan has happening? I think that this is possible too, and I think that with only 63 subjects enrolled in the Phase 3

hyponatremia trials with cirrhosis and hyponatremia treated with tolvaptan in these trials, it is really hard to know what to make of this data.

[Slide]

In beginning this presentation I raised three questions and before I close it I would like to raise one final issue, which is whether or not the findings in tolvaptan=s development program can be extrapolated to a population with more severe hyponatremia. In order to address this question we need to look at it from both an efficacy and a safety standpoint.

[Slide]

In this slide you see on the X axis baseline serum sodium level. On the Y axis you see maximum change in serum sodium during the course of therapy. There are very few data points, as you will note on the far left-hand side of the slide, hence, in subjects with lower baseline serum sodiums.

What the slide does suggest is that even at the lowest levels of serum sodium studied, it appears that tolvaptan=s treatment effect is preserved.

Now, I would like to add a comment about this

slide because I think it can be confusing. You have to remember that in treatment with tolvaptan patients were placed on titrated doses, with the goal of essentially bringing patients to a serum sodium above 135 which meant that, of course, subjects with higher baseline levels of serum sodium don't have much room to budge. But with that sort of caveat in mind, I think again there are very few data points at the lowest or extremes of serum sodium unless they suggest that the ability to raise serum sodium is likely preserved.

[Slide]

But what about safety? Here I think is really where we have a problem because very few subjects with low serum sodiums were studied. Again, to the extent that susceptibility to tolvaptan=s adverse effects are influenced by baseline serum sodium level, it will be hard to determine safety in this population based on the database that we have.

[Slide]

So, in closing, really it is for you all to answer these questions but as a reviewer I would like to just provide a few comments.

Who was studied? I think it was patients with mild and seemingly asymptomatic hyponatremia.

Is serum sodium a valid surrogate for benefit in this population? I would argue that the clinical significance of raising serum sodium in this population remains unclear.

[Slide]

Did the development program establish tolvaptan=s safety? I think that the database is limited. I think it is limited in particular to subjects with greater degrees of hyponatremia and to subjects with SIADH and cirrhosis.

And, just one final comment, I think that in the setting of uncertain benefits, the tolerance for risk should be low. Thanks.

DR. HIATT: Thank you. Let=s move on to the next FDA presentation.

Tolvaptan for Hyponatremia

FDA Overview of Patient-Reported Outcomes

DR. PAPADOPOULOS: Good afternoon.

[Slide]

My name is Elektra Papadopoulos and I am an endpoints reviewer in the Study Endpoints and Labeling Group

at the FDA. I will be discussing the FDA review of the patient-reported outcome measures in the tolvaptan clinical studies for the hyponatremia indication.

[Slide]

I will first introduce the patient-reported outcome measures that were used. Next I will discuss some principles and concepts from the draft PRO guidance. I will then discuss PRO measurement issues related to the tolvaptan treatment program. I will start with the 12-item Short Form Health Survey, SF-12, and then I will discuss the Hyponatremia Disease-Specific Survey.

[Slide]

The primary claim that the sponsor has proposed is tolvaptan for the treatment of hypervolemic and euvolemic hyponatremia and for the prevention of worsening hyponatremia. The PRO instruments in the clinical studies for the hyponatremia indication were included to support this primary claim.

[Slide]

The two patient-reported outcome measures in the clinical studies were the hyponatremia indication were the SF-12 and the Hyponatremia Disease-Specific Survey, or the

HDS.

The SF-12 was the only secondary endpoint that was a PRO and it was used as an outcome measure in both the Phase 3 clinical studies for the hyponatremia indication, which I will refer to as study 235 and study 238. The Hyponatremia Disease-Specific Survey was the only exploratory endpoint that was a PRO. The HDS was used in study 238 only and was added as a study assessment and an amendment to the clinical protocol.

This presentation is limited to the hyponatremia indication. Although other patient-reported outcomes were used in the studies of tolvaptan and congestive heart failure I will not be discussing these in this presentation. Specifically, I will not be presenting the dyspnea status instrument and the Kansas City Cardiomyopathy Questionnaire.

[Slide]

I will first discuss some important concepts from the FDA=s draft PRO guidance. The draft PRO guidance was published in February of 2006. The development of this guidance was based upon the principle that in defining a clinical benefit it is extremely important to determine how a patient feels, functions and survives as a result of

treatment. However, it is equally important that the instruments used in the clinical trials are valid measures of that benefit.

The guidance describes how the FDA evaluates patient-reported outcome instruments when used as efficacy endpoints in clinical trials, and it provides recommendations for developing and studying these instruments in order to support labeling claims.

[Slide]

The guidance defines treatment benefit as an improvement in how a patient survives, feels or functions as a result of treatment.

[Slide]

A patient-reported outcome measure is defined as any measurement that is reported as a direct response from patients without interpretation by anyone else. An example is asking patients to rate their pain severity on a scale from 1-10. PROs are the preferred means of measuring aspects of treatment benefit that are known only to the patient, for example pain. However, PROs are not designed to measure cognitive function because patients with compromised cognition or mental status are not able to

respond reliably.

[Slide]

Content validity is crucial for any PRO intended for establishing treatment benefit and for supporting claims of the treatment benefit. When the FDA approves a claim of treatment benefit the evidence to support that claim must correspond with the language represented by the claim. Content validity is evidence that the score produced by the PRO instrument represents the claim and the questionnaire items are appropriate, comprehensive and interpretable to patients in the clinical trial. Content validity is established with input from the patients in the target population through qualitative research, including patient interviews.

To be Afit for purpose@ the content validity needs to be established in the context of the target population and the disease. So, I will give a brief example. Physical functioning is a complex concept. In order to adequately develop an instrument to measure physical functioning input from patients is important to ascertain what clinically meaningful items should be included.

A physical functioning questionnaire for patients

with rheumatoid arthritis would require different items compared to a physical functioning questionnaire for patients with congestive heart failure. The rheumatoid arthritis questionnaire would probably contain items referring to ability to open doors or open jars, whereas, the congestive heart failure questionnaire would contain items referring to ability to walk distances or climb stairs.

Although both questionnaires would measure physical functioning, the patient input is used so that the questionnaires are tailored to the target patient population and indication.

[Slide]

Now I will discuss the issues concerning the use of the SF-12 and the HDS in the hyponatremia studies.

[Slide]

As I mentioned, to evaluate the content validity of a PRO instrument and whether it is Afit for purpose@ we need to assess the instrument in the context of its use. To this end, I will review again the major symptoms of hyponatremia. As we have already heard, hyponatremia results in neurologic symptoms ranging from mild confusion

to disorientation, to obtundation, coma and seizures. Hyponatremia may also result in other symptoms such as headache and nausea. The symptoms can vary according to the severity of the hyponatremia and its acuteness.

We know of no qualitative research in patients with mild hyponatremia that provides us a clear picture of how such patients feel and how their symptoms vary over small changes in serum sodium. A PRO measure to support treatment benefit claims in mild hyponatremia would need to be sensitive to the specific changes in the population. Physical examination of patients with symptomatic hyponatremia should include careful evaluation of mental status and cognitive function and, as I mentioned, PRO measures are not designed to measure cognitive functioning.

[Slide]

I will first discuss the SF-12.

[Slide]

The SF-12 was the only secondary endpoint that was a PRO in the clinical studies for the hyponatremia indication. Version 1 of the SF-12 which has a 1-week recall period was used. There is not a single score for the SF-12 but, rather, two scores, the mental component summary,

the MCS, and the physical component summary, or the PCS.

Neither the MCS nor the PCS can be scored unless all 12 items are complete. The change from baseline in the MCS and PCS was evaluated one or two weeks after randomized, depending on the study, and again at study day 30.

[Slide]

The SF-12 is a measure of overall health status that was developed for use in the general population. As such, the SF-12 does not assess the important symptoms of hyponatremia. Some items of the SF-12 do not appear relevant in the target population. For example, one item asked, during the past week how much has pain interfered with your normal work? In addition, the 1-week recall period limits the utility of the SF-12 as a measure of more acute fluctuations in health status.

[Slide]

A copy of the SF-12 is included in your briefing package. I will give an overview of the item content and describe some of the items in more detail. There are 12 items in all, and they are summarized in 7 numbered groups. The first item asks patients to rate their general health on a 5-point scale, from excellent to poor.

The second set of items asks respondents does your health now limit you in moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf, and whether they are limited in climbing several flights of stairs. There are three possible responses: yes, limited a lot; yes, limited a little; and no, not limited at all.

The third set of items asks as a result of your physical health, have you accomplished less than you would like, and were you limited in the kind of work or other activities? The response options for these items are yes and no.

[Slide]

The items identified here, under number 4, relate to limitations as a result of emotional problems. As a result of any emotional problem, have you accomplished less than you would like, and didn't do work or other activities as carefully as usual? Item 5 is related to bodily pain.

[Slide]

Item 6 asks how the respondent has been in the past week. Specifically, how much of the time during the past week have you felt calm and peaceful; did you have a lot of energy; and have you felt downhearted and blue? The

response options for these are on a 6-point scale.

[Slide]

The final question asks how much of the time has your physical health or emotional problems interfered with your social activities.

[Slide]

I will now present a brief overview of the scoring of the SF-12. As I said earlier, the SF-12 results in two summary scores, the MCS and the PCS. The same 12 item are used to calculate each of these summary scores but are weighted differently for each summary score.

[Slide]

For the MCS and the PCS higher values indicate better health status. The scores are standardized to the general population and range from 0-100, with a mean of 50 and one standard deviation equal to 10 points. All 12 items must be complete to generate the scores.

[Slide]

Next I will discuss the day-30 results from the SF-12 for both of the Phase 3 hyponatremia studies.

[Slide]

I will start with study 235. Recall that the

mental component summary and physical component summary are scored on a scale from 0-100, a mean of 50 and higher values indicating better health status. The mean baseline scores are shown on the left. We see that the mean baseline MCS score was numerically higher in the placebo group compared with the tolvaptan group. With treatment the baseline group differences and mean change from baseline in the MCS score was 3.9 in the last observation carried forward analysis and 5.3 for the observed cases analysis.

Note that there were substantially fewer patients with day-30 assessments compared with the numbers randomized. Although these results were statistically significant, the clinical significance of this finding has not been established. The mean change in the physical component summary score, in contrast, did not show any trends with tolvaptan treatment.

[Slide]

The results for study 238 are shown here. Again, the mean baseline scores are shown on the left. We see that the baseline mean summary scores for both MCS and PCS are comparable between the treatment arms. With treatment the between group differences and mean change from baseline in

MCS score was 2.2 in the last observation carried forward analysis and 2.4 for the observed cases analysis.

In contrast to the results for study 235, the results of this study were not statistically significant. Therefore, this study did not replicate the findings of study 235 in terms of the magnitude or statistical significance of the treatment effect. The PCS did not show any effect in either of these studies. Importantly, an a priori hypothesis in terms of what represents a clinically meaningful inter-patient change was not prespecified.

[Slide]

Interpretation of the mental component summary score is difficult for several reasons. Specifically, the content validity of the MCS as a supportive outcome measure of the intended claim is not established for hyponatremia patients.

The most important and relevant symptoms of hyponatremia are not captured by the MCS, and we do not know what acute changes might be experienced by patients. The inclusion criteria do not require patients to have symptoms of hyponatremia at baseline. In addition, the clinically important inter-patient change in MCS is unknown for

patients in the target population.

[Slide]

To summarize, the SF-12 MCS and PCS are not measures of the clinically important signs and symptoms associated with hyponatremia, and they have not been shown to be measures of mental and physical function in hyponatremia patients. The MCS does not measure cognitive functioning, an important concept needed to support the primary claim. Therefore, these measures are not appropriate as stand-alone measures to support labeling claims of treatment benefit in patients with hyponatremia.

[Slide]

I will now discuss the Hyponatremia Disease-Specific Survey.

[Slide]

The HDS was an exploratory endpoint in study 238. It is a 12-item instrument. Patients are requested to respond on the basis of the previous 2 days. It was assessed at baseline, week 2 and day 30, as well as post treatment. The endpoint was not included in the original study protocol and was first included in a protocol amendment once the study was already under way.

As such, the Hyponatremia Disease-Specific Survey was assessed in a subset of patients participating in the study. Of the 234 patients randomized, baseline summary scores were obtained in approximately 85 patients and both baseline and day-30 scores were obtained in approximately 62 patients.

[Slide]

I will now summarize the item content of the Hyponatremia Disease-Specific Survey. A summary is also contained in the sponsor=s briefing book on page 54. This is the initial question. It is a general self-report of overall health during the previous 2 days. Patients are requested to respond on a 5-point scale as follows, from excellent to poor.

[Slide]

Questions 2-5 request the patient to consider to what degree his or her thinking ability has resulted in limitations in concentration, ability to perform calculations, and ability to perform activities requiring language and memory. Response options are, again, on a 5-point scale.

Some of the items appear questionable. For

example, in item 2, watching television to many people would require a different level of concentration than reading a paper.

[Slide]

Items 6-9 request that the patient consider to what degree his or her strength and coordination has resulted in limitations in activities requiring endurance, strength, gross coordination and fine coordination.

[Slide]

The final three items of the instrument are summarized in this slide. In item 10 patients rate what they think their serum sodium is on a 3-point scale as follows, very low, a little low or normal.

In item 11 patients rate their thirst on a 5-point scale. Item 12 is an overall assessment of how the patient has been feeling since tolvaptan therapy, which is rated by the patient as well as the physician. Response options are on a 5-point scale.

[Slide]

The Hyponatremia Disease-Specific Survey, again, was an exploratory endpoint. The agency has noted several measurement issues which limited our ability to draw

inference from this outcome measure. The development history, evidence of validity and scoring information of this instrument are not available. Similar to other PROs, the HDS is not a measure of cognitive function, and the instrument has questionable content upon inspection of some of the individual items.

[Slide]

I will now summarize the PRO measurement issues as they relate to both instruments.

[Slide]

We have several concerns related to the patient population included in the two Phase 3 studies which impact our ability to interpret the patient-reported outcome measures.

One, the patients who were enrolled had very different underlying illnesses, including hepatic cirrhosis, congestive heart failure and SIADH. Most of the patients were outpatients but inpatients were also enrolled. In addition, the chronicity of the hyponatremia is not well defined.

The missing data raises questions about our ability to draw inference from the study results. Patients

were not required to have symptoms of hyponatremia at baseline, making it difficult to assess the treatment benefit. Finally, there are issues surrounding multiplicity without a prespecified analysis plan of the PROs.

[Slide]

In conclusion, the SF-12 and the HDS are not valid measures of symptoms of hyponatremia or of cognitive function or physical function to support the primary claim. And, the treatment benefit of tolvaptan in terms of how patients with hyponatremia feel or function has not been established. Thank you.

Questions from the Committee

DR. HIATT: Thank you very much. I would also just add one final comment. Usually if we think about an endpoint as leading to drug approval you would like to have two independent studies confer that endpoint to be statistically robust.

Now, I guess what I would like to do is maybe spend five or ten minutes for the committee to ask of the FDA presenters any questions or clarifications that they would like to have. Michael?

DR. LINCOFF: It is unclear to me, and maybe I am

just not reading correctly, but whose idea was the idea of doing a patient-reported assessment? I am looking at the FDA=s page 19 of the combined clinical statistical review where it says, on October 19th, 2007 the Cardiorenal response to proposed cognitive and neurologic outcome measures-Bthe statement that if approval for a specific indication such as treatment of cognitive and other neurologic deficits accompanying hyponatremia was sought, further discussion would be needed. Then it goes into the idea of getting an operational definition.

But short of that, since it doesn't seem like that is what the sponsor is asking for--they are asking for treatment of hyponatremia--was this sort of a request by the agency or was this essentially the sponsor=s--the reason being that if it is a request by the agency, I recognize the limitations, which were very clearly and elegantly shown, of these instruments but then what would one suggest?

Did one want serial neurologic exams or objective psychiatric exams? It seems like a very difficult thing to put a finger on in an otherwise sick population and I am just not sure what the best approach would have been, and if it was really necessary.

DR. HIATT: Before you answer that, when we get to the questions this will come up, but if you look at the label indication that the sponsor asked for it doesn't make any claim for clinical benefit. It says serum sodium. If you look at the questions, we are asked to consider if there is clinical benefit. So, it is a very relevant question for us to understand.

DR. STOCKBRIDGE: I guess what we are inviting you to do and what we have invited the sponsor to do is make the best case they could for establishment of a clinical benefit. You know, if you thought you saw one here, that would be fine. If you thought there was one, whether it was measured or not, that would be fine too. But you are right, they are not specifically seeking a claim that relates to one of these outcome measures.

DR. TEMPLE: Having said that, companies that were not specifically looking for something like that are willing to take it if it can be documented. Many, many cancer therapies, for example, while showing tumor response are also looking to see whether they can show that people feel better by using a variety of tests. There are cancer-specific tests. So, we see that all the time. And, we have

written guidance to people on how to do this. But it doesn't settle the issue because success in doing this comes hard.

I just want to make a couple of comments. The complaints about the SF-12 or, for that matter the SF-36, not being disease specific are perfectly true. You have to ask though does that make it easier to show something or harder to show something? To me, the fact that they are not specific makes it a very formidable challenge to show anything at all.

Now, they didn't replicate the findings. I am not making a case for that. But if they had replicated it and it was statistically strong, I am not sure I agree with Elektra entirely that it should be dismissed because it is not disease specific.

I mean, that goes to an argument that we have all the time. You know, we love the Living with Heart Failure Scale because it is heart failure specific. There are lots of other people who believe that these general ones are also informative and I don't think we have taken a position that they are not, but they clearly are not directed at specific diseases. So, maybe we should discard them; maybe we

shouldn't. But that seems like something that one has to talk about.

The other criticism that not all the people were symptomatic, to me, that makes it harder to show anything. You know, I am an enrichment guy. I would try to put people in who had that complaint. You would get a more powerful study. But if you show somethingB-if you did, not that they did, but if you showed something despite not doing that, that wouldn't be such a horrible thing because noise on the whole obscures. So, if you succeed in the face of noise, that is not really against you.

But, you know, I don't think anybody thinks this was overwhelming. The usefulness though comes here, after all, there is probably a view, and the company started out this way, that being hyponatremic is bad. I don't have to tell you anything more than that. It is just bad. Everybody knows it is bad. Well, we have obviously moved away from that. That is why we are having this meeting. That is why we had all those discussions.

It is not out of the question that if you are inclined to think that hyponatremia is bad and have some evidence that relieving it makes you feel a little better,

the totality might make you feel better about it one way or the other. That is where this stuff has importance. I mean, were those definitive results? Of course, not, for reasons that were well described. But, you know, could they help a little? That is why you need to discuss it.

DR. NEATON: I had a comment related to what Bob just said. I kind of looked at this as they are using a pretty blunt instrument for looking at cognitive function, and the fact that they see anything at all is kind of amazing. I think they kind of got there because they started out with this trial to raise sodiums and SF-12 was way down the list. If they had started out with a trial to study cognitive function, I don't think you would have started out with a trial with the outcomes that you measured. You would have put in some tests which are kind of widely used to study that.

But just to make two more comments, and I don't think we need to spend time kind of perseverating on this today, I disagree with the notion that an intent-to-treat analysis for mortality is conservative in a safety analysis. So, I think we are seeing the opposite. I don't think it is the appropriate analysis to do, the intent-to-treat

analysis, because I cannot believe that in almost any condition that life-threatening events couldn't occur that wouldn't impact mortality more than 7 days after stopping the drug. So, personally, I put more focus on the mortality analyses shown by the sponsor than those that were intent-to-treat.

But while I have the floor, and maybe the FDA can, because they prompted this question in my mind about the study design-Bwhat was the blind to sodium levels during the study of both the patients and clinicians that were making the evaluations? That becomes really important, as the point that was made before the closure here, that some of the patients were inpatients, and presumably seeing sodiums all over the place.

DR. HIATT: Could the sponsor take that one? Then what I would like to do is maybe finish with that question and take a ten-minute break. Bob?

DR. TEMPLE: Well, while they are looking, we all agree that we are trying to show a gain in something. We like intent-to-treat at least partly because we think it is conservative and takes care of possible biases.

But as we have pointed out repeatedly in ICH-10

and elsewhere, when you are trying to show no difference, when you are doing a non-inferiority study, which is sort of what a safety study is here, intent-to-treat can obscure things. For example, if everybody is in the study for six months and then you follow them for another six months and the drug doesn't do anything you can make an effect go away. This has come up in the newspapers about whether Merck should have done this or that. You know?

So, it definitely needs to be put in prospectively, but it isn't necessarily the best thing to keep following people for months after they are off the therapy. That can obscure an effect. So, I think it is sort of a tough question.

DR. NEATON: I agree with you for some issues, and I can't see it for mortality in most studies because that is a little different in my mind. But I would like to see them both, let=s just put it that way. So, a protocol that stops collecting dataB-and, as I understand it, those two studies that probably were done kind of got themselves into trouble because of the missing data at 30 days after study drug is stopped--is not a good idea because you can at least do the other analysis.

DR. TEMPLE: Well, you definitely should look at both, but take a case where the mortality is pretty high over the course of the year, if you get six months of data and let=s say mortality is constant over time and your drug doubles mortality during the first six months, okay, follow them all out, and let=s say there is no effect, that doubling is going to drop to 50 percent. You can predict that if it doesn't keep killing you, and why should something that isn't there keep killing you, at least not most of the time?

So, I am not sure we want to encourage counting people off therapy all the time. You have to say prospectively what you are going to do.

DR. NEATON: Yes, I agree.

DR. TEMPLE: You can't do it afterward. But it can obscure things.

DR. NEATON: Yes, I agree, and also kind of cloud the picture.

DR. HIATT: Go ahead.

DR. CZERWIEC: The question, as I recall, was were the patients and physicians blinded to the serum sodium levels during the trial. Clearly, the patients were kept in

the blind both as to treatment and their serum sodium levels. Physicians did use the serum sodium levels to guide the titration therapy. So, again, the objective was for patients to reach normal sodium level.

Now, a couple of points--

DR. NEATON: So, how did you keep the patient blind from the contacts with clinical staff and when they were inpatient from seeing sodium values? What precautions did you take to do that?

DR. CZERWIEC: Well, we didn't have any specific precautions saying, doctors, don't tell the patients. You know, we felt that was obvious.

But there were a couple of other points that were important with regard to the patient-reported outcome questions which is, I assume, in part why you are asking these questions.

Obviously, if there was an impact, as has been suggested by the FDA reviewer, on unblinding, patients would have been expected perhaps to have an improvement in the PCS as well as the MCS. That was not seen.

It is also important to keep in mind that the HDS, which was given, granted, in a smaller subpopulation of

patients in only the second study, the patients were asked very specifically what do you think your sodium or salt level is right now. And, this was done basically coincidentally with their having serum sodium levels drawn but not knowing what the answers were. There was actually a negative correlation. It was not at all significant. Patients had no idea what their actual sodium levels were, and we tested that prospectively.

So, I think it is fair to say that the patients really did not have a good sense of what their specific sodium level was; what their treatment was; and, therefore, what they should answer in the PRO. In fact, the results from the PRO seemed to support that as well.

DR. HIATT: Thank you very much.

DR. FLACK: The physicians probably weren't the ones who were administering some of the questionnaire data, the softer data. Were the study personnel blinded to the sodium who were querying about some of the softer endpoints?

DR. CZERWIEC: These were not queried by the study personnel; these were self-administered questionnaires so the paper would be given to the patient and they would check off the appropriate boxes.

DR. HIATT: What I would like to do is call for about an eight-minute break.

DR. WARNER STEVENSON: I have a question, Dr. Hiatt. Is this the last chance to ask the sponsor questions?

DR. HIATT: Not really. It is never over until it is over. Why don't we just resume at three o=clock? Of course, our intent is to shift into the questions but clarifications and all that will clearly be happening.

[Brief recess]

DR. HIATT: We are going to go ahead and get started. The sponsor has a few clarifications that they would like to provide before we transition to the questions.

DR. McQUADE: Thank you, Mr. Chairman. The sponsor would like to make a couple of clarifications based on the conversations that we have all been having this morning. I would like to ask Dr. Bichet to come up and comment on some of the risks of bleeds associated with von Willebrand=s Factor that I think were mentioned earlier in the day. Daniel, just briefly, could you discuss that?

DR. BICHET: Daniel Bichet, medicine, University of Montreal. I would like to address the V2 specific effects

and the endothelial stimulation and the generation of coagulation factors mainly from von Willebrand Factor.

As alluded to earlier by Dr. Robinson, DDAVP-V2 would be a strong stimulator of von Willebrand Factor release after pharmacological doses of DDAVP. As you may know, I have followed more than 50 families with loss of function of the V2 receptor, that is, it is as ifB-well, they have mutations in the V2 receptor and it is as if they will take a vaptan for all their lives. And, they have polyurea, around 14 L per day.

These patients are unable to stimulate their von Willebrand Factor after DDAVP infusion, yet they never bleed. They are able to stimulate their coagulation factors during stress conditions with other factors, like beta adrenergic receptors. So, I do think that these endothelial factor responses, which are mainly endothelial cells from the lungs, are not involved or not having any effect here in patients that we are studying, that is, patients with cirrhosis or patients with heart failure or patients with SIADH.

DR. McQUADE: Thank you, Dr. Bichet. I think the second issue that the sponsor wanted to try to address is

that I think there is some discomfort around who is actually going to get treatment. How can we decide which patient gets treated and perhaps for how long?

The company is certainly supportive, and the proposed labeling focuses on the fact that periodic reassessment of the patients would be necessary to decide if continued therapy was necessary or not. Obviously, if you discontinue therapy and sodium stays normal there is no reason to take the drug.

However, if the sodium falls then it might prompt the physician to treat again. But I would like to ask Dr. Verbalis actually to address, again using his algorithm, whether there is a way we might be able to inform physicians of who they should be able to treat via product labeling.

DR. VERBALIS: Thank you. Slide, please.

[Slide]

I showed this slide earlier and I really want to emphasize a few points that have been addressed about the tolvaptan trials relative to these proposed treatment indications. Again, treatment indications based on our current practice guidelines, and we recently published in The American Journal of Medicine on accepted current therapy

of hyponatremia, and this basically distills the clinical wisdom of the experts on that panel-Bas I told you, severe symptoms shouldn't be targeted initially to an AVP receptor antagonist because they need to be corrected quickly. It is these modest symptoms of nausea, confusion, disorientation, altered mental status significantly that should be targeted.

Now, a point that needs to be very clear to the advisory committee, most of these patients were excluded by design from the tolvaptan hyponatremia trials. Why? Because we demanded that. We, as consultants to every company that has a vaptan program, have told them that it is unsafe and probably unethical to place a patient with symptoms like this that could rapidly progress here on a placebo-controlled, randomized trial.

So, in fact, you don't see in the tolvaptan cell studies the very population that would derive the greatest benefit from treatment with tolvaptan for hyponatremia. They were excluded by design. And, if anyone=s fault that is, it is our fault because, as treating physicians, we advised not only Otsuka but also Estalis and Sanofi the same thing.

So, anyone with a serum sodium under 125, in my

opinion, should be treated because of the possibility of moving into that state. Anyone with a serum sodium between 125 and 130 should be treated if they have demonstrable symptoms. And, anyone without symptoms, including the vast majority of the people between 130 and 134 should not be treatment candidates unless they meet one of the specific criteria, such as recurrent hospitalization for hyponatremia or, as described in the psychiatric patient population, recurrent seizures that clearly improve with treatment of their hyponatremia.

Those are clear guidelines which can be defined based on current accepted practice, and I would add practice that we are presently employing with conivaptan for treatment of inpatients, and I don't see that there would be any difference with tolvaptan except that the therapy would be prolonged. Prolonged how much? Depending upon the patient.

As I mentioned in response to an earlier question, in the conivaptan studies we found that only about 30 percent of patients treated as inpatients actually retain the stimulus to SIADH and continued hyponatremia.

So, obvious within the treatment guidelines would

be a need to intermittently reassess the presence, the continued presence of the stimulus to AVP secretion and inappropriate hyponatremia in those patients. So, not all patients certainly are going to be treated for prolonged periods of time. Some will. Mostly likely the majority will not.

The last point actually, since I am up here, if I can, I would like to point out that we are now employing therapies for hyponatremia including fluid restriction, hypertonic saline, demeclocycline, urea, none of which have controlled data safety basis, none of which. There is not a data safety base for hypertonic saline. We know it can cause osmotic demyelation.

You can say and argue that fluid restriction obviously must be very safe. That is not true. In studies of subarachnoid hemorrhage fluid restriction, after the hyponatremia subarachnoid hemorrhage, clearly causes vasospasm and results in increased incidence of strokes and cerebral ischemia. Demeclocycline clearly is nephrotoxic.

So, in fact, you may be unhappy with the size of the safety data base with tolvaptan. It is the largest existent data safety base of any treatment for hyponatremia,

and the only one that competes is conivaptan and that is only short term because it is limited to four days in-hospital use. Thank you.

DR. HIATT: Thank you.

DR. ROBINSON: This is related to that and maybe, Joe, either you or people from the FDAB-because I obviously wasn't involved in any of those discussions around conivaptan, but as I read through all of these materials I wondered whether any similar questionnaires were done with conivaptan, or was it accepted that an endpoint of raising the sodium was a valid endpoint all by itself? What is the answer to that?

Questions to the Committee

DR. HIATT: Perhaps we could more formally pose that. I think what I would like to do is to just begin this transition to the questions and understand, from the FDA=s perspective, what it is we are trying to accomplish. Because the labeled proposed indication is that tolvaptan is indicated for the treatment of euvolemic and hypervolemic hyponatremia for the prevention of worsening hyponatremia, so the treatment of this condition.

A lot of our questions that we are going to be

wrestling with really ask I think whether that treatment is clinically relevant. Perhaps Dr. Stockbridge or Temple could clarify for us the charge in terms of these questions and how the answer to these questions might influence voting.

DR. STOCKBRIDGE: Well, I mean there are a variety of ways in which you could ultimately decide you want to vote to approve this. You can decide they have actually shown something that matters. Or, you can decide that you know enough about hyponatremia to extrapolate from what is clearly an effect on sodium level to a clinical benefit. Either of those is a perfectly valid way to vote.

DR. TEMPLE: You may have read, if you read the paper or watch television, that there is a lot of interest in the adequacy of surrogates as a basis for approval. That doesn't mean there aren't some we don't use. I don't think anybody wants to leave somebody with a potassium of 6, and I don't think anybody wants to study it in a placebo-controlled trial either or, for that matter, to 0.5. I don't think we usually make people show that lowering uric acid is good for gout.

So, there are some things we have come to believe.

The question is whether sodium is one of those, and if it is, what level. You know, 110? Probably everybody would buy that. These other ones are where it gets iffy. And, the previous approvals I think were based largely on changes in sodium. But, as the company said when they came in there has been some evolution of thinking and the purpose of this, as much as anything, is to raise the question, which comes in two flavors, do you believe in sodium at all? If you do, where? What level?

DR. HIATT: Then, if it is all right with the committee, I would like to transition to the questions. The way we can structure this is that as we have specific questions or issues for the sponsor we would like to ask you those questions, but in terms of sort of spontaneous response to our discussions, maybe to hold that in abeyance.

So, why don't we put these questions up? The first one is a long introduction. I hope people can read this. I am not going to go through it entirely. Let=s get the question up though. This is the introduction.

The introduction is we have been asked to opine on the appropriate basis for approval of a product developed to treat chronic hyponatremia associated with these conditions,

SIADH, heart failure, or cirrhosis.

Because tolvaptan=s development program for hyponatremia was conducted as if serum sodium were a surrogate for clinical benefit, the committee is being asked whether that designation is appropriate. So, we are focusing on the appropriateness of the surrogate in these discussions, and you saw the data.

In addition to the hyponatremia indication, tolvaptan has also been developed as a treatment for worsening heart failure, regardless of baseline sodium, and that is being excluded from today=s discussion.

So, are we ready to go through these questions, at least to begin them? So, question number 1, from the list of outcomes, signs and symptoms of hyponatremia which of these does the committee believe are attributable to hyponatremia rather than the underlying disease. There is a long list here. Actually, our list here is not shown on the slides. I hope everyone has that list. It is quite a bit, it starts with death and coma and it goes through a bunch of symptoms.

Why don't we go around and start to wrestle a little bit with any of these. Maybe we can dispense with

all of them fairly quickly. Comments on whether any of these signs or symptoms of hyponatremia truly reflect the serum sodium, or do they reflect the underlying disease process, or is there some interaction between the two?

DR. ROBINSON: I looked through these and these were just taken out of a list like Afor example@ and then there are a bunch of symptoms that might be symptoms of hyponatremia. I found it very difficult, I should say, to say yes or no on these without putting them into some kind of category. So, are they due to hyponatremia?

Well, there are clearly some symptoms in there that I don't think anyone would dispute. Seizures and coma and neurogenic pulmonary edema can be symptoms of acute hyponatremia. So, I think you have to categorize these things to decide whether they are symptoms of hyponatremia. There are some things in that list that I think it is indisputable they are symptoms of acute hyponatremia with brain edema. There are others in where I think there is some pretty good evidence.

I went through and put 3+, 2+, 4+ about whether I think they are really symptoms. Ataxia, I think, yes, there is some pretty good evidence that ataxia is due to

hyponatremia and gets better when you correct it. But when you talk about dizziness, I don't know. I think it is very hard to say whether that is or isn't. In some patients it probably is. In most patients I am sure it isn't.

DR. HIATT: Right. So, is there anything on that list that people feel is really closely related to hyponatremia?

DR. LINCOFF: Can't we sort of generalize here that these are all symptoms that can be but they are very nonspecific? It also depends upon the underlying disease state. But, you know, I mean, they all can be but most of them are very nonspecific.

DR. HIATT: So, that is fairly obvious. So, unless there is something unique here, obviously almost any condition can be associated with any of these signs or symptoms and so none of them really are pathognomonic of hyponatremia.

DR. WOLFE: Could I just add something?

DR. HIATT: Yes.

DR. WOLFE: I mean, in addition to any disease or many diseases, as was pointed out by the FDA medical officer, a certain number of these things are more likely

adverse drug reactions. When you see people on thiazides getting hypotension and falling, it is probably as much or more related to the fact that they have blood pressures that are tacking on the low side. And, I think that a number of these other problems could be adverse drug reactions if the person has a disease and a drug that may be causing it.

So, I think there are two things. One, it is confounded by coexisting disease and, two, it is confounded by drugs that are being used to treat the diseases that many, if not all, of these people have.

I mean, I think Alan=s analysis is right. There are some that are more 3+/4+ but others it depends, you know. I am sure that at some time or other every one of these has been found with some or with groups of patients with hyponatremia. I am not sure how helpful it is to say anything more than that. I mean, I don't think that the FDA is asking us to spend the time that Dr. Robinson spent and categorize which is which because they are all imaginably there at some point or other.

DR. HIATT: And we would probably agree that as the serum sodium concentration decreases the probability of these signs and symptoms increases, and maybe their

association becomes slightly more related than unrelated.

DR. WOLFE: Yes. There is a recent review article on hyponatremia, on drug-induced hyponatremia, in The American Journal of Nephrology and one of the points that is made there, and other places, is that whereas when you get to the specific things such as death, coma, neurogenic lung problems, and so forth it is one thing, but at the early stages and from the standpoint of the clinician it is a conundrum. They are very, very nonspecific. And, if you also have a low sodium and you have one of them it still may not be that it is the low sodium of 128 or 130 that is the cause of that symptom.

DR. HIATT: Norman?

DR. STOCKBRIDGE: I would just sort of point out that question 1.1 and 1.2.1, which you have displayed up there, really were to try to get you to say I think we have a valid surrogate and you would tell me what the clinical thing was I was going to avert by treating sodium. And, what I hear already is some pretty good confidence that there is some set of these where if the sodium is in the life-threatening range you can expect to see some of these signs.

DR. WOLFE: Norm, are you finished with what you are saying?

DR. STOCKBRIDGE: But what I hear people sort of leaning towards now with respect to this list is an unusual characteristic for a surrogate endpoint, which is, you are not going to tell me exactly what things I can expect to have changed, but something on this list. And, that is not usually what we deal with in surrogate endpoints.

DR. HIATT: Correct, it is a bit nonspecific.

DR. WOLFE: Can I just respond to that? I think that one way of interpreting what at least several of us have said is that the ones that are the clearest are the ones that are most associated with the most extreme levels of hyponatremia and they are in categories that the company said should not be treated with this drug. These are people who you wouldn't want to go through that. It is an emergency situation.

The combination of a very low sodium and those symptoms says don't use this drug. So, whereas generally we have found at some level or other all these things, the ones that are more specific you don't use the drug and the ones that are less specific you have no idea whether it is due to

the drug, or disease or the drugs that you are taking.

DR. ROBINSON: I agree with you but not completely. I mean, there is no question that the very acute--somebody who has cerebral edema, the company wouldn't say you should treat that with the drug and I think the things that Verbalis put up you wouldn't treat with the drug.

But that middle group, I believe the way that I understood it is that that middle group, that group that had a low sodium and had some symptoms that you, in fact, probably thought were due to the hyponatremia, I don't think that the company is saying those shouldn't be treated. They were saying that they didn't put those in the treatment protocol because they thought they shouldn't be treated, even were there a V2 antagonist, they would have used a V2 antagonist.

DR. WOLFE: I agree. I wasn't making that point. I was just saying that as you get away from the things that we would all agree need acute treatment you are getting to things that are much vaguer and not necessarily associated. I wasn't talking about their algorithm for the study. I was just talking about the difficulty for a clinician making a judgment as clear as they could be with the severe

symptoms with many of these other ones.

DR. TEMPLE: What it sounds to me like is that people are saying that all of these are fairly unequivocally potentially consequences of, say, a very low sodium. How low, I don't know, but that in any given case, since these occur for other reasons, you can't really tell.

It is just worth noting that even if they did a study unequivocally showing that these kinds of symptoms are improved by putting people in a trial who had those symptoms you still won=t know that for any given patient. You won=t know whether the dizziness is for some reason or this one. But you would know perhaps, more than you know now, that you can in general take a bunch of people who are hyponatremic and have these symptoms and improve the group. At least so far, that has not been the intent of any of the studies in a very rigorous way.

DR. ROBINSON: You know, when I looked at these symptoms and looked at all those various scales, I honestly thought you couldn't get much more beyond saying, hey, do you feel better than you did? Because there are just so many different symptoms in there, I found it very difficult to try to even make a list of symptoms that you would ask a

patient to respond to.

DR. FLACK: I would approach it in a little bit of a reductionist way and say that, yes, some of these things are linked to really low levels of sodium but, despite the imperfections and the bluntness of the instruments used, there is something that is being picked up in a randomized study. The patients are reporting they feel differently in a favorable direction with a change in their sodium.

And, in the absence of there being some kind of identifiable bias, all the criticisms not withstanding, it is picking up something. So, I would say it is sort of like high blood pressure. People say, oh, it is asymptomatic and it is really not. You get symptomatic at relatively low levels of pressure and you feel better with modest blood pressure reduction.

So, after hearing all the conflicting information and recognizing the merits and problems on both sides of the argument, my gut tells me that people are feeling better and differently, and there is no identifiable bias I can put my finger on that would cause it to be differentially reported in favor of treatment. And, it very well may be a rise in sodium in some patients. It may be something that is due to

the underlying disease condition. But there is something that I believe we are picking up.

This whole list of symptoms here, we could be here until the cows come home and we would never work that out. And, I think the blunt instrument is probably a better index.

DR. HIATT: So, that might segue to more specifically focusing on what data showed that specific therapy to correct hyponatremia produces a change in the outcome sign or symptom commensurate with the change in serum sodium.

Were you convinced by the SF-12 mental component score that its relationship between change in serum sodium and change in that score was convincing?

DR. NEATON: To go back just to the symptoms, I actually approached it I think the way Norm said. I looked at the trial data and there are some of these symptoms that related to the question you just read that were clearly impacted by treatment, or I think you can say with pretty good confidence that were not impacted by treatment.

So, treatment impacted thirst but there were a lot of events for nausea and fatigue that didn't impact. So,

raising sodiums there didn't seem to have an impact on those symptoms. So, they are very nonspecific and not related to the low sodium at all.

DR. HIATT: If you don't believe that this laundry list is all that associated, why would you expect the therapy to necessarily make them better?

DR. WARNER STEVENSON: I think it is remarkable that there was any change in symptoms. I have to say for heart failure in general I regard hyponatremia as both a biomarker of severity and an adverse condition, and I would opt to treat the adverse condition as long as treatment isn't associated with some additional risks. So, this issue of are the symptoms better or not, I have to say, from my standpoint, it treats the serum sodium which I am very enthusiastic about as long as there isn't a high risk associated with that. So, my feelings is somewhat independent of this laundry list of symptoms going up and down.

DR. HIATT: Can anyone then further clarify this change relationship? If we are sort of saying, to summarize this first part of the question, that most of the things on this list don't seem to be related--may be slightly

associated with hyponatremia, don't seem to respond to the therapy, did you see anything in the database that would suggest that there was some clinical measurement that did respond and was associated with hyponatremia? Michael?

DR. LINCOFF: I don't know if we will get to this later because there are some sort of general questions later, but there was the ability in the heart failure study to more effectively diurese, drawing off more fluid. I mean, that is real. Any of us who take care of heart failure patients know that we are often limited by hyponatremia in terms of the intensity of the diuresis that we can accomplish.

Now, they didn't show that the doses of the diuretic were higher, etc. You know, they didn't look, mechanistic process-wise, at why there was more diuresis. Maybe it was the drug itself or maybe it was because the correction of the hyponatremia allowed that. That is a benefit. I don't think there is much argument that removing excess fluid in that hypervolemic patient in heart failure is not a benefit.

DR. HIATT: And avoidance of other kinds of interventions to correct the hypervolemia was also shown.

DR. LINCOFF: Yes, limiting the fluid restriction, and we all know that fluid restriction is a very unpleasant experience for patients.

DR. HIATT: Yes.

DR. LINCOFF: So, it is part of the paradigm of making you feel better. Certainly, less often having to resort to that is a real benefit.

DR. HIATT: Then, there is the relationship of the change of sodium to the mental component score. Now, maybe it is a separate discussion to ask was that a really robust finding in terms of two independent studies verifying that that is a good endpoint. But if you take their overall analysis there was some relationship there too.

Does anyone see any other signs, symptoms or outcomes? Of course, the comments we just made were primarily limited to the heart failure population studied in terms of fluid loss and these other interventions. But are we missing anything on this list here that might be related? Because that relates to the next part of the question, was that effect seen in the sponsor=s development program?

DR. HARRINGTON: I mean, a piece of compelling analysis that we saw this afternoon was the FDA description

of the neurology exams which took place throughout the studies, and an objective measure of things which would be pretty important-Bfocal neurologic findings, etc.--that there is not a whole lot of demonstrationB-some changes in Achilles tendon reflexes; one measure of ataxia. So, there is not a lot of objective evidence that the neurologic findings were demonstrably improved with the treatment and I thought that was an important observation pointed out this afternoon.

DR. HIATT: I agree. Related to that, what chronic serum sodium level would you expect to see these outcomes manifest? We kind of got that very early in the day actually. Biologically, is this relationship that we are looking at a fairly linear one? I am actually fairly convinced it is. So, if there is a relationship, it seems that further down the scale you are on the serum sodium level perhaps the bigger the magnitude of the clinical benefit of any of these markers. If you are just slightly abnormal it may be that there is some relationship occurring there but it may be very hard to discern.

DR. HARRINGTON: I mean, I thought it was pointed out by the clinical experts that there is a fair bit of

individual patient variability in when they begin having symptoms. You are absolutely right that when you look at it from a group effect the lower you go, the worse things seem to be. But for any individual patient when symptoms manifest themselves I think is a bit more challenging to say.

DR. HIATT: As I reviewed this, you know, it was divided a bit around the 135-130 and less than 130. So, was anyone convinced that if we believe that the amount of fluid loss, the avoidance of fluid restriction and the mental component score benefitsB-were they easily segregated into better benefit less than 130 versus over 130 if you were to define a threshold that might be relevant here?

DR. ROBINSON: What I am hearing, and I am just telling you the way I am hearing some of these comments around the table, is that most of us, as clinicians, have an idea that low sodium is bad. So, we have that as an impression, and the lower the sodium, we think that is even worse.

So, if you say would we all try to treat somebody with a sodium less than 120, I think probably most of us would say, yes, we would try to treat that. Would we look

for specific signs and symptoms? Would we ask whether they are fatigued before we started to treat them, I think we probably--

DR. HIATT: But the question is not the general question. The question is what did you see in the data that informs you about making a decision?

DR. ROBINSON: What I am saying is that many of us have an idea that is independent of that list of variables. You know, I have heard that in terms of congestive heart failure, low sodium is seen as something that does get in the way of other therapies and we make decisions based on those numbers. So, if you want numbers, then I think that below 130 most of us would certainly give serious consideration, and below 120 everybody would be treating.

DR. PAGANINI: I have a bunch of different things. Give me about three seconds and I will get through them all. The first is that these are both chronic and acute patients. Those are different. So, numbers are going to be different depending upon whether they are a chronic or an acute patient. So, a specific number is going to be very hard to come up with.

DR. HIATT: In which setting?

DR. PAGANINI: In any setting with hyponatremia. If you go from a 140 to a 130 all of a sudden that could be very dramatic and, yet, you are not below 130. So, I would be very careful about a specific number of sodium. Although, as I said before, when they are above 130 I don't get too worried about it unless they are very chronic. That is the first thing.

Second, I think we are sort of mopping up here and I will say this in a generic way. I hope I don't get myself into trouble, but these people came before the FDA and said what do you want? We want to show you that changing the sodium is important. That is our endpoint. The delta sodium is an endpoint for our drug. And, FDA said, yes, that is a good idea; go ahead and do it.

You heard around the table most people say, gee whiz, low sodium is a bad thing. Normalizing that sodium is probably a good thing. So, go ahead and get a drug that has a physiological basis for it. I mean, think about it. This is a drug that has been developed based on a physiological basis of disease entity and malfunction, which I think is an unbelievable thing.

Then, all of a sudden, 70 percent of the thing

passes, time passes and then the FDA says, you know what, I am not sure that sodium is really a good surrogate. So, let=s go back and do it. So, these guys sit there and they say, Christ, how are we going to do this? We already started these studies and now you want us to do this study? Okay, we will do this. Then we are saying, well, you don't have it in all the people and, gee, it was a crummy study. Children, what do you want from them? That is number two.

Then, finallyB-and I am sorry about that. That is why I have been so quiet; I tend to get like this every once in a while. Sorry about that. Then, finally the third, we have heard from folks that, gee whiz, you know, this is a bad disease. I have been trained in that situation as a nephrologist. Hyponatremia, you don't have to tell me, geez, it is a bad disease. Yes, it is and it should be treated.

Then, finally, where should we start? I think it really is patient dependent. So, it is very difficult to get a specific number for all of these. Then I will keep quiet. Sorry.

DR. HIATT: Dr. Temple might take a bit of the moving target questions.