and robustness of a surrogate endpoint in relationship to clinically meaningful outcomes in deciding whether this drug can be approved or not for the treatment of hyponatremia. There are many components to trying to make that determination.

So, the first question I want to ask you is there does appear to be some relationship between the serum sodium concentration and clinically meaningful events or outcomes or patient status measures. Could you help clarify how, in your mind, that relationship can be developed? Is that a linear relationship or does it behave in some threshold manner? If you can state which one it is, could you defend it? And, if you can't define the relationship, could you say that too?

DR. McQUADE: Thank you. I will start with a couple of comments and perhaps ask Dr. Verbalis to comment as an expert in the field.

The data support, as Dr. Czerwiec showed, that as you improve serum sodium by different increments you see a correlation with the improvement in the SF-12 score. There does not appear to be a specific threshold at which suddenly you get an improvement. It seems to not be a linear

relationship and, therefore, we believe that the correlation between the two activities, while valid, is not specified. There is no threshold there. Maybe Dr. Verbalis can make it clearer.

DR. HIATT: The first point is just in a population, before we talk about the effects of therapy. As the serum sodium level decreases progressively in any one of your populations, can you define how that change in serum sodium relates to clinical manifestations of hyponatremia? Before we get to the idea that maybe treating this surrogate changes some clinical outcome, let=s establish the relationship between the surrogate and some clinical meaningful endpoint.

Clearly, at one end of the spectrum in chronic hyponatremia there is a lot of physical and mental dysfunction and, clearly, at another end of the spectrum there is none. The question is what does that relationship look like? Can you define a relationship, and what is that relationship? Is it linear or is it nonlinear?

DR. VERBALIS: Therein lies the problem of calling serum sodium a surrogate because that relationship that you are looking for, that we all would like to have, is, in

fact, very clear for acute hyponatremia. It is clear and it is linear and there is a threshold.

With chronic hyponatremia, because of the brain volume regulation, you cannot define a threshold or symptomatology because of the process of brain volume regulation. So, if you just go to acute hyponatremia, that occurring within 24-48 hours, it is clear that if you reach a drop in serum sodium concentration of 8 percent you will have an 8 percent increase in brain water and you will have a potentially life-threatening hyponatremia.

The exact onset of symptoms has not been as carefully documented, but if you take the very earliest symptoms that I showed of headache, nausea, some disorientation generally that occurs at about the halfway point of about a 4-5 percent drop in serum sodium concentration, which takes you right around the threshold of 130. A few patients will get symptomatic between 130 and 134. With acute hyponatremia virtually all patients are symptomatic at 130 or less and potentially fatal complications occur at 125.

That whole scheme, that whole relationship is of uncertainB-you cannot make it for chronic hyponatremia

because we see patients at 110 that are relatively asymptomatic because of the process of brain volume regulation, which is why in my treatment algorithm I did not characterize the serum sodium but the presence of symptoms. But if you want a threshold, a threshold for acute hyponatremia is at 130.

DR. HIATT: I am not asking for anything other than what you can conceptualize that relationship to be. Dr. Harrington?

DR. HARRINGTON: Part of what we are going to be discussing today is how we believe the patient-reported outcomes are a valid representation of the treatment effect. When I read the briefing material, it noted that there were a number of tools used at the outset to assess patient-reported outcomes in addition to the SF-12 and all you presented to us was the SF-12 data.

Can you clarify for us what was the testing procedure here? You did all of these outcome tools. I think it was totally valid to go into this as a bit of a fishing exercise because, as was said, you didn't know what might be the effect. But can you clarify for me what were the other tools that were used? What were the effects

observed? And, was there a pre-stated hypothesis that the SF-12 was going to be the dominant test that you believed at the outset? Was that something you came to at the end of the day?

DR. McQUADE: Thank you, Dr. Harrington. The SF-12 MCS and PCS, the mental component score and the physical component score, were the two prespecified endpoints in the SALT studies, which are the pivotal Phase 3 studies. They were prespecified as secondary endpoints in their component scores.

In addition, there was an exploratory scale, called the Hyponatremia Disease-Specific Survey, that was implemented only in one of the two studies, in SALT-2. It tried to measure specific symptoms. I think Dr. Czerwiec presented a little data on that and he can present it again if you would like.

Those were the only two outcome scales in the studies. Now, there were other neurological outcome tests that Dr. Czerwiec can comment on as well that we did not discuss during our presentation. But in terms of patient-reported outcome scales, those were the only two in the SALT studies.

DR. HARRINGTON: And then in the larger EVEREST study the Kansas City Cardiomyopathy Questionnaire was used and suggested no difference between the two treatment arms. Is that right?

DR. McQUADE: That is correct.

DR. HARRINGTON: Then, was the SF-12 used as part of the EVEREST study or was it confined to the earlier SALT studies?

DR. McQUADE: It was only in the SALT studies.

DR. HARRINGTON: And in the earlier SALT studies you defined both the mental and the physical component of the SF-12 as secondary endpoints?

DR. McQUADE: Correct.

DR. HARRINGTON: You didn't have a hypothesis that one of them was preferred over the other?

DR. McQUADE: We did not. Those were supportive data to the change in serum sodium which was the primary endpoint.

DR. HARRINGTON: Good. Thank you.

DR. NEATON: I also have a question concerning the validity of the SF-12. Mine comes from my counting. You presented data on 290 or 448 randomized patients. So, over

30 percent are missing data. So, I can accept for the serum sodium differences, because they are so striking, the potential impact of missing data on your findings but I have a hard time accepting the potential impact, without some additional analyses, on the SF-12 differences.

So, one question I have is can you provide some additional analyses to demonstrate the robustness of those differences to all the missing data that you have in the trial, if my calculations are correct?

Secondly, I appreciate your response to the FDA=s question, I guess, about the components of the MCS scale. Can we see those individual data? I would like to see more than the p value. I would also like to see the 8 dimensions outlined for the two treatment groups in each study.

DR. McQUADE: I will ask Dr. Czerwiec to address both those questions. We will start with your first question around the analysis of the SF-12 data and missing values.

DR. CZERWIEC: To begin to respond to the question about missing data, the SF-12 physical and mental component summaries relied on the composite answers to all 12 of the questions. So, if any patient missed or was unable to

complete any of those 12 questions their score was missing entirely. We did do a number of sensitivity analyses to account for different methods of evaluating the impact of these missing data. If I could have the slide on, please?

[Slide]

This slide represents the prespecified and several post hoc sensitivity analyses of these data for the SF-12 mental components summary. The top bar shows the ITT, LOCF, or last observation carried forward, the observed case carrying the baseline forward or worst case analysis. In each case you can see that the robustness of the effect was held regardless of which method you used to account for the missing data.

DR. NEATON: So, this is the SF-12 at 30 days?

DR. CZERWIEC: That is correct.

DR. NEATON: So, your worst case analysis, how was that defined?

DR. CZERWIEC: If I could ask our statistician--

DR. NEATON: I mean, I would think worst case might be treating placebo a different way than the active drug.

DR. CZERWIEC: I am sorry, treating placebo differently?

DR. NEATON: Right. It looks like the placebo has been dramatically affected as well.

DR. CZERWIEC: If I could ask one of our statisticians who performed this analysis to step forward? Dr. Onyang?

DR. ONYANG: John Onyang, Otsuka. For the worst case analysis we did the worst case observed data and then applied it equally to placebo and the tolvaptan group.

DR. NEATON: So, what value was imputed?

DR. ONYANG: If I remember, it is about 11.

DR. NEATON: If we could have just a bit more detail on these analyses because I think it may be important. If I am understanding that correctly, 30 percent of the people are missing the outcome data at 30 days?

DR. CZERWIEC: At 30 days there was a substantial number of patients who were not able to complete this, yes. The second part of your question again, please?

DR. NEATON: The second part was that you actually said in one of the slides, as I understood it, that you looked at the different components of the mental health summary score and you showed which ones were significant, I believe, and which ones were not. It would be interesting

to see the individual data, not just the p values, for each study.

DR. CZERWIEC: Thank you. If I could have slide on, please?

[Slide]

So, for the 12 questions for the SF-12 questionnaire, and this is last observation carried forward for all hyponatremia subjects, these are the responses for the individual questions. As you can see, some of the ones that I had mentioned in terms of accomplishing less work or doing that work less carefully were significant or favored tolvaptan.

DR. NEATON: Do you have the results for the 8 domains?

DR. CZERWIEC: We will see if we can pull those up. The dimensional analysis was not used a priori in this but it was part of the validation package that Dr. Ware and his company provided for us to the FDA and we will see if we can find that.

DR. NEATON: While you have this one up, could you just point to the ones that are part of the mental summary score?

DR. CZERWIEC: Dr. Ware, would you mind stepping up for that? I hope that our abbreviations are not too confusing.

DR. WARE: This is abbreviated item content, and there might be a word or two missing. This is from the vitality scale. This is from the social functioning scale. This is from the role disability scale due to the mental component. The item specifically asked about accomplishing less than your usual activity but attributing it to mental health.

This is the same thing, attributed to mental health. This is from the mental health scale. This is from the mental health scale. This is from the physical functioning scale. This is from the physical functioning scale; physical functioning scale. This is the pain scale. This is the general health scale. And, these physical functioning limitation reports are specifically attributed to the mental component of health.

So, you have 2 role performance items with an attribution to the physical component and you have 2 role performance items with an attribution to the mental component. So, you have 1-2 items in each of 8 scales. I

believe the dossier given to the agency has the domain by domain analyses.

DR. NEATON: Can we have a copy of the slide perhaps?

DR. McQUADE: Certainly. We will get you copies of it. Would you like to see a slide with actual scores on it? Because that is just a rank analysis that you just saw.

DR. NEATON: That would be actually preferable. To clarify, you mean the specific domains?

DR. McQUADE: The specific domain scores and the item scores that we showed you a moment ago.

DR. CZERWIEC: Just to clarify, this is what you were looking for? This is part of the validation package presented to the FDA so you have the 8 domain scores for SF-12 and their relative significance. We can provide that as a paper copy to you.

DR. NEATON: That is a nice analysis by sodium. I am interested in the analysis by treatment group.

DR. McQUADE: We will pull that out for you.

DR. FLACK: I have a comment and a question or at least a clarification. I was a little surprised to see the people with cirrhosis on here. Even though you can argue

that their extracellular fluid volume is expanded, their intravascular volume is not. They are many times hypoalbuminic. Their ADH levels are going to be high and they are going to be high appropriately, not inappropriately.

And, I don't really see this as a patient population that I would really want to treat with this drug for hyponatremia unless it was something that was really, really severe and I would be really making a judgment that despite their volume depletion or hyponatremia was so bad and I couldn't deal with it any other way. And, I am surprised that the effect was less in that group because they don't have very much distal tubular flow and they are volume depleted.

So, one concern I have is that if this drug is going to be out and used for many of the patients whom we treat in the hospitalB-well, let=s just go back to the cirrhosis patients. I don't see this as an appropriate group to be receiving this drug, and I would like to have a little thought about the rationale for actually including them, given the fact that they are intravascularly volume depleted despite their extracellular fluid volume expansion.

I am also a little concerned about some of the blurring of the hyponatremia with what may also be volume depletion. For example, in the elderly, looking at hyponatremia, some of what you may be picking up is simply being admixed with volume depletion. I mean, the volume depletion may be very linked to the actual hyponatremia. We see this very often because many of the patients come in and they lose GI fluids but that is hypotonic fluid. They get hyponatremic because they can't clear the free water they are taking in, in excess. So, could you all give some comment and clarification on that?

DR. McQUADE: I will ask Dr. Czerwiec perhaps to answer your second question first. Then I will ask Dr. Wong to address your first question about cirrhosis.

DR. CZERWIEC: Actually, the second question, again, with regard to the issues with elderly patients and potentially treating patients who are hypovolemic.

DR. FLACK: No, I am actually a little concerned that some of the relationship between hyponatremia that you may see is actually drivenB-for example, falls by volume and not necessarily by hyponatremia per se. I don't know if you can totally separate it but you can't ignore the fact that

the volume depletion per se is linked to hyponatremia because they can't clear the free water and many of them get dehydrated and they are taking in hypotonic fluid.

DR. McQUADE: If it is okay, why don't I ask Dr. Verbalis to step up since he presented those data on falls?

DR. VERBALIS: First of all, the data that I presented to you for the gait instability, those were all patients with SIADH, and documented. I am going to get to your question but I just wanted to make that clear.

DR. FLACK: That is not what I am talking about.

DR. VERBALIS: As I said, I am getting to the fall data.

DR. FLACK: But that is not what I was talking about.

DR. VERBALIS: Right. In the fall data all the patients were attributed to have asymptomatic hyponatremia and had a clinical assessment of their volume status, which was clinically euvolemic and not hypovolemic. In fact, the FDA approval criteria for conivaptan excludes hypovolemia as an indication for a vaptan treatment, and it would do so for any other vaptan. Part of the criteria for treating with a vaptan would be exclusion of hypovolemia.

How we would do that in the elderly would be how we do that for SIADH, that anyone who has a urine sodium concentration which is significantly low is considered to be solute depleted and a candidate for solute repletion, not for a vaptan. So, there are means to deal with that in terms of not inappropriately treating elderly people who are actually volume depleted. We can do that clinically and that would be part of the approval indication.

DR. FLACK: What I was referring to was, I believe it was the Journal of National Medical Association, one where it was thiazides and the data was presented about falls in hyponatremia. Unless I am mistaken, there is a potential for volume depletion with a thiazide as well as hyponatremia, and that is the data set I was talking about kind of blurring a bit, inferring that this is all hyponatremia, the falls.

DR. VERBALIS: I would agree with that. I would never infer from that study that you would attribute falls to hyponatremia. The confusion and obtundation I think you would, but the falls, that would be a grey area. We don't know.

DR. FLACK: Yes, that is what I was getting at and

I am a little concerned that there is some blurring, something that may be underlying that is also contributing to this and not just hyponatremia because the implication is if you just correct the hyponatremia this will go away, and it may have an impact, but I think there may be something else buried under there, at least in that kind of data.

DR. VERBALIS: I agree, but I would point out that the study from Belgium looked carefully at volume status and, to the best of our abilities, excluded patients who were hypovolemic in that study.

DR. McQUADE: Dr. Wong, could you address the question on cirrhosis? Dr. Flack, we have also included the contraindication for hypovolemia in our proposed labeling.

DR. WONG: I am Florence Wong, from the University of Toronto. I want to beg to differ with this member of the committee. Cirrhotic patients have an underlying pathophysiology and that is sodium retention. That is the hallmark of cirrhosis. When you have sodium retention you have water retention. There have been ample studies showing that in cirrhotic patients the ANF levels are significantly elevated.

With respect to your comment about cirrhotic

patients do not have edema, a lot of these cirrhotic patients have ascites and there is return of acidic fluid at the rate of approximately 400-500 mL per day so the volume is being replenished.

The other question relating to inappropriate vasopressin levels, there is a resetting of osmoreceptors in cirrhotic patients and there are studies showing that the AVP levels are inappropriately elevated in this population of patients.

DR. FLACK: Okay, excuse me. I was just kind of remembering renal physiology. I fully understand the sodium retention, and it is high in part because they are volume contracted. We use aldosterone antagonists regularly and we have trouble keeping their blood pressures up many times because not only is their sodium retention high, but they can't hold onto it because their oncotic pressure is low because they have low albumin. I never said they don't have edema because that would be silly because they do have edema. They have lots of edema.

I admit that they are extracellular volume expanded. My concern here has to do with what is in the vasculature. The ADH levels are high but they are not high

inappropriately for what is going on in the vasculature. That is the only point I was making, and the point that I am concerned about is a group of cirrhotic patients getting a drug like this unless there is a really, really, really important reason to do it.

DR. WONG: Well, one of the reasons for needing a drug such as a vaptan in cirrhotic patients is that, like in cardiac failure patients, the presence of hyponatremia prevents us from using diuretics effectively in these patients.

DR. FLACK: Thank you, but my concern still remains about the volume status, ADH, and I am not surprised that the effect was less, which you predicted would be less because they have less distal flow into their tubules because they are volume depleted intravascularly.

DR. McQUADE: Can Dr. Berl give you one more comment, Dr. Flack?

DR. BERL: Tom Berl, from Denver, Colorado, nephrology. I think you are very correct. The pathophysiology of sodium and water retention in cirrhosis is very complex, as Dr. Schrier has shown. There is peripheral vasodilatation affecting blood volume. But these

drugs that we are talking about today will not cause negative sodium balance which could make the intravascular volume contraction worse. They are purely aquaretic.

Now, I could understand your concern if this drug had a V1-related effect. After all, we are infusing V1 agonists into patients with cirrhosis all the time. The virtue of this drug compared to the other one that is available, that is a V1 and V2 antagonist combined, is that this has no V1 antagonistic effect and is not likely, therefore, to have undesirable effects on systemic pressure. We struggle with this all the time. These patients are hypotensive, vasodilated. But I don't think there is a significant effect on peripheral vascular resistance if the drug is purely an aquaretic agent.

DR. FLACK: Just one follow-up then, is there any data on blood pressure from your studies in patients with cirrhosis to back up what you are saying? I can accept what you are saying but can you show any data to support that?

DR. McQUADE: Dr. Czerwiec?

DR. CZERWIEC: Yes, early in our development program, in Phase 2 actually, we conducted a small study specifically in patients with liver cirrhosis. It is

referred to as the 96203 study. In that study we saw no changes in blood pressure in patients who were given tolvaptan. We can provide that data to you later.

Just to complete the questions, you also asked why you would use it; why you might need it in cirrhosis. Just for informational purposes, there are data that we will also bring to bear later for you that suggest that up to about 50 percent of patients with cirrhotic ascites may have more severe forms of hyponatremia which, obviously, in a patient population prone to encephalopathy might be relevant if the effects that we see in mental functioning would translate to those. We haven=t shown those specifically, other than what we showed you in the SF-12, but we think it may be clinically important.

DR. HIATT: Thank you very much. We can continue the questions or we can take a break and then continue the questions. Why don't we go ahead and do a 15-minute break and then let=s finish the presentations and then we will have lots of time for questions?

[Brief recess]

DR. HIATT: We are going to have a few clarifications now and then we will go on to the safety

presentation.

DR. McQUADE: Thank you, Dr. Hiatt. Committee members, we have distributed the two pieces of data that Dr. Neaton asked about in the statistical analysis of the SF-12. We also would like to address the statistical question more completely by asking Dr. Koch to comment.

DR. KOCH: Gary Koch, Biostatistics Department, University of North Carolina. Could you bring up ST-2?

[Slide]

The analysis labeled worst case involved in imputation of a value of 11 which was the worst possible value among those observed at day 30. So, basically, the database at day 30 was searched and the worst value at day 30 among all of the patients with data at day 30 was 11. Then a change from baseline was calculated for the missing patients using that worst value and then the results are then shown.

Probably the most informative imputation is the one that involves carrying forward the baseline because, as you saw, the benefit on serum sodium is lost when the treatment is withdrawn and patients would have essentially a return to baseline on their serum sodium. So, the carry

forward of the baseline involves an analysis of all patients with a reasonably logical imputation.

Have I explained adequately how the worst case analysis was done?

DR. NEATON: You have. Would you please also kind of differentiate the last value carried forward from carrying forward baseline because I thought baseline and 30 days were the only two time points?

DR. McQUADE: I will address that. There was a second time point in either week 1 or week 2 in the studies. In one study it was week 1 and in one study it was week 2. But because they were different time points we didn't present the data. So, it is possible that there were evaluations for patients at those interim time points.

DR. NEATON: Well, are the short-term changes consistent with 30-day changes?

DR. McQUADE: They are smaller in degree. You saw continued separation between placebo and drug as you went out in the course of the therapy.

DR. NEATON: And I just want to correct. I think one thing that was said in the presentation, as I understood it, is that the difference between the groups--if you just

take the intent-to-treat, what you called the first line up there I guess is what is cited here--is about 0.28 standard deviations. It is true that the change within the treatment group was half a standard deviation but the net different is pretty small.

DR. McQUADE: Thank you.

DR. HIATT: Dr. Koch, could you just define if these patients were missing at random or not?

DR. KOCH: The patients were missing at equally prevalent rates.

[Slide]

So, if one were to go to CC-64, which I think was the disposition table in Dr. Czerwiec=s presentation, this gives you the fraction of discontinuing patients for different reasons. The different reasons for discontinuing basically have similar incidences so that does not suggest a departure from random, although typically patients discontinued for any variety of reasons and it is very difficult to argue whether they were random or not.

DR. HIATT: That is not what I meant. I meant were the missing SF-12 data missing at random.

DR. KOCH: The missingness on SF-12 I do not have a

slide on. Dr. Czerwiec can probably speak to that to some extent.

DR. CZERWIEC: If you could just clarify, Dr. Hiatt, when you say missing at random do you mean a disproportion by site or by type?

DR. HIATT: Was there any disease predisposition to missing this quality of life endpoint? I think you can tell us the way you impute missing data probably suggests no, but I want to make sure that the findings are generalizable to the broader population.

DR. CZERWIEC: I don't believe we have done an analysis specifically focusing on SF-12, but if you do look at the total disposition of patients that was presented in the previous slide, the disposition was generally random in terms of adverse event discontinuations. They were equal between the two treatment groups.

The only subtle difference was in withdrawal or loss to follow-up. What I can say about that is that in some cases in the placebo group, which did have a slight excess for those reasons, patients who were severe tended to be withdrawn either by themselves or by their physicians when a treatment effect or when a lack of progress in the

serum sodium might occur.

So, we did evaluate, for example as a secondary endpoint, the numbers of patients who required saline infusion as a rescue therapy and that was seen more frequently in the placebo group.

DR. KOCH: Let me just add a comment. Aside from whether the discontinuations were at random or not, the carry baseline forward analysis treats all the discontinuations as if they were treatment failures. So, there is no particular advantage being given to the analysis by discontinuation and that is why I tried to indicate that the carry forward of the baseline was probably the most informative robustness analysis.

DR. NEATON: I think what you said initially I would agree with, that the data suggest, because there is an equal amount of missingness and reasons for missingness by treatment group, that there may not be bias. However, we don't know for sure. I mean, you just don't know for sure. You know, you can do these analyses but the potential for bias is there and it is substantial when 30 percent of your data is missing. So, if you are going to do patient-related outcomes, which are very important, you need to kind of make

certain that you get the data on everybody.

DR. KOCH: I understand that but, at the same time, if you say missingness is indicative of failure and you essentially assign patients with missing data an outcome of zero change from baseline, which manages them as a treatment failure, then I think you are partly addressing that particular issue. Although obviously one would prefer to have as much data as possible on all patients, you cannot compel patients to stay in a study for its full duration even if you would like to.

DR. NEATON: No, I agree with the last point, although the reasons for missingness may vary. So, imputing the baseline may be a reasonable thing to do for treatment or perhaps even something worse but not the same for placebo and there is uncertainty around that.

DR. KOCH: Yes, I would agree there is uncertainty about it but, at the same time, the extent to which there was information on serum sodium it didn't change much over time for the placebo patients and, correspondingly, when you looked at the patients in the study drug group, once they had their improvement in serum sodium, whether it was SALTWATER or the SALT studies, they tended to preserve their

benefit until the treatment was taken away.

So, I agree missingness makes the interpretation more difficult but carrying forward the baseline here I think is a plausible way to try to understand the robustness of the data.

I did have two other comments. Hopefully, they will be briefer. One was on ST-4 and you can bring that up.

[Slide]

These analyses were done by rank analysis of covariants because the individual items are actually ordered categorical scales with anywhere from 2-6 categories and that did not lend itself necessarily to a traditional analysis of covariants, although one could certainly do that as a numerical exercise.

The estimated treatment difference is actually a difference based upon standardized ranks that are basically normalized to the 0-1 interval, and essentially corresponds to a Mann-Whitney probability of a randomly selected person in one group having more favorable outcome than a randomly selected person in the other group. That probability is a half under the null hypothesis and these differences show a consistent positive deviation from that null value, albeit

small.

The sponsor will try to get you means for each of the treatment groups for these particular variables, as well as a parametric result, to the extent they have it but the rank analysis was considered a more informative way of looking at these kinds of individual items.

The final comment is based on CC-87, which again is from Dr. Czerwiec=s presentation. It is a slide that speaks to Dr. Hiatt=s question. Slide up.

[Slide]

This basically is compatible with a semi-linear relationship for the change in the SF-12 MCS with the change in serum sodium. Your question was more with respect to at any given time was there a linear relationship. This is addressing what the change during the treatment period was using one of the particular methods of analysis. It does suggest a semi-linear relationship with essentially more favorable differences for both as the serum sodium change increased.

DR. HIATT: The implication being that if it is linear all patients respond, just to different degrees. If it is a threshold you need to cross a certain value before

you see the benefit.

DR. KOCH: Yes, and that is somewhat evident when you maybe later in the day look at change in serum sodium in terms of its cumulative distribution because virtually all of the patients had some improvement in serum sodium. Although many patients had bigger improvement, other patients had small improvement. Dr. Czerwiec can talk to that later. But when you look at those cumulative distributions there is favorable change in serum sodium for nearly everybody.

DR. HIATT: Thank you very much. Lynn?

DR. WARNER STEVENSON: I had one quick point before we get to the safety discussion. I think we all appreciate that it has been a complex development program in terms of heart failure versus hyponatremia. It would be very helpful, as we move into the safety discussions, if the speakers could be very clear about what you mean by each group when hyponatremia is less than 130, when it is less than 135, when it is 130-135, when it includes heart failure patients only or all hyponatremic patients. If you could just be very careful to specify as we go along, I think it would be easier for us to sort out the safety issues. Thank

you.

DR. HIATT: A very relevant comment. A quick comment?

DR. WOLFE: CC-130, if you could put that up?

[Slide]

It wasn't clear to me, given what the data were, why all of those groups except the last were deemed highly statistically significant. I mean, the difference between tolvaptan and placebo was pretty much nil in most of those. How did those very highly statistically significant p values arise?

DR. McQUADE: Are You talking about the numbers on the slide itself?

DR. WOLFE: Yes.

DR McQUADE: Those are the number of patients in each analysis.

DR. WOLFE: So, it is not the outcome at all?

DR. McQUADE: Correct.

DR. WOLFE: It is just telling us at various stages--

DR. McQUADE: How many patients, that is all.

DR. HIATT: Let me also say that we are going to

have more time to deliberate the presentations from this morning on efficacy. What I would like to do is get to the remainder of the presentations and then we will continue with the questions.

DR. McQUADE: Thank you, Mr. Chairman. With that, I would like to introduce Dr. Carson who will present the safety presentation.

Tolvaptan Safety Overview

DR. CARSON: Good morning.

[Slide]

I am Bill Carson and I am Vice President for Global Clinical Development at Otsuka. I will present an overview of the safety of tolvaptan.

[Slide]

The first few slides will define the primary safety population, the hyponatremic population, the general safety population and the general safety profile of tolvaptan in each of these populations. I will then address key issues of mortality, overly rapid sodium correction and GI bleeding in cirrhosis raised in the FDA backgrounder. I will then review topics of special interest. The presentation will end with conclusions regarding the overall

safety profile of tolvaptan.

[Slide]

This presentation addresses question number 6 from the FDA. The tolvaptan safety database is the largest currently available for any vaptan. The primary safety population comprises almost 3,300 patients exposed to tolvaptan compared to 2,700 patients on placebo. The patients in the primary safety population are from the EVEREST trial which enrolled patients with congestive heart failure, the SALT-1 and 2 trials which enrolled all-cause hyponatremia patients including subjects with cirrhosis, SIADH and CHF and the Phase 2 tolvaptan trials.

The hyponatremic safety population is a subset of the primary safety population, comprising 607 tolvaptan-treated and 518 placebo patients. The analyses presented are based on an intent-to-treat population from the Phase 2 and 3 placebo-controlled studies, grouping all tolvaptan doses from 5-120 mg. All doses were groups because there were no clear signs of a dose relationship for tolvaptan.

[Slide]

In the primary safety population some patients have been exposed to tolvaptan for over 2 years. The total

exposure is equivalent to almost 2,000 patient exposure years and 1,300 patients have been exposed for at least 6 months and over 800 for at least 1 year. In the hyponatremia safety population the total exposure is equivalent to over 190 patient-years.

[Slide]

The age range is reflective of the population for both the primary and hyponatremic safety populations. Over 45 percent of the patients were over 65 and 21 percent over 75 years old. Males represented 70 percent of the study populations. The distribution of race and ethnicity reflects the fact that the majority of the studies were in North America and Europe.

[Slide]

The occurrence of treatment emergent adverse events in both the primary and hyponatremic safety population was similar between tolvaptan and placebo groups. Serious adverse events occurred slightly more frequently in the placebo group. Slightly more tolvaptan patients discontinued due to adverse events, and deaths were similar between the two groups.

[Slide]

Events associated with the mechanism of action of tolvaptan were among the most commonly seen in both the primary and hyponatremic safety population. The most common terms were thirst and dry mouth.

[Slide]

I will now address key issues raised in the FDA backgrounder. These are mortality in the hyponatremic heart failure population, overly rapid correction of sodium in the hyponatremic patients and GI bleeding in cirrhotic patients.

[Slide]

In the FDA backgrounder the discussion on mortality focused on a particular subset of patients from the EVEREST trial where there is nearly a four percent difference between tolvaptan and placebo. This slide represents different subsets of those populations. However, we believe that the primary subset population, which includes the large number of patients from the EVEREST mortality trial, provides the most robust way to understand the overall mortality related to tolvaptan. In this analysis of the largest available safety data set there is a small difference in mortality which numerically favors tolvaptan.

[Slide]

To further investigate the mortality and hyponatremia I would now like to focus on the Kaplan-Meier survival analysis from the EVEREST trial. These are survival curves from the adjudicated data in these trials and represent all patients in an ITT analysis. For the patients with sodium above 135 mEq/L at baseline, on the left, and patients with sodium less than 130 mEq/L, on the right, you see that both of these curves show essentially equivalence between tolvaptan and placebo regarding mortality.

Again, when reviewing the subset of patients with hyponatremia in this large study which focused on mortality at baseline, we believe there was no issue with regards to overall mortality for tolvaptan.

[Slide]

Now to overly rapid correction of sodium in hyponatremic patients.

[Slide]

In the SALT program a predefined conservative desired rate of sodium increase was set, and 3.2 percent of tolvaptan patients went above this desired rate. None of

the placebo patients exceeded the rate. The maximum rate of increase of 17 mEq/L in about 27 hours was observed in one patient at day 4.

[Slide]

This graph shows the data for the 7 patients in the SALT programs who exceeded the prescribed rate for sodium increase. Of those who experienced this increase, 4 had fluid intake of less than 1 L/day, reflecting that they were fluid restricted despite instructions otherwise. The most clinically important consequence of the rapid increase in sodium is osmotic demyelination syndrome.

There was no occurrence of such an event in the tolvaptan studies. To protect patient safety with regard to the target rate for correction of sodium with tolvaptan we suggest that guidance be applied in the labeling.

[Slide]

Now to GI bleeding in cirrhotic patients.

[Slide]

Twenty-one cirrhotic subjects enrolled in the tolvaptan studies experienced hemorrhagic events, 15 on tolvaptan and 6 on placebo. The time to onset ranged from day 1 to day 41. With regards to these hemorrhagic events,

6 patients on tolvaptan and 1 patient on placebo had a GI bleed.

However, there is a difference in the medical history of these patients. Five of the cirrhotic patients who received tolvaptan had a history of esophageal varices versus 1 in the placebo group. Overall, there were more patients with a history of varices randomized to tolvaptan, 36.5 percent in the SALT trials, versus placebo 22.8 percent.

In addition, some of the cirrhotic patients were taking medications more likely to make them bleed. Since cirrhotic patients with a history of varices are predisposed to further bleeds, this predisposition may be the explanation for the discrepancy seen in this population. The other bleeding episodes in the cirrhotic patients included bruising, bleeding gums and epistaxis.

[Slide]

Having addressed the key issues raised specifically by the FDA, let=s now review additional special interest topics, blood pressure, QT prolongation, renal and hepatic safety and drug-drug interactions.

[Slide]

Reviewing either an increase or decrease in blood pressure in the hyponatremic population, there is no evidence of increased risk of untoward effects associated with the use of tolvaptan. The lack of hypertensive effect provides additional evidence of the V2 receptor selectivity of tolvaptan.

[Slide]

Reviewing the results of studies on tolvaptan=s effects on cardiac rate and rhythm across all healthy subjects and patients exposed to doses up to 300 mg daily of tolvaptan, there was no difference in 12-lead ECGs compared to placebo. No evidence of QT prolongation was observed in the in vitro studies, on cellular repolarization, nonclinical studies in conscious dogs, or in the thorough QT study.

[Slide]

In reviewing patients with impaired renal function, tolvaptan-treated patients, shown on the left, compared favorably with those receiving placebo with lower incidences of AEs related to renal function. The data for patients without renal impairment is shown on the right and shows similar results.

[Slide]

This table summarizes the percentage of patients who developed liver function abnormalities that meet Hy=s criteria, defined as alanine and aspartate transaminase elevations 3 times the upper limit of normal and total bilirubin greater than 2 times the upper limit of normal with an alkaline phosphatase less than 2 times the upper limit of normal.

In the population studied the percentage of subjects satisfying Hy's criteria was greater in the placebo groups than in the groups receiving tolvaptan. For subjects with liver disease or cirrhosis at baseline, those in the placebo group who entered the trial were almost twice as likely to develop transaminase and bilirubin elevations than were the subjects receiving tolvaptan.

[Slide]

The final topic is drug-drug interactions. In healthy subjects tolvaptan was shown to increase the concentration of digoxin by 20 percent. In both the primary safety and the hyponatremic populations tolvaptan-treated patients experienced the adverse event of digoxin toxicity more frequently than placebo. The proposed labeling

includes information regarding necessary precautions.

[Slide]

Tolvaptan is a CYP3A4 substrate. Co-administration does not significantly impact other substrates. However, tolvaptan concentrations are decreased by potent CYP3A4 inducers and increased by potent inhibitors, including the potential for a 5-fold increase of tolvaptan with potent inhibitors. When tolvaptan concentration increases to a level greater than observed following a 60 mg dose, the magnitude of the pharmacodynamic effect is unchanged. However, the duration of the maximum effect is increased.

[Slide]

No significant differences were observed in the safety profile for patients concurrently taking tolvaptan and a CYP3A4 inhibitor compared to tolvaptan alone. The most frequently used CYP3A4 inhibitors and the percentage of patients taking these medicines in the tolvaptan studies are listed here.

[Slide]

Tolvaptan had no effect on the pharmacokinetics or dynamics of warfarin. Tolvaptan had no significant effect

on the pharmacokinetics or dynamics when co-administered with the diuretics furosemide and hydrochlorothiazide.

[Slide]

With regards to the issues of regulatory focus, the following conclusions on the safety profile of tolvaptan can be made: There is no apparent risk of excess mortality for tolvaptan. A small number of patients exceeded recommended rates of sodium correction without neurological sequelae. The apparent increase in GI bleeding in cirrhotic patients may be related to an imbalance in the preexisting condition, for example esophageal varices, between tolvaptan and placebo.

[Slide]

With regard to overall safety conclusions, tolvaptan is generally well tolerated and the side effects are manageable. The most common adverse events are generally anticipated based on the mechanism of action. No increased risks for tolvaptan regarding blood pressure, QT prolongation, renal impairment or hepatic impairment. Rigorous monitoring of the product profile through pharmacovigilance processes will facilitate ongoing risk assessment and implementation of actions to mitigate.

I believe that the information I presented supports these conclusions and offers responses to question 6. This concludes my presentation. Thank you.

[Slide]

I would like to now introduce Dr. Schrier from the University of Colorado.

Clinical Importance of Treating Hyponatremia

DR. SCHRIER: I am Bob Schrier, professor of medicine, University of Colorado. I was asked to say a few words about the clinical implications of treating serum sodium concentration.

[Slide]

I want to first say a few words about public health issues related to hyponatremia. Within the next 20 years the percentage of patients over 65 or individuals over 65 in the United States will go from 12 percent to 20 percent. And, we know that hypertension increases with age and the number one drug that is recommended for treating hypertension, namely thiazides, is associated in a significant number of patients with hyponatremia.

We know that the number one discharge diagnosis in the elderly is heart failure and that hyponatremia is

frequent and is a risk factor for mortality, and the same is true with cirrhosis, and with age cancer increases. These effects of hyponatremia are primarily related to brain function and the central nervous system and involve both physical and cognitive abnormalities, as you have heard.

[Slide]

This is data showing the odds ratio relating to age in hospital-acquired hyponatremia. You can see, starting at around 50 there is a substantial increase in all three areas of low serum sodium concentration.

[Slide]

The reason that hyponatremia clinically is most important in the brain has been alluded to. There is some experimental data that cardiomyocytes and hepatocytes don't like cell edema. But the clinical data for hypo-osmolality and hyponatremia is primarily in the brain because of the skull limiting the ability of the brain to expand. That is shown here with hyponatremia water movement into the brain cells and brain cell expansion. Now, this an adaptation chronically, but also with the extrusion of potassium or organic osmolytes the brain is very much predisposed to osmotic demyelination with rapid correction of hyponatremia.

[Slide]

Dr. Verbalis showed these different symptoms chronically and life-threatening. I learned about the subtleness of hyponatremia on brain function when I was at Walter Reed, here, during the Vietnam period. We had a retired soldier. He had stable SIADH. He didn't control his fluid intake and had frequent admissions for confusion. He was a very nice man and he agreed to be studied over a period of time with different fluid intakes, sodium balances, looking at whether it is water retention or sodium loss. One of the reasons he liked to stay in the hospital for a number of months was because he was allowed to weave and that was his hobby, and almost every nurse and every doctor had either a rug or a purse that he had weaved.

We made rounds on him every day and once his serum sodium fell to 128 we didn't notice any difference at all. The nurses had to tell us he totally stopped weaving. I think what we know is that the degree of hyponatremia and the effect on the brain is very subtle and, in fact, more subtle than what we see here.

Certainly, patients with heart failure who are hypoperfusing, patients with cirrhosis who have arterial

under-filling and have a tendency towards encephalopathy may be even more predisposed, as might be the case in the elderly. All these balance studies in this patient were published in the American Journal of Medicine.

I would like to mention another patient that I think was quite interesting as far as understanding the importance of hyponatremia on brain function. This was when I was a junior faculty member at the University of California San Francisco. There was a young woman, 34 years old. She got pain when she had cystitis and it was frequent. Her doctor told her drink a lot of water when you have that cystitis pain. She came in with a serum sodium of only 128, totally confused. We were worried that she would progress to this stage and, as you probably know, hyponatremia post surgery in women has been associated with a lot of morbidity and mortality, and a lot of legal cases.

The thing that bothered me about just giving hypertonic saline is she had normal kidney function so she might decrease her brain edema acutely and then dump the sodium and the brain edema could occur. We knew it was due to water. So, we said if we give furosemide, the problem with that is you lose all these electrolytes but we can

replace those electrolytes in the urine in a small volume. So, if you get a liter out with furosemide and you replace the electrolytes in 150 mL of 3 percent saline you, in essence, have negative free water.

She responded beautifully and we did a series of studies, published in The Annals of Internal Medicine. I think at least in the nephrologic community furosemide hypertonic saline has been used for the last 30 years.

At that stage I was asked to write a paper in The New England Journal to discuss fluid restriction, lithium, declomycin, hypertonic saline, furosemide. At that stage, what I concluded was what we really neededB-none of these were optimal and what we really needed was a V2 vasopressin antagonist. It looked promising at that time because there were peptide V2 vasopressin antagonists available that worked in every species except man, where it was an agonist. That was 30 years ago.

[Slide]

The caveat about these hyponatremic patients was legitimate. Some of it is hyponatremia that is causing this, but also some of it probably is the negative sodium balance. But what we know is that this reversal that you

can see with diuretic-induced hyponatremia, we can't have that type of success in other patients, SIADH, heart failure or cirrhosis.

[Slide]

This gives an example I think of how ineffective, and how we need these compounds in clinical medicine. You start out here with patients mostly below 135, even very, very low, and obviously not effectively treated. With many of these patients, if you are going to use fluid restriction, you are talking about half a quart a day. That our weaver could never comply with and always came back in, confused with hyponatremia. You can see that ultimately these patients had to be admitted to hospital as their serum sodium concentrations fell.

[Slide]

Well, there was a period of time when vasopressin levels, antidiuretic hormone levels were measured by bioassay. When hyponatremic patients were compared with normonatremic patients the vasopressin levels were totally comparable. The antidiuretic hormone levels were totally comparable. So, what this said was this must be ADH independent, vasopressin independent. It must a delivery

problem to the distal diluting segment of the nephron.

[Slide]

In fact, this cartoon shows water therapy and how good the kidneys are in excreting the water. You can actually calculate this. If someone has a kidney function of 100 mL/minute you are filtering 144 L and 20 percent of that gets down to the distal nephron, which is impermeable to water in the absence of vasopressin. So, theoretically, the maximal ability to excrete water over a 24-hour period is huge, yet you look at the patients that develop hyponatremia they are taking in a reasonable amount of fluid, not an excessive amount of fluid. It is 2.4 L.

So, to us it seemed highly unlikely that a majority of the hyponatremia was due to decrease in distal delivery. Maximal water excretion, yes. But what you have to do to get rid of free water is to dilute the urine, and the thing that prevents that is antidiuretic hormone. Well, that question was answered only because of the development of the sensitive radioimmunoassay for vasopressin.

[Slide]

This is one such study, 196 patients with plasma sodium less than 130; fatality rate very high; plasma

vasopressin levels measured in 73 of those, not suppressed in 71. This suggested that most of the hyponatremia clinically is the nonosmotic release of vasopressin. I say nonosmotic because the degree of fall in osmolality osmotically should turn off ADH, but there is a barrier receptor, nonosmotic pathway related to arterial under-filling and other events that stimulate vasopressin and override that osmoreceptor pathway.

[Slide]

Well, you have seen this data, but this is all cases and, clearly, you can see the advantage of tolvaptan. You can see the reversibility. You can see this duplicated in two different studies. But I would say that at least clinically, having run a big department of medicine for 26 years, that our physicians get concerned when the serum sodium falls below 130. Are you going to discharge the patient with a serum sodium of 128 for example?

[Slide]

In the data starting out with those patients lower than 130, you can see clearly that there is an improvement in both and a reversibility with stopping.

[Slide]

Well, I know there is a lot of discussion about the SF-12, but what we know for sure is that hyponatremia affects the brain acutely and chronically. So, it isn't surprising that the mental component of the SF was what was significant and not the physical. In fact, if there was bias because of the effect on urine you would have thought it would have been in both groups. You can see the combined p value of 0.02. Those with serum sodiums less than 130, 0.04; mild hyponatremia, 0.18; SALT-1, 0.04; SALT-2, 0.14.

Well, since the publication of this study we get a lot of calls. The authors get a lot of calls from physicians and patients wanting to know when this compound is going to be available. Just last week I received a call from a doctor who said his mother had terminal lung cancer with metastasis and hyponatremia secondary to SIADH and she was very uncomfortable, and he wanted the last months of her life so that she could not be hyponatremic, dysfunctional, to drink adequate amounts of fluid, and wondered when these drugs were going to be made available.

When one thinks about the safety issue, I can remember when Lasix and furosemide were being considered, and people said they are so potent that you are going to

have so much trouble with volume depletion you are going to have hypokalemia, metabolic alkalosis, hypomagnesemia. It is going to be an extremely dangerous drug.

Well, we know that all drugs have side effects. But we also know that thiazide diuretics cannot treat in many cases the advanced edema with cirrhosis; the advanced edema with heart failure. In patients with sodium retention in advanced renal disease and hypertension thiazides don't work. So, Lasix has been very important as far as clinical medicine is concerned, and I think these aquaretics where you are only increasing urine flow without electrolytes are going to be a very important addition to clinical medicine.

I would conclude by saying I have been fortunate enough over the past four decades to be involved in the study of body water homeostasis. I think this is the most important time ever. I say that on the background of Peter Agre's discovery of the water channel that we really know how vasopressin works now. But the reason I say this, even more important than that Nobel-winning discovery of Dr. Agre, is that we have a chance now to help a number of patients.

Thank you for your attention, and I would like to

introduce Dr. McQuade.

Conclusions

DR. McQUADE: Thank you, Dr. Schrier.

[Slide]

I would like to present Otsuka=s closing comments. Otsuka hopes that the data presented at today=s meeting supporting the medical utility of treating hyponatremia, especially in those patients with baseline serum sodium levels of less than 130 mEq/L, has been established for you by the expert testimony of Drs. Verbalis, Udelson and Schrier.

The data presented today have demonstrated the clear unmet medical need for the treatment of hyponatremia, especially in patients with serum sodium concentrations less than 130. The decision of which patients to treat, however, is not solely a function of absolute serum sodium concentration and factors including rate of change, the presence of symptoms and the risk of allowing the hyponatremia to worsen all contribute to the clinician=s decision of which patients to treat.

Currently available treatments are inadequate and it is clear that vasopressin antagonists represent the first

class of therapeutics that directly target the primary underlying pathophysiology of hyponatremia.

[Slide]

The symptoms observed with hyponatremia are generally associated with neurologic dysfunction. Neurologic symptoms in acute hyponatremia include stupor, coma, convulsions and respiratory arrest. These symptoms are clearly correlated with cerebral edema, as discussed in Dr. Verbalis= presentation.

In chronic hyponatremia the symptoms are less severe but can still be very troubling to patients. They can include neurologic manifestations of headache, irritability, mental slowing, confusion, delirium and/or disorientation.

It is unclear if symptoms of chronic hyponatremia are associated with lesser degrees of cerebral edema or depletion of solutes and neurotransmitters, both of which may arise from adaptive brain volume regulation.

[Slide]

Tolvaptan clearly and reproducibly has been shown to increase serum sodium concentration. The effects of tolvaptan occur regardless of the severity of baseline serum

sodium levels and occur independent of the underlying etiology. The effects were also clearly shown to be sustained with continued therapy. Drug discontinuation was shown to result in a decrease in mean sodium levels, while in long-term studies tolvaptan was shown to be superior to placebo for up to ten months and the effects of tolvaptan were sustained in open-label studies for over two years.

[Slide]

As I stated in the beginning, the pivotal Phase 3 studies were designed primarily to assess the effect of tolvaptan on increasing serum sodium concentrations. Otsuka decided in 2003 to use the SF-12 scale, a broad, generally applicable measure to determine the effects of tolvaptan on mental and physical outcomes. Because the potential symptoms of hyponatremia are so broad and the underlying disease is so varied, it was necessary to assess them using a broad-based generic scale.

However, as we came to understand the effects of tolvaptan with greater clarity, Otsuka was able to implement a second scale in the second pivotal study that attempted to specifically investigate the more specific symptoms of hyponatremia.

The Hyponatremia Disease-Specific Survey focused on the manifestations of the abnormal mental functioning hypothesized to be associated with hyponatremia, including the ability to pay attention, to calculate and have normal memory function.

The correlation between the effects of tolvaptan on the general SF-12 and the more specific effects on the HDS support the validation of the SF-12 as a scale sensitive to the effects of drugs on hyponatremia.

[Slide]

With regards to tolvaptan=s effects on the SF-12, there were consistent benefits on the mental component summary score. It is interesting to note that there were not benefits on the physical component summary score, suggesting specificity in the effect. The improvement seemed to be generally independent of baseline illness or severity of hyponatremia. The effects were positively correlated with improvements with serum sodium levels and were confirmed by the effects on the Hyponatremia Disease-Specific Survey.

[Slide]

In the large study of patients with worsening

heart failure tolvaptan was shown to improve the symptoms of CHF in patients with hyponatremia, most notable on decreases in body weight and improvements in dyspnea. It is interesting to note that the placebo-corrected magnitude of effect on dyspnea in the hyponatremic patients was twice that observed in the general population.

Coupled with these symptomatic effects, tolvaptan appears to have beneficial effects on cardiovascular mortality and morbidity in CHF patients with serum sodium levels less than 130 mEq/L.

[Slide]

The safety analysis of tolvaptan shows no consistent or clinically relevant risk of mortality in a very large database. In addition, in a single study designed to assess mortality as the primary endpoint the risk of excess mortality was ruled out.

In general, tolvaptan was well tolerated and the most commonly occurring adverse events were associated with the mechanism of action. As with every pharmaceutical product, there are small differences in reporting rates of specific adverse events for tolvaptan relative to placebo. But Otsuka believes that physicians can be adequately

informed or, when necessary, warned about the risk of these side effects in the product labeling.

[Slide]

Let me close by reviewing the benefit/risk assessment of tolvaptan for the treatment of hyponatremia. Hyponatremia represents a clear unmet medical need which is not adequately addressed by currently available treatments. Tolvaptan shows clear effects on increasing serum sodium levels. In addition, it demonstrates specific effects on symptoms of mental functioning as assessed by both general and disease-specific patient-reported outcome scales.

The safety profile of tolvaptan is favorable, with most common adverse events being associated with the antagonism of vasopressin at the V2 receptor. Otsuka believes that tolvaptan exhibits an overall positive benefit/risk ratio and merits approval for the treatment of hyponatremia. Thank you.

[Slide]

We would now be pleased to answer any additional questions you may have. In addition to my Otsuka colleagues, and Drs. Verbalis, Udelson and Schrier, we have seven additional outside experts, some of whom have already

spoken, and who are listed on this slide for your information. Thank you very much for your attention.

Questions from the Committee

DR. HIATT: Thank you. We have some time now before noon for the committee to ask the sponsor questions and any clarifications.

One place I would like to start is a better understanding of your safety database. You have nice data in the EVEREST study looking at all-cause mortality and CV mortality or heart failure hospitalizations at CC-129, with upper boundaries of the 95 percent confidence intervals that exclude a risk of 11 percent to 14 percent increase, which one could argue is fairly tight. This was in the heart failure population.

If you then look at the adverse event reporting in the all-patient populations, there are interesting numeric excesses of events of concern, such as cardiac arrest in all patients in the Phase 3 heart failure trial and now hyponatremia. These excesses are small numerically but because the number of events are small may represent higher confidence intervals than what you have shown us in just the heart failure studies.

So my first question is can you better define the safety of this drug, not just in patients with heart failure but in the other populations that you propose to develop this drug for in terms of the upper boundary of levels that might cause concern?

DR. McQUADE: Thank you. I will ask Dr. Zimmer to address this question.

DR. ZIMMER: Chris Zimmer, with Otsuka. Good morning, Dr. Hiatt. As you mentioned, the issues raised in your question I believe relate to cardiac safety in general. There are three basic points that I would like to make.

First, relating to the extensive evaluations that occurred during the preclinical, nonclinical development; second, relating to electrocardiographic evaluations; and, third, relating to adjudicated outcomes specifically in the subset of patients that you are interested in.

First, cardiac safety was an extensive focus of nonclinical development, with extensive studies conducted in a number of different models designed to look for cardiac signals or signals of cardiac safety, models consisting of action potential duration studies in guinea pig papillary muscles, HERC assays, 4- and 52-week repeat dose, multiple

dose oral toxicities in canine models. Throughout all of the nonclinical development there was no evidence of any sign or signal relating to cardiac safety.

Second, the proarrhythmic potential of tolvaptan was evaluated in a thorough QTc study which looked at the super-therapeutic dose of 300 mg. No effects on any electrocardiographic parameters, but particularly no effect on the QT interval.

Beyond that, 18,000 ECGs were collected in 27 Phase 1 and Phase 2 trials, reevaluated in a centralized fashion; 45,000 ECGs in the EVEREST trial. No signal of any effect on any electrocardiographic parameter relating to repolarization or conduction.

But finally, and most importantly, cardiac safety was a specific focus, as you mentioned, of the EVEREST trial which randomized 4,000 of some of the sickest heart failure patients and collected 1,000 mortality events, 1,600 cardiovascular hospitalizations. As I mentioned and as you noted, there was no difference in the overall population. But when we looked at subgroups of patients specifically with sodium less than 130, that reassuring trend continued.

Can I have the slide up, please?

[Slide]

The Kaplan-Meier curves shown here show the subgroups that Dr. Carson put in his presentation as well. Again, all-cause mortality, ITT population, a conservative ITT analysis showing all-cause mortality using a cutoff of sodium less than 135, hazard ratios and p values in the lower left of each figure, cutoff using 130 on the right.

Again, all of the lines of evidence, whether it is the nonclinical data, the extensive cardiographic evaluations, the database of prospectively defined and independently adjudicated outcomes from a long-term outcome trial using sodium cutoffs of 135 and 130 support the idea that there is no signal of cardiac risk in these patients.

DR. HIATT: I am glad you brought this slide up. I would just point out for the committee to note that the upper boundary of the hazard ratio would exclude as much as 37 percent to 29 percent excess mortality. Correct?

DR. ZIMMER: That is correct.

DR. WARNER STEVENSON: While that slide is still up, I have one question because most of the patients with a sodium less than 135 who had heart failure, in fact, were between 130 and 135. Do you have that group as well which,

presumably, is part of the curve on the left?

DR. ZIMMER: We do have that. I know my colleagues are looking for it furiously. So, in just a moment, hopefully, we will be able to pull it up.

DR. WARNER STEVENSON: I actually had a question for Dr. Schrier.

DR. HIATT: Okay, what I want to do is just get some more clarity on this aspect of the safety because I think it is pretty clear that this was being developed as a symptomatic treatment. Correct? This therapy is being proposed as something that treats a symptomatic endpoint and the surrogate of serum sodium is a marker of what that clinical benefit might be.

In that context, I am just trying to understand the risk around symptomatic therapy, and I would agree with you that in heart failure the highest risk population would be perhaps the best population to detect a signal of concern, and there, because you have a lot of events because they are sicker patients, you have excluded a lot of risk I think.

The question is if you extrapolate that thinking to the broader population of hyponatremia where the event

rates are much less, then with numerically fewer events you have bigger boundaries of the confidence interval around the potential risk. What I am trying to understand is how broad those confidence intervals might go in, for example, cardiac arrest in the total population, 32-94 on treatment, 27-38 on placebo. With a 1.5 percent incidence of cardiac arrest on treatment and 0.9 percent on placebo, that means a total of 76 events. Then I would imagine the confidence interval around those differences are much broader.

The question is can you define the risk of this drug if we extrapolate from heart failure to less sick populations which may have different risk than the heart failure population?

DR. ZIMMER: The best answer that I can give you, Dr. Hiatt, again comes back to two lines of evidence. The first would be looking at the primary safety population, as you did, for any signal of an increased risk relating to cardiac arrest. In the FDA=s analysis on page 74, table 7.3.2-5 they themselves conclude in combining the terms cardiac arrest and cardiorespiratory arrest that the effect is essentially, quote, lost or diminished.

Beyond that, let me focus on the adjudicated

outcome most closely related to cardiac arrest because that is where you are going to be able to define the confidence intervals that help give you the reassurance that you need. In the database of adjudicated outcomes, the adjudicated outcome most closely relating to cardiac arrest would be sudden cardiac death. When we looked at the database in the intention-to-treat analysisB-if I could have the slide up, please?

[Slide]

You will see that the overall incidence of adjudicated sudden death in the overall ITT population occurred with an incidence of 7.05 versus 6.5. When we then looked at the subgroups of patients with sodium less than 135 and 130B-slide up, please--

[Slide]

B-what you will see is that in the subgroup of patients less than 135 there was a small numeric imbalance that favored tolvaptan, with an incidence of 7.82 versus 9.05, an incidence that was essentially comparable in the subgroup of patients less than 130. We can develop the confidence intervals around these evaluations as well.

But I offer this data by way of helping you to

understand what the risk associated with this particular adverse event term really means.

DR. HIATT: Thank you. That is the kind of thing I am looking for, and I would just note that the incidence rates numerically are a little less but the percentages are higher in the more severely hyponatremic patients and it appears to be somewhat increased so as the serum sodium level goes down the rate goes slightly up. But with 5 and 7 events you have very broad confidence intervals around that, don't you?

DR. ZIMMER: Understood completely, Dr. Hiatt, and that is one of the challenges in evaluating the data, and one of the reasons why in adopting a structured and disciplined approach to understanding signal interpretation we look up at the primary safety population, consisting of over 6,000 patients; we look at the database of adjudicated outcomes for any indications that there is a replication or amplification of the signal; and we look at the population of the sickest patients, again, convergence of the evidence trying to see if there is anything that makes sense.

DR. WARNER STEVENSON: I think it is important to recognize, however, that it may not just be that the benefit

is greatest in the people with the lowest sodium, it is also possible that the risk is actually less in that group. Because their sodium is so low, the chance that you might have adverse events from increasing the sodium or other changes may be different. So, I think it isn't just a question of a change in events. There really may be different populations who have truly different benefit/risk ratios and I think we have to bear that in mind as we look at efficacy versus risk.

DR. PAGANINI: Bill, can I ask for slide CC-154 to go back up again?

[Slide]

Do you have any data on delta sodiums related to mortality in less than 130, to follow up on Lynn=s question?

DR. ZIMMER: One second, Dr. Paganini. Dr. Paganini, if I understand your question correctly, it relates to those patients that experienced an increase of, say, 2 or 3 mEq of sodium and what their mortality looked like relative to those that did not experience that.

DR. PAGANINI: Yes, I guess the hidden questions here are two. One is that we have been asked as a panel to look at serum sodium as a surrogate for outcome and whether

or not that is truly a surrogate for outcome, versus the serum sodium being basically an outcome risk indicator as opposed to a true surrogate for the underlying disease.

What we are seeing across a mix and match of different presentationsB-while there is no question that low serum sodiums are not a good thing to have, when I see things like this, especially at 130 or less, 135 to 130, I am personally not that concerned with it and I know everybody is going to go crazy and say how can a nephrologist not be concerned with that.

But 130 or below is when I really get a little bit worried, and here we are seeing an improvement in outcome potentially with drug as far as mortality is concerned. So, I am trying to now find out whether or not that improvement was associated with changes in sodium, attributable perhaps to the drug versus just underlying disease entity.

DR. ZIMMER: Understood, and, Dr. Paganini, you have sort of honed in on a source of a lot of debate which is, is low serum sodium a biomarker or a modifiable disease target. Slide up, please.

[Slide]

Let me show you this analysis in which we looked

specifically at patients experiencing a sodium improvement of greater than or equal to 3 mEq versus those that had no sodium improvement, a post hoc, retrospective analysis for the purposes of clarifying the question that you just posed.

All patients represented on the left, the subgroup of patients with sodium less than 135 in the center, the subgroup of patients with sodium less than 130, all-cause mortality evaluated using the log rank test. Those patients that experienced an increase in sodium of greater than or equal to 3 mEq in the subgroup of patients less than 130 experienced a statistically significant-Ba nominal p value, I should say in the log rank evaluation of time to all-cause mortality. Does that help answer your question, or at least begin to get there?

DR. PAGANINI: Yes, it does. Thank you.

DR. ZIMMER: Thank you.

DR. WOLFE: This is a corollary or a different way of getting at the concern that Dr. Hiatt and I am sure many of the rest of us have, and this is taken from the longer FDA review as opposed to the short one they are going to be giving. The point they make is how adequate is the safety database. What they said here is of 3,294 subjects with

heart failure and/or hyponatremia, I just calculated only 5.7 percent of these people, 189 subjects, had serum sodiums under 130.

So, when we hear the safety data we are hearing it heavily weighted by people with heart failure who don't have hyponatremia and, yet, for the purpose of this meeting the proposed indication is hyponatremia. When you have such a very small database to actually raise concerns about safety, I don't see how you can answer those concerns. The confidence intervals obviously would be huge if you just looked at that group of people with the serum sodium under 130. I think that is really what you are saying, Dr. Hiatt, and I just don't see any answer to it.

I mean, if we were considering this for approval of heart failure, and most patients don't even have hyponatremia, it would be a different kind of discussion. But we were told by the FDA that the discussion is mainly about the indication of treating hyponatremia. Given the problems, particularly when we are talking about outpatient treatment of hyponatremia by physicians who may or may not be able to make the determination that they have hypo- or euvolemic hyponatremia, may not be aware probably of over

100 drugs that can cause hyponatremia, I am not comforted at all with this very small safety database in this group of people. It is a comment more than anything else, the small group of people that are studied for the indication.

DR. HARRINGTON: I want to follow up on Dr. Wolfe=s comment and ask to clarify, and maybe Dr. Verbalis can help me out here. For the treatment of these patients with the typical patient with cirrhosis or heart failure of SIADH with a serum sodium of less than 130 how long would you anticipate that treatment would occur? What would be the duration of treatment?

DR. VERBALIS: That is very patient specific.

DR. HARRINGTON: So, give me the range. Give me what you think the average is and some confidence around that, the range around that.

DR. VERBALIS: You know, I would like to give you a direct, simple answer but it is a complicated situation, as you well know from the nature of your question.

Let me give you an analogy with conivaptan which is the only approved V2 antagonist. In an open-label study looking at about 200 patients with serum sodiums less than 130, which is the range we are talking about, and the

majority of them corrected within a 4-day infusion period, they were then brought back at 7 days and 30 days after correction and 70 percent of them maintained a normal sodium level despite no additional V2 antagonist, and the half-life of conivaptan, like tolvaptan, is less than 12 hours.

So, clearly, there is a large reservoir of patients with acuteB-I don't want to say acuteB-with inpatient hyponatremia which is caused by an underlying comorbidity where treatment of that comorbidity will abolish the stimulus to AVP secretion or they won=t have chronic hyponatremia. That leaves about 30 percent of inpatient hyponatremia that will not be durable where the correction will persist for prolonged periods of time, and one would envision that group as being treatment candidates.

Now, you know, depending upon the disease, so if you have acute decompensated heart failure/hyponatremia and then have successful implementation of standard therapies, such that the hyponatremia is no longer present, obviously, it is not an indication for long-term therapy. If you have SIADH from a small cell cancer to the lung, which is not going to go away, then it is going to persist. So, the range is anywhere from 2-4 days to years in terms of

treatment duration.

DR. HARRINGTON: That is what I thought you might say. So, it is fair to say that there will be people who potentially will be treated with this therapy, if it were approved, for months to years.

DR. VERBALIS: Yes, and we have patients now on the SALTWATER open-label study who are being successfully treated. My patients are out past two years of therapy with continued benefit in terms of decreased symptomatology in terms of better neurocognitive function, ability to do their daily activities.

DR. HARRINGTON: Now I just want to clarify, to follow up on Dr. Wolfe=s question in terms of the confidence that we have in the safety database, my looking at the numbers was that there are 111 patients with hyponatremia who have been treated for up to a year and less than 70 currently reported to us who you have data on beyond the year with hyponatremia. Is that correct or do I adjust those numbers?

DR. McQUADE: Slide on, please, and can I also have the slide that includes the open-label exposure?

[Slide]

In the placebo-controlled studies in the hyponatremic population there were about 69 patients who were greater than a year and 132 greater than 6 months. If we also include the open-label extension to get additional safety data I believe the numbers are approximately 220 for 6 months and 150 for over a year.

DR. HARRINGTON: So, it is a small experience given the magnitude of the problem and the potential patient population who would be treated with this, as we heard from the previous speaker.

Bill, can I switch to a different safety topic?

DR. HIATT: Yes, I do think there is more to discuss with safety. Maybe Dr. Temple would chime in here.

DR. TEMPLE: I just wanted to ask whether the company had any response to the question that Sid raised, which is basically that you have a limited database in the group you want to treat even though the total number of people treated is large.

In some situationsB-I just want to give a little history, we have accepted the idea that study of a fragile population that wasn't the one you were planning to treat was informative. For example, in the two treatments we

approved for maintaining normal sinus rhythm, dofedilide and nanolol, we took reassurance from the post-infarction study of nanolol that showed a strong trend that was favorable, and from two things called the DIAMOND studies of dofedilide, one in heart failure and one in I guess post-infarction were reassuring but they were certainly not in atrial fibrillation. But those were thought to be fragile populations.

I guess I should note that the paper you wrote with Ray Lipicky suggests that you want to pick a fragile population for your long-term safety study that every drug should have.

So, I am curious as to how people feel, both the company and everybody else, about whether the heart failure population is the sort of sickies you want to study, or whether in some way it is irrelevant because they are not as hyponatremic as the others. That could be an afternoon discussion but I just want to raise it.

DR. HIATT: Bob, to clarify that, you are talking about an interaction, essentially, that the risk is not proportionate. So, if you just say heart failure it is a great model because they have a lot of events, and it is

events you want. That may not be representative if there is an interaction between serum sodium level and risk of mortality.

If you look at all the hyponatremia subjects from all studies, cardiac arrest is 2.3 percent versus 1.0 percent, and one would say those point estimates are still, quote, equivalent but the numeric disadvantage seems slightly greater. And, once again, the number of events is extremely small.

So, let me just clarify that. You are asking is the heart failure population who is not hyponatremic representative of the safety concern with this drug?

DR. TEMPLE: Yes. I mean, in some settings we have thought a heart failure population is the very sort of fragile population you want. They have a lot of sudden death, by the way. And, I am just wondering how people feel about it because that is going to help decide whether it is a large safety database or a small safety database.

DR. HIATT: Correct, and I think we have been dancing around that issue a little bit here. I would be curious to hear what the committee thinks. I think there is a lot of merit to a sick population, frankly, but the

sponsor is probably not going to be able to convince us that the hyponatremic patients and their risks are really mirrored in some way by the larger heart failure population.

DR. HARRINGTON: I personally, Bob, am comforted by a large heart failure population which has a very sick group of patients who are taking a lot of the medications that we would be concerned about in terms of potentially other effects, other interactions. It does lend a measure of reassurance.

I don't think it solves all of the issues that you are then taking a very small, select group of heart failure patients who are at very high risk of bad outcomes, and then the safety database becomes a lot more limited. So, personally, I am comforted by it but I am not convinced that it is necessarily enough in this particular situation.

DR. McQUADE: When Otsuka began these studies we worked with FDA, and I recognize that things have changed and that times have changed, but at the time it was not thought that sodium was a surrogate and we were actually primarily looking at increasing serum sodium in the hyponatremic patient population.

As such, we performed those studies that we felt

were necessary. And, you are absolutely right, I can't make the database bigger now because of what we did in 2003 and beyond. I would like to ask Dr. Zimmer to briefly comment on sort of the generalizability of the hyponatremia data set to the heart failure data set because that is where we do get the majority of our safety information from and we think it is relevant to predicting the outcomes.

DR. HIATT: And, is there any directional difference between the heart failure population who are not hyponatremic and their safety signal compared with all the hyponatremia patients without heart failure?

DR. ZIMMER: Dr. Harrington, let me see if I can respond to your question first. If I could have the slide up, please?

[Slide]

In seeking to understand how to interpret signals and seeking to understand how to interpret these imbalances one of the things, as you mentioned, that we did was acknowledge that we were working with a severely ill heart failure population. You saw the baseline characteristics.

In further exploring how to interpret signals, in addition to rolling up to the primary safety population,

rolling down to those patients who were even sicker, as represented by their low serum sodium, the point that I would just respectfully try to draw your attention to again is this series of analyses, again, looking at the adjudicated outcomes, all-cause mortality, cardiovascular mortality, heart failure hospitalization, cardiovascular mortality, cardiovascular morbidity in the sickest group of patients, sodium less than 130.

DR. HARRINGTON: Let me preface my remark by saying I think you have done a series of very elegant analyses, and when I looked at this I said, boy, you have a terrific hypothesis here and you have laid it out beautifully as a hypothesis.

DR. ZIMMER: Hypothesis in terms of?

DR. HARRINGTON: That the group of patients with low serum sodium, in this case defined as less than 130, may have a very favorable effect of the drug on clinical outcome.

DR. ZIMMER: But the important thing to remember is that that is not what we are going for.

DR. HARRINGTON: I understand that.

DR. ZIMMER: I just wanted to be sure it is clear.

DR. TEMPLE: Well, imagine for a moment that they are going to get that claim, the question is whether it is somewhat reassuring in light of the discussion we are having. That is all.

DR. McQUADE: Dr. Temple, we agree completely and that is the way we have referred to it. It is reassuring--

DR. TEMPLE: I knew that, right.

DR. ROBINSON: I would like to comment on Dr. Temple=s statement, and to the question of whether the cardiac population is a good at-risk population for the general population-BI think that is what you are asking, so if you have an outcome that seems reasonable in a very high risk population, in what way is that reassuring?

The thing we haven=t spoken about here is a mechanism of why that might be true. One mechanism why that might be true is that in these patients who are hyponatremic it is possible that when you give them an aquaretic agent and you then increase their sodium there will be an increase in their inherent vasopressin secretion. It might be the inherent vasopressin secretion that would have some adverse effect on the heart so that it may well be that that would be a reason why an at-risk cardiac population would be a

good population to have an excess risk of the treatment with a V2 antagonist.

DR. WARNER STEVENSON: I continue to be very interested in that group between 130 and 135. Under 130 is very small; over 130 is very large but some of them don't have hyponatremia. So, I really think we have to see that middle group which may give us increasing confidence.

In terms of Dr. Temple=s question, I think clearly if we look at the heart failure and cirrhotic groups, they have a lot in common in terms of hemodynamic instability, shifts in volume, electrolytes, and I think those two groups we can consider, I think, to have some things in common in terms of risk. The SIADH group I just can't comment on at all. I don't know what their particular risks would be and whether we are comforted about those from this data.

DR. McQUADE: Dr. Stevenson, we will try to pull some of that data for you over lunch, if that is acceptable, and try to present some of it to you this afternoon.

DR. NEATON: Could I just ask a question of clarification going back to the mortality, either the tree graph or the life table? Are these all deaths that occurred in those subgroups throughout the duration of the trial

irrespective of whether they took treatment or not? Because there was a discrepancy, which maybe we will come back to this afternoon, between the FDA tables and the tables you are showing for the number of events. I just want to make certain what we are looking at.

DR. McQUADE: I understand. Can I have the mortality table from Dr. Carson=s presentation?

[Slide]

I called this up because I think it is one of the more easy tables to follow, and I just want to orient the audience to all the different analyses on this, and I will ask Dr. Zimmer to comment specifically on how we defined fatal treatment emergent adverse events.

The primary safety set is all hyponatremia and all heart failure in Phase 2/3 placebo-controlled trials. Here there is a slightly lower incidence with tolvaptan than placebo. The all-hyponatremia safety data set includes all patients from the SALT studies, as well as all patients with baseline hyponatremia in the EVEREST study, and that represents a smaller number, obviously, and there is a small difference between the two treatment groups, with placebo being slightly lower.

If you then limit this data set again to less than 130 you end up with this number of patients, and now you see a rate slightly lower with tolvaptan. If you look at the all-hyponatremic heart failure patients you see a different rate. If you look at the EVEREST hyponatremia set you see the rate that FDA first referred to in their original briefing document. Then if you see the rate with EVEREST less than 130 you see another rate.

Our position is that this is the data set that is most important because it gives you the greatest confidence in the confidence interval, as Dr. Hiatt was talking to. The rest of the difference, we think, just represents different subset analyses basically due to chance.

DR. NEATON: I accept that. I am just trying to understand something very simple, how you are counting--

DR. McQUADE: I understand. Dr. Zimmer, would you explain that?

DR. ZIMMER: Dr. Neaton, good morning. I understand. It can get confusing. Let me just state that in the Kaplan-Meier analyses that I shared with you just a moment ago, those were from the intention-to-treat population so these were all patients randomized. In the

analyses that Dr. McQuade just showed we tried to use the definitions that were in the briefing package. Those are fatal treatment emergent adverse events. Those are all adverse events that occurred on treatment, protocol defined treatment period, which is defined as patients who received a dose of study drug through the date to discontinue study drug.

DR. HIATT: Could you put that slide back up, please?

[Slide]

What I would like to see, if you can do this, is the all-hyponatremia safety. Could you calculate the confidence intervals around whatever that point estimate is, the 131 events versus the 108 events? Is that possible?

DR. ZIMMER: Yes.

DR. HIATT: If you could do that this afternoon?

DR. McQUADE: Yes.

DR. HIATT: Thank you.

DR. NEATON: Just to make sure again, put up the life table, the intention-to-treat. Maybe the FDA presentation this afternoon will clarify but they came up with a different number of deaths in what they called Aall@

and maybe that is not intention-to-treat. But in your analysis in those life tables is every single patient counted to the end of the trial in both groups, irrespective of treatment? That is what you are calling intention-to-treat?

DR. McQUADE: That is in the Kaplan-Meier curves, that is correct. Can we call up the Kaplan-Meier curves?

[Slide]

DR. ZIMMER: Just to clarify, Dr. Neaton, this would be in the ITT population. Those were regardless of whether they received treatment or not.

DR. NEATON: Right, so these data go out to the end of the trial irrespective of treatment. Is that correct?

DR. ZIMMER: That is correct.

DR. HIATT: It is getting near noon. I that we might break for lunch. There are a few things the sponsors have to come back with at one o=clock. Then we will have FDA presentations and we can get to some more questions.

DR. WARNER STEVENSON: One other thing perhaps they could come back with is that I think we need to deal explicitly with the issue of the frequency of thirst, which is not only an adverse event but, in fact, could in some

ways help protect against worse events if patients drink ad lib. So, I think that is a very complex adverse event that was common and needs to be discussed.

DR. HIATT: Since we are creating a list for this afternoon, I would like to go back to the bleeding data this afternoon because there were no denominators given on the table that we saw and I would like to understand if they have done any work with interactions with aspirin and clopidogrel because there is a biological reason to believe the drug could be associated with bleeding, other than being given to cirrhotic patients.

Then, the other thing I would like to see, given some of the generalizability, is where the trial was actually done and the type of investigators. Were these highly specialized renal docs? Were these general practitioners? I would just like to get a sense of that.

DR. ROBINSON: I would also like to see something more on the bleeding data. I mean, the explanation that was given seems reasonable, that there were more subjects with esophageal bleeding, with esophageal varices, but there is a well-known effect of V2 on blood clot parameters. As I recall, the safety data we saw on that was that there was no

adverse event in a normal population. But if there was data in cirrhotic patients, I didn't see that but maybe it is there. I would like to see that.

DR. HIATT: We will break for one hour. Thank you all very much.

[Whereupon, at 12:00 noon, the proceedings were recessed for lunch, to reconvene at 1:00 p.m.]

A F T E R N O O N P R O C E E D I N G S

DR. HIATT: This is the phase of the open public hearing. There is someone who has registered to do this. You are going to read the statement first?

Open Public Hearing

DR. FERGUSON: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the adverse event committee meeting, FDA believes that it is important to understand the context of an individual=s presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationships that you may have with the sponsor, its product and, if known, its direct competitors. For example, this financial information may include the sponsor=s payment of your travel, lodging or other expenses in connection with your attendance at this meeting. Likewise, the FDA encourages you, at the beginning of your statement, to advise the committee if you do not have such financial

relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement it will not preclude you from speaking.

The FDA and this committee places great importance in the open public hearing process. The insights and the comments provided can help the agency and this committee in their consideration of issues before them. That said, in many instances and for many topics there will be a variety of opinions. One of our goals today is for this open public hearing session to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy and respect. Therefore, please speak only when recognized by the chair. Thank you for your cooperation.

DR. HIATT: May we have the first speaker?

DR. JOSIASSEN: I am assuming that is me.

DR. HIATT: Only you can tell!

DR. JOSIASSEN: Sometimes I wonder. I am Dr. Richard Josiassen. I am a professor of psychiatry at the University of Pennsylvania, Department of Psychiatry. But more importantly to the issue of this day, I also direct a

research foundation that is nestled in the context of probably the largest psychiatric state hospital in Pennsylvania where we focus a lot of our attention on various aspects of schizophrenia research, both treatment of the illness and some issues in its etiology.

This morning we heard a lot about hyponatremia in the context of more of a general medical discussion-Brenal problems, cardiac problems, SIADH, and so forth. My interest today is to at least bring your attention to this problem in the context of mental health, but specifically or particularly the context of schizophrenia.

In terms of financial transparency, truth in advertising, I have done some clinical trials with what used to be called Yamanouchi with their drug conivaptan. I have been involved with the tolvaptan project as a principal investigator, more recently involved with Cardiokine and their new compound, and probably over time will be involved with Sanofi as well; we will see.

They have not paid for my transportation down here, nor bought me any Chardonnay last night. As far as I know, I have no financial arrangements with any of them. But the one thing I do need to say is that in the

development of the data for the tolvaptan papers Otsuka was kind enough to actually let myself and Dr. Murray Goldman have access to all the schizophrenia data that was collected as part of the overall SALT-1 and SALT-2 trials to write an independent paper.

We do have several of the Otsuka personnel listed as co-authors on it but Murray Goldman and I were the actual ones that did the paper and are responsible for the analyses, and it was accepted for publication last week in Biological Psychiatry so there is also some academic involvement with Otsuka. But, again, that was something that we initiated. They didn't pay for it or pay us to write the paper.

Schizophrenia, just really quickly, most of you probably are familiar with this but I just need to put it in context. Roughly one percent of the adult population in the world is afflicted with this illness. It is a chronic illness. Generally it rears its ugly head around age 18, 19, 20 just when one is beginning to move from adolescence into adulthood. It is a chronic illness. We are beginning to get a better handle in terms of how to treat it in terms of the psychiatric component.

Most of us in the field are fairly convinced that it is genetic in nature, at least the transmission of it. In most cases it winds up being expressed as a genetic illness primarily in the central nervous system. But we are also beginning to be more and more aware that not only is schizophrenia an illness that has a clear, frank psychiatric picture, but it also carries with it the burden of an enormous number of other medical comorbidities, some of which are recognized, some of which are not recognized in a general psychiatric mental health community or the medical community at large.

I would just say that part of the reason for that is that, as you all know, mental health psychiatry, severe psychiatric disturbances, in terms of their care have been carved out ofB-I love that word, carved out of-Bthe general medical profession so that, in a sense, psychiatric patients with profound medical problems are mostly seen in the psychiatric context with modest or maybe sometimes better than that medical concern. But for the most part, they are treated primarily as psychiatric patients with a secondary nod to medical problems.

Some of the medical problems, of course, are

cardiovascular problems, metabolic problems, smoking problems. But the one we are going to be speaking about today and that is I think perhaps one of the major problems to have as a comorbid condition is hyponatremia.

So, we ask the question is hyponatremia an important clinical issue in the overall care of these folks? I want to start with a patient, the second patient I ever worked with who I recognized and tried to do something for who had hyponatremia. This is a gentleman who gave me permission to take his picture. He has also given me permission to use his first name. His name is John.

When this picture was taken the 64-year old fellow had been hospitalized for at least half of his life as a chronic schizophrenic patient. When he was first diagnosed with hyponatremia no one really knows. But he had multiple, multiple, multiple hyponatremia-related seizures. He was selectively mute for most of his days in the state hospital.

If you did look at the records that were available, his serum sodiums ranged from 118-125. He had problems with motor skills. His gait was impaired and he had tremors. When his serum sodium began to go down he would often times, even though mute, as one of the little

quite schizophrenic guys that sat in the corner and didn't relate to most people, he could become pretty aggressive and was often the person who stimulated fights amongst other folks in the unit.

I guess I would say that this was the first person that ourselves and others in the country who began to try to define hyponatremia in this context. He was one of the ones that I began to pay the most attention to from a pharmacological point of view, what goes on with him symptomatically.

Others in the field, I should just mention, are doing work comparable to usB-of course, Murray Goldman at the University of Chicago, Art Siegel up at Harvard and a few other folks scattered around the country who have a secondary interest in hyponatremia and schizophrenia.

The problem, of course, has been recognized for a long time. I just cited some of the earlier papers that I have discovered back in 1923, 1933, 1938. If you go back and look at the literature that was written about schizophrenia in that period of time, you will see any number of book chapters and articles about fluid dysregulation, electrolyte imbalance, and so forth in this

population. So, it has been recognized for almost 100 years as an important issue. That bottom reference down there, 1938, was the first published report of a hyponatremia-related death.

So, the question is, of course, in my mind and I don't know the answer to it, if this problem has been recognized for so long why has it sort of fallen off the radar screen as something that is important? I suppose one answer is that when the medications came on the screen, the antipsychotics in the late '50s and early '60s, a lot of these kinds of issues were being looked at in the field and began to be eclipsed by the hope that these antipsychotic drugs would solve most of the problems.

How much of a problem is it? Unfortunately, there is very little good evidence to talk about the prevalence of hyponatremia in schizophrenia. Most of the published papers have used surrogate measurements to come up with numbers. There are only three reports that I am aware ofB-two reports and this data here that actually looked at serum sodium levels specifically to determine hyponatremia.

The two reports, other than this slide here, used a cutoff score of 133. One sample was quite large, one

sample was rather small. And, they suggested that the prevalence of hyponatremia in a chronic schizophrenic population was around maybe 5 percent, 4 percent.

We took the opportunity at our hospital to gather in all of the serum sodiums that were available for a 3-month period from our entire population. There were 328 patients who actually had given serum sodium within that 3-month period, some multiple times but we only included them once in the sample.

What we found if we used a cutting score of 135 as indicative of hyponatremia is that we had a 7.9 prevalence rate of hyponatremia in this hospital. We made no efforts to discern what the causes of this were. Of course, we all know that some folks are delusional with this illness and some of their water consumption and polydipsia contributes to some degree to this. Medications contribute to it.

But there also are a fair number of folksB-I have used the term idiopathic hyponatremia to suggest that they have hyponatremia in the absence of fluid intake, in the absence of a drug side effect that is still an issue for the quality of their care.

One other thing we looked at was whether serum

sodium levels were associated with any kind of way with the antipsychotics they were taking either in terms of class or dose, and we found no correlations whatsoever.

You have already seen this kind of information. I show this only to say that we have already seen it in various kinds of formulations this morning, but if you look at these symptoms that are related to hyponatremia not so much as symptoms of hyponatremia but in the context of schizophrenia you can see what a conundrum it is to know how to deal with this problem.

Not only are these symptoms of hyponatremia but many of them can also be characterized as symptoms of psychosis-Bconfusion, agitation, hallucinations. The rate of seizures in a hospital like ours is not trivial. Of course, Victor Hedwig documented in the late '80s that hyponatremia-related death was one of the leading causes of premature deaths in an institution like this.

Also, as noted before, hyponatremia can be both acute and chronic but in this population it has important implications. In acute patients I think the neurologic symptoms are best demonstrated in this case here. The patient=s scan shows this patient at day 1 with 104; came

into the hospital with seizures and comatose; day 2 121; and day 3 140 millimolars per liter of sodium. You notice the edema on day 1 that reduces and becomes much more normal by day 3.

But in the more chronic patients, which is the kind of hyponatremia we see, although we do see seizures and we do see this sort of edema from time to time, the morbidities we are more familiar with are the impaired cognition associated with hyponatremia which also is confounded by the impaired cognition that is part of schizophrenia in general.

We see impaired gait and balance in this population, again, something common in schizophrenia in general but also common to hyponatremia. At least in a hospital like ours, we see a fairly non-trivial increase in pathological fractures, non-traumatic fractures and osteoporosis related to the condition.

So, at least from a financial point of view, from a service point of view these kinds of comorbidities create additional burdens on the patient and the hospital as well.

For review, Art Siegel just wrote a very nice review that came out in The Harvard Review of Psychiatry

looking at hyponatremia in mental illness, just published last March.

The treatments in the past that have been available are listed here. They have been discussed in the past. For the most part, they have been not particularly useful for our population. You think it is tough to control people in a general hospital and put them on fluid restrictions, trying to deal with it in a chronic psychiatric hospital where the staff is already limited and the folks are in a whole different state of being is probably not doable.

Two years ago there was a review. I suppose it was written for one of the pharmaceutical companies, I am not sure, reviewing all 30 publications that have attempted to treat hyponatremia and schizophrenia. They broke it down in four different classes of drugs, those to treat reduced fluid intake, reduce idiotypic behavior, increase water excretion or increase plasma tonicity. The conclusion that these authors gave, they are listed on the bottom, was that the trials offer little useful data to the clinicians to guide effective management of either polydipsia or hyponatremia. I have to say that would be the conclusion I

would have to write, and did write as well.

When we discovered that vaptans were being developedB-here are some of them or maybe this is all of them, I am not sure, the first that we got involved with was the Yamanouchi conivaptan. Real quickly, when the decision was made to not have it be an oral drug we had about 12 patients on conivaptan who were doing very, very well out in the community. The problem was what are we going to do with them now? At that point I actually had a phone call with Chris Zimmer, whom I never really met but we talked on the phone several times. He was willing to take a risk that we might want to think about moving our schizophrenic patients into this SALT study as well. This is the paper that just got accepted.

Out of that entire SALT sample there were 24 patients with schizophrenia. We looked through all of them. Of the 24, 5 of them had primarily medical problems, heart disease, renal disease, so those 5 we excluded from any of our analyses because we wanted only idiopathic schizophrenic patients. They also were not taking medicines that induced hyponatremia.

Since they were part of this ongoing double-blind,