DR. TEMPLE: You know, we try hard to stick to the policy of never changing our mind no matter what the data show, but every once in a while we move from that and we reconsider something that we have said in the past. We are provoked to do that when we discover that having a lot of VPVs after a heart attack is bad for you but the remedy for it kills you, and a wide variety of other experiences that have made people chary about too casually relying on surrogates.

Speaking for me here, that does not mean to me that there are no reasonable surrogates. I gave potassium as one before. I don't want you to do a placebo-controlled trial in people with a potassium of 7, please.

So, this is really, as much as anything, to discuss what had been taken for granted, which is that a very low sodium needs to be remedied, and probe it. Now, one factor here is that if you are too casual about it and have no data and you assume everything is okay, that is one thing. We have a lot of data but it is not quite in the people we want to treat, but you are going to have to figure out whether that is germane or not.

But a lot of the discussion that I hear going on

here, to which I can't begin to contribute since I haven=t treated anybody with hyponatremia in my life, says that you are not that uncomfortable with the idea that a very low sodium, to be determined, is probably bad for you; probably causes a lot of these symptoms but that in any given case you can't tell which, of course, is true and is going to be true. Then, you are also weighing the smallest evidence they have that they actually did show some clinical improvement.

But I just want to point out again that it was not set up to show clinical improvement. If you wanted to show clinical improvement you would make sure they all had symptoms and most of them didn't have much in the way of symptoms. So, they had very little chance to do that.

They were also told by their consultants that if you take somebody who is very low and has a lot of symptoms I won=t put them in the trial and it would be unethical for you to do that, which is a further difficulty in how to go. So, that is why we have advisory committees to help us deal with all that stuff.

DR. HIATT: Sid, go ahead.

DR. WOLFE: Just to add something to what Dr.

Paganini said, which is that the sort of elephant in the room which we were told not to discuss is heart failure. I mean, most of the people in trials that we have looked at don't have hyponatremia. They were in trials in an effort to see whether this drug could be approved for heart failure.

So, just to sort of temper the degree of unfairness that you are attributing to the FDA, I mean, it was the company that sought approval for heart failure here and we aren't discussing it. I don't know the full scope of why that is the case, but that is where most of the patients were, of the company=s choosing. They asked the FDA for permission to do clinical trials to see whether this drug would be useful for treating heart failure in patients who, most of them, don't have hyponatremia.

So, I think that balances a little bit of the unfairness that you were attributing to the FDA, not that I am reluctant to be unfair to the FDA.

DR. PAGANINI: Again, I am just trying to be a true nephrologist and just piss somebody off.

DR. HIATT: Lynn?

DR. WARNER STEVENSON: One of these things comes

down to what level do we feel we have to treat at, and I would emphasize that that is limited a bit because we don't actually have any good treatments.

Fluid restriction, as we know, is horrible. The patients hate you; the nurses hate you; everybody hates you for that. That doesn't work. Hypertonic saline, nephrologists are very comfortable with that. I don't even like doing the arithmetic to figure out how to give hypertonic saline and count up the urine losses.

So, when you ask us what level we would treat, it is difficult to answer because right now we haven=t had any good way to treat it before now.

DR. HIATT: I think what we heard from the sponsor as well is that there is no particular number that would drive your decision. It is a constellation of symptoms, how rapidly that number was achieved, how clinically impaired the patient might appear to be because we are now talking about mostly chronic therapy. So, in terms of 1.2.3, I am not sure the committee is going to give you a number.

Now, there may be strategies to achieve that which would require further study, but we haven=t seen a number today. Is that fair to say?

DR. WARNER STEVENSON: Would we be comfortable saying it is probably somewhere between 130 and 135? I mean, generally we wouldn't treat at 138. We probably usually treat at 128.

DR. HIATT: Well, my guess is that the bias coming into this is probably somewhere below 130. Does anybody want to vote on a number?

DR. WARNER STEVENSON: From a heart failure standpoint, I have to say when you get below 133 you start pulling off other therapies; you start getting pretty nervous. So, I am not sure it would be as low as 130 if I were comfortable that I had a safe treatment.

DR. HIATT: But let me just say that that is what you might do when you go home today. But what we are trying to wrestle with are actual data that may or may not inform us about whether that is a good decision or bad decision and, based on what we have actually had to look at here, can you defend a number? Bob?

DR. TEMPLE: Well, there are lots of situations where we don't tell people exactly what number to treat to. We don't say a word about what the right blood pressure to get to is, for example, and there are lots of opinions on

that, lots of guidance. It changes every couple of months but there is lots of guidance.

So, there are things one can say about this, that this is what it is for. You have to make a decision. There is guidance out. I mean, there are a lot of things you can say in the presence of uncertainty and almost everything we treat comes with some uncertainty.

DR. HARRINGTON: In fact, to Lynn=s and Bob=s point, that is what is in the sponsor=s proposed indication. It just says for the treatment of euvolemic and hypervolemic hyponatremia. It does not define it. They do list the alternative indication which they would, presumably, accept which then raises the bar by saying it is now only for chronic euvolemic and hypervolemic hyponatremia with baseline sodiums less than 130.

So, they very clearly distinguish the two. On the first they leave open the possibility of acute. They leave open the possibility of a decision at 133, 135, 136. In the second indication they specify a bit more.

DR. HIATT: Why don't we go to the next question, question 2? The sponsor=s development program demonstrated effects on serum sodium levels. Does the committee agree

that these effects were seen across the different diseases, SIADH, cirrhosis and heart failure? Do people think that was a pretty consistent signal? Yes.

Over the range of the observed baseline sodium levels, tolvaptan=s effect on sodium was preserved or larger at lower baseline levels? Did the baseline matter?

We did see some figures that actually showed that relationship. So, on an absolute basis it seemed to have an effect. Right?

DR. WARNER STEVENSON: Except that for some of that it was titrated to effect. So, if you were aiming for a higher number you used more drug to get there.

DR. HIATT: That is a good point. So, we don't really have, let=s just say, all the information to make that claim.

DR. ROBINSON: Also, they didn't treat any severe hyponatremia. They were excluded.

DR. HIATT: Yes, but across the range that you saw.

DR. ROBINSON: Yes.

DR. TEMPLE: What struck me was that the apparent increased effect at lower sodiums could be just the result of what Dr. Stevenson suggested, that you had more room to

go and you pushed it. So, it is not clear that the effect per dose is bigger. But it does look preserved.

DR. HIATT: Yes.

DR. HARRINGTON: It appears to be titratable depending upon where you start, absolutely.

DR. HIATT: And that the results were sustained during the long-term 30-day use. That was pretty clear. Then I like the drug withdrawal piece of this which is, in fact, if this drug is used clinically it ought to be incorporated into the thinking about how you would prescribe this drug.

DR. HARRINGTON: That is a conversation I would like to have because I asked this morning about how long they think people might need to be treated. One of the experts helped answer that and suggested that the majority of patients, once corrected, would maintain their serum sodium. But, yet, at least the data that we saw from the trials is that when they come off drug they drop down and back to their lower level.

I am trying to reconcile those two perspectives. Is it a sustainable effect for the majority of patients with 30 days worth of treatment? Or, do we think that the

majority of patients are going to need treatment beyond 30 days? Because where it starts to matter isB-you know, we had this discussion late this morningB-do you believe that the safety database--six months, a year, beyond a year--is adequate to recommend that likely it would be used long term in the majority of patients?

DR. HIATT: I think what we heard is that there are a number of patients for whom very long chronic therapy would, in fact, be indicated.

DR. HARRINGTON: But it was suggested that was the minority of patients, but the data that we have seen doesn't suggest that. They suggest that you come off therapy and you drop back down.

DR. FLACK: It would seem like it would depend on the underlying reason.

DR. HIATT: Sure.

DR. FLACK: It is going to be driven by that and whether that gets better. Some of these heart failure patients in the hospital get out, they get tuned up and get going and you will be able to stop, and some of them you probably won=t. But I don't even know how you can really predict that.

DR. HIATT: Except that what was studied, to Dr. Harrington=s point, exactly demonstrates pretty tight, you know, confidence. It doesn't look like there is a lot of heterogeneity there.

DR. VERBALIS: Could I clarify what I addressed to Dr. Harrington this morning? I said that in the conivaptan open-label study, if you were started on conivaptan as an inpatient for inpatient acquired or inpatient present hyponatremia, 30 percent of those patients did not require long-term therapy.

The tolvaptan trial, the SALT trials, were devised to enroll patients with demonstrated chronic long-standing hyponatremia. So, by design the patient population groups were different. So, if you are taking patients who have an inpatient hyponatremia, putting them on a vaptan, they will not all require outpatient therapy. If you have a patient who has been proven to be hyponatremic, you know, for weeks and months, the likelihood is they will require chronic therapy. And I can't break down what the relative numbers of those are for you.

DR. HARRINGTON: That is really helpful. So, the suggestion would be that in the chronic situation it is

likely that people would need chronic therapy.

DR. VERBALIS: Yes, I believe so.

DR. HIATT: I think we should assume that.

DR. KASKEL: Bill?

DR. HIATT: Yes?

DR. KASKEL: I haven=t heard any discussion about the interaction of the drug with the renin-angiotensin system. I am assuming many of these patients will be on ACE inhibitors, A2 receptor blockers and now possibly even aldosterone antagonists. So, for long-term treatment one is going to need to pay attention to these subgroups because that may determine how long they remain on that.

DR. HIATT: Good point, yes. Other comments on this second question? Yes, Bob?

DR. TEMPLE: Actually, the heart failure study, you would think, ought to give us information about interaction with all those drugs since it is a relatively recent study and they should have been on all those things.

DR. HIATT: Correct.

DR. TEMPLE: So, if that hasn=t been looked at, it clearly should be.

DR. HIATT: Next question. Now we are going to go

through a series of things and I think perhaps we should focus most of our comments on the SF-12, and I imagine we can see how those compare with the other questionnaires.

With regard to the validity of the SF-12 physical and mental component scores, which of the symptoms attributable to hyponatremia are assessed by the test? John has it on the tip of his tongue. He is going to tell us.

DR. FLACK: I am choking; it is not on the tip of my tongue.

DR. HIATT: Well, we have commented that it is picking up something that seems to be related to the disease, hyponatremia; that it seems to change with treating the serum sodium. But can you tell us which of those questions is rather specific? This is a generic questionnaire. We know that so we are not looking necessarily for high correlations. Can anyone name anything? Yes?

DR. WOLFE: I thought Dr. Papadopoulos pointed out that there wasn't really anything in there that was specific to hyponatremia, and I think her original comment is that we know of no qualitative research in patients with mild hyponatremia that really focuses on those kinds of things as

historical to go back to. The point that she made was that this is very general.

DR. HIATT: It is a bit rhetorical because it was never designed to be a disease-specific instrument for any particular disease, but we accept it as providing useful information.

DR. WOLFE: No, but your question was whether there are things in there that look like they are a response to hyponatremia specific symptoms. I am just repeating what she said, that she did not think that any of those components were put in there because of hyponatremia. That is all.

DR. HIATT: Clarification?

DR. TEMPLE: Well, I am just reminded that for a number of kinds of psychiatric trials it was common to do both a good test, like a HAM-D for depression and something called the patient global, which might be a scale from 0-10 where the patient sort of said how they feel overall. Then there would be a physician global to do the same thing. Sometimes they came with landmark, sometimes they didn't.

I think people are now getting more structured scales like this, but that was not a crazy thing to do

because you didn't exactly know what it was to ask in those settings. To me, this reads like something close to a patient global, you know, how you do it. I don't think that is inevitably wrong. I think these quality of life things have a lot of those characteristics, but they are improved by being somewhat more specific. But they still really are sort of a global.

DR. HIATT: I agree. I mean, I don't think it necessarily invalidates the utility of that information. It is just not terribly specific to the disease.

DR. NEATON: Just maybe to pick up on where I think Bob was going, I think what we have is pretty good evidence. I am concerned about the missing data and the potential for bias there but, you know, it is blinded. The discontinuation rates, the missingness is similar in the two treatment groups. There is pretty good information that the treatment improves quality of life across a number of dimensions.

From the handout they gave us and the slide they showed, kind of across the board there is some improvement. Repeatedly I heard this morning, and I think this is why I said earlier that we are kind of using a sledge hammer here,

a pretty blunt instrument to kind of study thisB-people talked about gait abnormalities, balance abnormalities, cognitive dysfunction. You would measure those things in very different ways.

So, we don't have that data. So, I think what we are missing, in my mind, is a good safety database on the people with low sodium levels because they didn't enroll the patients. And, what we are missing at the high sodium levels are outcomes that really make a difference potentially that are really subtle, that you need to have for those instruments to pick up and that may be very important.

So, I guess I kind of think there is evidence here, weak because on the Cohen scale not even 0l3 standard deviations in terms of the treatment difference, something less than that under optimistic situations. But it is consistent with the low sodium and the higher sodium group that they studied. But I think we should just call it what it is, some evidence that quality of life is improved.

DR. HARRINGTON: But, Jim, doesn't it bother you, not bother you but isn't it even weaker or less robust in that the two studies, 235, 238, only hit 1.0? You know, the

p value is, what?, about 0.12. It is less than half the effect that they saw in the first trial.

Now, we didn't delve into all the issues. I think the first trial was only U.S. The other one was more global. I am assuming that the SF-12 was used in the appropriate language, in the appropriate culture, etc. We didn't ask that. But in one trial they made it and in one trial they didn't. So, to me, that even makes the association weaker.

DR. NEATON: I agree, although the treatment differences were consistent in the two trials and the pooled results shows some evidence of difference. I am much less concerned about that than I am about 30 percent of the people missing the data.

DR. STOCKBRIDGE: The other weakness to remind you of is that both PCS and MCS were named as the 12 secondary endpoints and they only won on one of those in one of the studies.

DR. NEATON: That is the reason I took the focus off of it because if you look at the dimensions across the board, generally there is a trend for most of the dimensions for quality of life being improved.

DR. PAGANINI: Does the fact that the moderate group was arbitrarily excluded through ethical reasons enter into the study population that probably is not going to show you much anyway? Again, this is an assumption, if you had less ethical concerns about treating the moderately hyponatremic person that you might have seen more of an effect on these global issues. Because those are the people that would seem to have gained the most effect from normalizing sodium.

DR. HIATT: Maybe, but I think the other comment that is related here is had that been sort of floated up as the main secondary endpoint and had there been a more focused hypothesis to test that, it might have been perceived as a bit more robust than it is. Sid?

DR. WOLFE: I mean, you have really three things. We have talked about them. There are missing data. There is the still unanswered comment by the reviewer that they are not convinced that blinding was not breached. But then, granted that for physiologic reasons there had to be decrease in sodium, and that is not a surprise at all and no one disputes that that happens across various diseases, but generally for approving the effectiveness of a drug FDA

requires two or more randomized, controlled trials. They went with one with AZT, and so forth, and here we have two trials. One of them is positive and one of them just isn't positive and it is not statistically significant.

So, I think we have several things beyond just the question of content validity and the lack of specificity for hyponatremia that raise a lot of questions about this, the only measure other than serum sodium that is being used to put forth the idea of approving this drug.

DR. HIATT: Yes, and just to emphasize that, the most positive data for any clinically relevant outcome would have to be the mental component scores. Anyone disagree with that? So, as we focus our effort here that is the one that is going to inform us the most. Lynn?

DR. WARNER STEVENSON: Again, I would just emphasize that I think this reaches its peak of importance if we don't think that it is a good thing to raise serum sodium. I would emphasize that in a heart failure trial, particularly one in which this wasn't specified at the beginning, a 30-40 percent non-completion rate of questionnaires is about what we usually see, and it is exceedingly difficult to get any measure of improvement in

any of these questionnaires in any heart failure trial for any therapy. I just want to put that in perspective in heart failure trials.

DR. HARRINGTON: But, Lynn, in the heart failure trial they used the Kansas City Cardiomyopathy Questionnaire and there was no effect on that. Does that bother you?

DR. WARNER STEVENSON: Not really. Again, it is really hard to show a benefit in symptoms with any of our questionnaires with therapies that we know have various benefits. So, it doesn't really bother me, and I am surprised that there is a trend towards improvement in any of these things which were really done post hoc or at least after beginning the trial design.

DR. HARRINGTON: But, Lynn, if serum sodium is so good in 4,000-plus patients there is not a whiff that it actually makes people feel better or live longer.

DR. HIATT: Just to clarify what you just said, if that is really true, then the probability that the mental component findings are real is much less because it is one of many secondary endpoints. There is no adjustment for alpha. It hits it on one trial. And, if it is really hard to show any kind of quality of life benefit in the heart

failure population where most of the data come from, then that would make your interpretation of that finding far more consistent with random effect than a signal.

DR. WARNER STEVENSON: Well, I don't necessarily want to put it that way, but I think we have to recognize that this is a very blunt instrument even when you look at heart failure questionnaires.

DR. HIATT: Right.

DR. WARNER STEVENSON: I mean, hydralazine or Isodril improve quality of life by V-pacing dose. Not much else has been shown to improve that. And, for the serum sodium I think some of the benefit is the way people feel, but also we think hyponatremia is a bad thing for how it limits our ability to use other therapies over the long run that are good, not necessarily in a 9-10-month period. So, I think there are many issues aside from what was measured in the questionnaires.

DR. HIATT: John?

DR. FLACK: Yes, I hear what you are saying, Bob, but the second trial that didn't hit was headed in the right direction and the pooled effect, when you put it together, was there. It could be something that is chance but you

have two things moving the same way, just one a little more statistically sort of getting below that p of 0.05 in one trial and not quite making it in another trial. But both were headed in the same direction.

So, I would actually say it is probably a bit more for consistency, though I would actually argue that we can talk all we want to about all these other symptoms and tell you how doctors are going to basically look at this. They are going to say what are the options for treating hyponatremia when I decide I want to treat? And, the options for treating hyponatremia are kind of a laundry list of things that can work but most of them appear to have either some tolerability issues or issues of safety that either haven=t been explored very well or we know that they are toxic or they are problematic.

So, I would also look at this not just as is this a pretty drug, but also I would look at it putting this in context also to what practitioners already out there are using at least as a tertiary consideration, and all, because at the end of the day the practitioners by and large are not going to look at a threshold and say is this patient a little fatigued, tired, or whatever, having dreams at night?

They are basically going to say the sodium is low; it has been low; it is probably below 130 and what can I do about it?

What I would say is even if you don't believe that there is any benefit on this stuff, and I think there probably is, it is pretty hard to argue that there is no harm, is what I would say. Actually, this is a better study treatment than most of the other stuff. And, there is already one drug that you can use intravenous in the hospital and now you have something that you can go from the hospital into the ambulatory area.

So, my biggest concern about this probably is the lackB-some of these patients are going to be on this a long time and there is just nothing out there for any real long period of time. But some of the other stuff, I would probably give the benefit of doubt.

DR. HARRINGTON: So, when I am home, taking care of patients I have a different perspective than when I am sitting here, trying to think about the public health issue of whether or not a drug should be approved. Once a drug is on the market we all use things for different indications that we think are tailored to the situation.

But remember that part of what we do here is that there is some precedence. So, let=s say the next guy comes along and, well, you know, one of the trials was positive, the other one was kind of there, and, you know, come on, you guys did it last time why not this time? I mean, I think the wiggle here needs to be, frankly, higher than what goes on in clinical practice.

DR. FLACK: But I guess what I am saying is that what we are arguing about on the MCS, and stuff, is really not a lot of drugs being approved, drugs being approved to raise serum sodium, and it is nice if you can throw some other things in there. I think it makes us feel better if it is something in the positive domain and I admit that you could legitimately take the line that you took. I sort of look at it more as the glass is half full and I think there is consistency between those two studies, and all. But I am not arguing that that should be the basis of approving it.

I think that the real nuts and bolts are is this going to raise serum sodium, which we believe is bad and many practitioners do, and they are going to treat it. Okay? Does this make sense from a safety perspective? Does it actually raise serum sodium? Yes, it raises serum sodium

and it is an orally effective drug, and it appears to have a better profile than a lot of other things we use.

DR. HIATT: Bob?

DR. TEMPLE: I just want to comment in agreement on the last statement. If the quality of life stuff was the effectiveness trial, the one trial they have was a failure and the second I don't believe would even come close to making it. We don't approve things on that basis. One trial that is very powerful, maybe.

But as was just said, I don't think one should be thinking of it that way. I think what I am hearing people say is they feel pretty good about sodium and this gives them a little nudge. But if that was the pure effectiveness trial, as you said, I don't think that would be the usual standard. We are not going to think of it that way. You know, whatever we decide to do, that is not how we are going to think of it, as two effectiveness trials. It has to be based mostly on the surrogate with some support and with opinions, and things like that. But those are not the effectiveness trials.

DR. NEATON: I just want to kind of maybe clarify one point I made. I agree with what has just been said, and

this was a secondary endpoint, like 12 levels down. So, if I stand back and look at the bigger picture of what I heard today, I guess--going back to the question of surrogacy, at higher sodium levels I would like to see stronger evidence of data on patient-reported outcomes. I wouldn't call it that. I would call it basically cognitive dysfunction and other outcomes that matter to the patient.

So, while I am comfortable that in this quality of life, given all the caveats, there is probably a signal there and that might apply to, say, some segment of this population, a very small percentage of it, say less than 130, at the higher sodium levels I guess I would like to see better evidence that raising the sodium really makes a difference. And, the data wasn't collected. We can't blame the sponsor because that is not the kind of trial they did. But I think going forward it should be collected.

DR. HIATT: In that light then, let me suggest that we just kind of go through these last bits of this question. I think we have flushed a lot of the issues out, just to clarify anything else we might want to say about them.

So, 3.1.2., if the SF-12 scores have utility for measuring clinical benefit in patients with chronic

hyponatremia how large does the effect need to be for an individual patient to perceive the benefit? Are there other findings for clinical benefit for tolvaptan? If so, in whom do these benefits apply?

I think we have sort of discussed these things already, that it is hard to put a number on it; that it would be hard to identify an individual response characteristic for a list of symptoms that are fairly nonspecific to pick that out.

Then, the next series of questions go to these other questionnaires. I am not sure we need to address all these exhaustively. I think we can comment about these generally. The HDS. Norman, do you maybe want to clarify?

DR. STOCKBRIDGE: Yes, I mean, you can go through them or not as you see fit. If you think they don't really contribute to an argument, then just skip them.

DR. HIATT: I am not impressed that they add any more understanding than what we have already had.

DR. HARRINGTON: I will say I give the sponsor credit for attempting to validate it in the patient population of interest. They really made an effort here by creating this new score. I think that is admirable.

DR. HIATT: And I would also amplify that. I think that at some stage here there is lots of opportunity for the sponsor to learn a lot more about the clinical benefits of treating hyponatremia in these different populations, particularly in the mild.

Let=s go to question 4. Are there any other benefits of treating hyponatremia, for example, on neurological or cognitive function, that have been shown in the sponsor=s development program?

I think the answer is probably no. Anyone disagree with that? Let=s go to the next one.

There are two voting questions and I do think we need to be really clear on what it is we are trying to accomplish here. Is there adequate evidence that tolvaptan can be expected to produce clinical benefits in the treatment of patients with chronic hypervolemic or euvolemic hyponatremia?

So, this question is not asking us whether we should approve this drug because it raises serum sodium or not, but whether we have been convinced from what we have seen that there is a clinical benefit to doing that. Comments?

I also want to clarify, normally when we get to this stage we have these little devices that allow you to vote anonymously. We don't have those today. The point of that is that what we would do is vote simultaneously and not influence our thinking around the table here. But, unfortunately, there is going to be some contamination.

Is there anything that needs to be clarified about this first voting question?

DR. WARNER STEVENSON: I am sorry, can we clarify what we mean by clinical benefits? I mean, for instance, if you feel it is good to treat hyponatremia is that a clinical benefit, or do you mean a clinical benefit that we have measured in some other assay?

DR. HIATT: Well, I kind of think what they are saying is you tell me, and I do think that I would ask you to reference your thinking now to what you have seen today because I am a little worried about a slippery slope to say I am going to go home and, of course, these low numbers are bad, and I am just worried that our clinical thinking here should be a little bit separated from the rigorous review of the data.

So, really this question, as I interpret it, says

whatever these measurements that were provided for us today, and they weren't just the mental component score, they were fluid losses and other things that we thought might be useful. Those are clinical outcomes maybe. They may be strong for you or they may be weak for you. Did the sponsor show you convincing evidence that there was a clinical benefit to treating a surrogate? Norman?

DR. STOCKBRIDGE: Yes, I can probably make it even a little bit easier. The next three questions ask you whether or not, either from the observed data or your general impression of hyponatremia, there is a clinical benefit here associated with the use of the drug.

The next question then asks you what safety concerns there might be that mitigate this. Then, the last question asks you to sort of put those two things together.

DR. HIATT: So, Norman, you are saying in general now is there a clinical benefit to treating hyponatremia?

DR. STOCKBRIDGE: Well, that is not a net clinical benefit. That is, is there a clinical benefit either in the data or in your imagination that you can reliably ascribe to tolvaptan? That is what the question is.

DR. TEMPLE: I think that is completely consistent

with the discussion you have been having where it depends at least a little bit on some of the data, which we all acknowledge is not definitive the way one would hope it might be, and beliefs you already have about sodium and its benefits and allowing you to treat heart failure the way you want to treat, all that stuff that he is saying. All of that.

The other thing I wanted to contribute was that it is probably, in the absence of a machine, good to have everybody say their piece about it and then have a vote.

MS. FERGUSON: No, no, no. Have the vote first. We would like you to just vote first and then have discussion later. Everybody vote.

DR. TEMPLE: I hate to bother you but what sense does that make? How can they discuss it afterward? I mean, not to try to influence people or try to say how they are going to vote, but have your discussion about it.

DR. HIATT: We can discuss the question and then vote.

DR. TEMPLE: Well, I don't want to violate any rules but you think that is not acceptable?

DR. TEMPLETON SOMERS: [Comment inaudible]

DR. TEMPLE: Well, that is to explain their votes. I am not talking about explaining their votes, but lay out what you think about stuff so you can talk about it.

DR. TEMPLETON: That is the intent, laying out what you think about it but not providing what your vote is but laying out your comments.

DR. HIATT: Then why don't we just go around the room.

DR. FOX: As a non-voting member of the panel, can I make a procedural suggestion that might avoid some of the vote contamination that the Chairman referred to and I think is potentially a problem? That people vote by just hitting their mike buttons. Not all the mikes will go on at the same time but the little red lights will and you can count those.

DR. HIATT: Let me suggest then that this is a discussion point. Why don't we just go around the room and each person tell us how you think about it and then we will take a vote. Is that okay? You can discuss it; you can't vote.

DR. FOX: I would agree with the agency=s sort of broad view that if you think there are specific data that

provide evidence of clinical benefit, that is sort of the easy part of the question. If you think that there are trends in the data as provided by some of the other analyses that give you additional comfort, that could be added as supportive information.

DR. KASKEL: I think the evidence has shown that the agent significantly and rapidly improves serum sodium and urine output versus placebo. I think it was a sustained effect. There was improvement in overall well being without improvement in the physical component, but that may need to be addressed later. I think that the efficacy of this agent as a V2 receptor antagonist in the outpatient setting is very strong. And, I think it needs oversight for future studies, and it is a promising new generation of a receptor antagonist.

As a pediatric nephrologist, I would like to see down the line application to another subpopulation that also suffers from acute and chronic hyponatremia of which one of the major side effects is neurocognitive impairment that is permanent. Thank you.

DR. WARNER STEVENSON: I feel that there is benefit to treating hyponatremia. I am not sure exactly at which

level that threshold begins. I think it is also very difficult to sort out the signal of symptomatic benefit because in the hypervolemic patients this agent also affects fluid balance and some of the symptoms that are associated with hypervolemia.

DR. LINCOFF: I think that, imagination not withstanding, there is evidence from medical literature, etc., that hyponatremia has adverse effects on clinical outcomes. Some of that is clearly related to the illness that produced the hyponatremia so some of the predictive value that hyponatremia is associated with bad outcome is not directly through the hyponatremia but some of it certainly is.

And, I think that aside from any of the other measurements that were made that are suggestive, one can make the connection that hyponatremia does cause adverse events and that correction of hyponatremia by a mechanism that would not be expected to create other problems, and that relates to the separate safety data, but correction of the hyponatremia by a mechanism that is pathophysiologically appropriate will improve some of those clinical events.

So, from my mind, it is sufficient to focus on

whether or not we think this agent has efficacy in correcting the sodium, independent of the other suggestive data.

DR. NEATON: Well, I think that there is no question low sodium is bad and the drug corrects it. From my imagination point of view and what I have heard today, it seems like at lower levels of sodium treatment is warranted. However, the risks associated with low sodium, as has been pointed out are related to the level of sodium. So, I think at the higher levels of sodium we need better evidence that the treatment really makes a difference. Just because the treatment lowers sodium does not mean it is going to correct all the risk and it is not associated with risks that are not, you know, documented in the smaller studies that we have seen.

So, I am okay in my imagination with sodium levels below 130 or certainly below 125, but feel uncomfortable and uncertain about the data above that.

DR. FLACK: I think the direct information we have seen today is best clinically for heart failure particularly with a low serum sodium, less than 130. I believe from what we have seen today, maybe with some creativity in my right

brain, that people overall feel better and I don't necessarily know that that is a threshold effect.

And, my overall enthusiasm for treatment though would be for persistent levels of sodium less than a serum level of 130 and probably not higher outside of special situations which have been sort of described, I think several of them real rapid, etc. But for more modest reductions in sodium I would be less enthusiastic based on what we have seen, but for levels below that I think that this makes sense and I think it is particularly good for heart failure.

DR. HIATT: So, I could just echo the comments. I mean, clearly, serum sodium and hyponatremia is a clinical syndrome of concern. There are levels that warrant therapy. The sponsor has already told us that. They convincingly raised serum sodium level. That, I thought was very clean.

What I am not convinced about is the clinical relevance of that, and I am concerned that we would approve something based on a surrogate that has not been fully evaluated or is convincing. So, my only hesitation in these comments is that I am not convinced that this development program had demonstrated clinical benefit.

DR. ROBINSON: I think that we are in a position that is not dissimilar to when desmopressin finally came on board to treat diabetes and syphilis. Here we have all been looking for an agent that would be as specific for hyponatremia as that drug is specific for hypernatremia. I mean, I believe that hyponatremia is something that needs to be treated and that it will be a benefit to a variety of diseases and, therefore, I would favor using it.

DR. PAGANINI: I think Achronic@ is the important word. If hyponatremia is an outcome indicator and we treat that, it is probably not going to do anything. If, on the other hand, it is a surrogate marker and we treat that, yes, it will have some effect. I think you can sort of run a parallel to urea.

Bear with me. Urea in acute renal failure, if you don't do anything with it, the first time you put somebody on dialysis if the urea is very high that is a predictor for poor outcome. However, if you dyalize you are trying to bring that urea down so you are using urea as a different thing. I think hyponatremia could be looked at sort of similarly.

With that in mind, I would say 130 or below was

where I would probably put a mark and that mark would be for mild to moderate symptoms. But if there are no symptoms above 130 I probably wouldn't treat.

DR. ZANETTI: I believe hyponatremia is a symptomatic condition in the vast majority of time, and that the agent improves hyponatremia. I think we have been offered good guidelines by one of the consultants as to indications, use and labeling.

DR. WOLFE: I am inclined to agree with Dr. Hiatt. To me, the key words in this question 5 are adequate evidence that tolvaptan can produce clinical benefits. I think if we start out with the evidence that was presented, there just isn't any on tolvaptan. If we use what has been described as imagination we know that at certain levels hyponatremia is dangerous. A lot of those levels are ones that were excluded from the clinical trials here. So, we really don't have data on those and it also presents the dilemma that those people may get treated if it gets approved, and we have very little safety data.

So, I would say that we have not seen evidence that tolvaptan can produce clinical benefit. The only thing put forward beyond the sodium was that patient survey, which

I don't believe is clear at all nor is it specific to hyponatremia.

DR. HARRINGTON: I too think that Dr. Hiatt and Dr. Wolfe have capture the essence of my interpretation of the proceedings. There are sort of four things that I key in on in the question that was asked: adequate evidence, the drug itself, clinical benefit and chronic setting.

I think that we can be swayed by thinking about the acute situation where, obviously, hyponatremia can be a catastrophic clinical situation but that is not what we are being asked here; it is the chronic setting. I think it is likely that low levels of sodium brought up to higher levels of sodium are likely a good thing, though I would say that the clinical evidence we saw for that with this particular agent is weak, and I would say weak at best. And, we are bringing a lot of external data to support whether or not we believe that the drug itself has an effect.

I am not sure, particularly in the more modest levels of hyponatremia, if raising sodium ultimately changes the patients= outcomes amongst these patients or if it just makes us feel better, what our house officers call euboxic, that when you get everything looking normal that must be a

good thing. Who does it make feel better? The patient or us? I am not sure that the data have helped tease that out.

DR. HIATT: So, based on those comments, could we just go around the room--

MS. FERGUSON: Could you have everybody raise their hand at the same time?

DR. HIATT: So, we are going to raise our hands. That way we won=t have to go around. Is there adequate evidence that tolvaptan can be expected to produce clinical benefits in these patients? Raise you hand if you believe that that statement is true.

[Show of hands]

MS. FERGUSON: We will go around to everybody=s vote. State your name and then state your vote.

DR. HARRINGTON: Robert Harrington. I disagree with the statement.

DR. WOLFE: Sid Wolfe. I disagree with the statement.

DR. ZANETTI: Paul Zanetti. I agree with the statement.

DR. PAGANINI: Paganini. I agree with the statement.

DR. ROBINSON: Alan Robinson. I agree with the statement.

DR. HIATT: William Hiatt. Disagree.

DR. FLACK: John Flack. Agree.

DR. NEATON: Jim Neaton. Agree.

DR. LINCOFF: Mike Lincoff. Agree.

DR. WARNER STEVENSON: Lynn Stevenson. I agree.

DR. KASKEL: Rick Kaskel. Agree.

DR. HIATT: Those of you who agreed, in which patient subgroup baseline, etc. are these benefits established? I think just a couple of comments, if you need to, on that. We have already flushed out these issues quite extensively.

DR. FLACK: Heart failure, serum sodium less than 130.

DR. HIATT: So, you have heard a general sentiment that that 130 threshold is something thatB-no?

DR. LINCOFF: I mean, I think we have to be self-consistent. I voted on the basis of believing the drug raises sodium. On that basis, it raises the sodium at 133 as well. So, you know, depending upon the individual patient, I think it is clinical judgment what would later

confer clinical benefit. The whole basis for my voting was that I felt that raising sodium would confer clinical benefit, but that level of benefit would depend upon patient situations. So, I think it is artificial and arbitrary to pick either the setting of heart failure or pick a specific cutoff.

DR. NEATON: Actually, I viewed it the other way around. I think at some level 130 is probably where I would cut it too. We need better evidence of the treatment=s effect on outcomes beyond sodium.

DR. HIATT: Any other clarifications on this? Let=s now go around and ask the next question, number 6.

MS. FERGUSON: Were you going to get, for everybody who said yes, what the baseline characteristics are?

DR. HIATT: I am not sure we need to. I think we have flushed out these subgroup issues quite a bit.

MS. FERGUSON: I am sorry, we need to get a vote count to read into the record. I am sorry, it went around too fast and we didn't get a count.

DR. HIATT: Those of you who voted yes, raise your hand.

[Shoe of hands]

DR. HIATT: You have eight for and three against. Question number 6. This is not a voting question. Are there safety issues that impact approvability? Are there findings of concern? Are there enough data on which to base a decision? Let=s go around the room and do that one. We can all comment on this.

DR. FOX: To 6.1, no and to 6.2, yes.

DR. KASKEL: I would say for 6.1, no and 6.2, yes.

DR. WARNER STEVENSON: I still remain interested and somewhat concerned over the issue of thirst, which I think is not a minor one, particularly if someone for someone reason has a condition and they are not able to follow their thirst. So, I would say I have a little bit of concern about that. Overall I don't have concern.

There have been a lot of different analyses, some of which are more or less reassuring. From the FDA table on page 70 I really find absolutely nothing to be concerned about in terms of overall mortality issues. So, I think I would say not really in terms of concern for 6.1 and yes for 6.2.

DR. LINCOFF: I would say no for 6.1 and I would say for 6.2 overall yes, although I think there is limited

long-term follow-up data in a drug that will likely be used over a much longer term than was studied in most of these. That would perhaps lead to some, you know, future studies at some point.

DR. NEATON: I think the bleeding findings in the patients with cirrhosis was a concern, and I think the safety database among the large fraction of people for whom we have heard this may be indicated, those that were excluded from the trial, needs to be built.

DR. FLACK: For 6.1, no, with the caveat that I remain concerned about the cirrhotic patients and bleeding, and I would like really more detailed information about blood pressure and hemodynamics in those folks than sort of what was presented today. Clearly, for 6.2 yes again, with concern about long term.

DR. HIATT: I can certainly second those caveats. But I do think the safety database is reasonably good that, if we split the pie up a little bit, the confidence intervals still excluded a lot of risk. I think this is symptomatic therapy, and my thinking about symptomatic therapy is that I like to see upper boundaries of these hard endpoint risks excluded at a level of 25-50 percent and I

think they are close enough to that. I do think that the heart failure population is a reasonable population to look for drug risk effects. I didn't see any sort of heterogeneity in the data.

So, are there findings of concern? There always are but I think the data are pretty robust to make a decision.

DR. ROBINSON: Well, there will be some restrictions. I guess we will get to that in a minute. Are there findings of concern? I think without enough data, I would say yes. With the exception of long-term use, I agree on that; we just don't know.

DR. PAGANINI: I agree with long term, especially if you are talking about a population that may, in fact, be committed to this drug over a long period of time. We have one-year submission and nothing really beyond that and very poor in that regard, and we have no data on drug-drug interaction at all, again in subpopulations that may, in fact, be affected by this drug by other drugs. Finally, there is a very small amount of data on rapid changes, especially in the outpatient environment with ongoing drug therapy and whether or not that would have a negative effect

on what happens with sodiums.

Giving those as a caveat, I would say that the rest of the stuff was available and shouldn't stop its approval.

DR. ZANETTI: No for 1; yes for 2.

DR. WOLFE: Yes for 1 and, again, if you just look at the three groups of people, the one that the company and we agree are severely hyponatremic and that they really need to be treated with other measures; the one at the high end that makes up the sum of the 189 patients that were hyponatremic in this trial; and then the middle group which, for ethical reasons which I agree with, that they excludedB- the middle group is the one with the lowest possibly treatable hyponatremia and even in the trial with people who had generally higher levels, a significant number of them, 7.5 percent, had a rise of greater than 8 mEq at 8 hours.

So, people can get comforted, as at least some people are, by the safety findings from a group, most of whom don't have hyponatremia, but let=s just look at the hyponatremia. The more severe hyponatremia, which was excluded from the study, is more likely than the group that was included in the study to have these dangerous, rapid

shifts up with the concomitant adverse effects that go with that. So, I just think that is a concern.

And, the same answer applies to 6.2. I don't think there are enough data on which to base a decision. I mean, there are basically no patients in this middle group that were excluded and a very small number in the group that was included.

DR. HARRINGTON: So, I too have concerns. I am comforted, Bill, by the large number of patients in the overall safety database, largely, though, being patients without hyponatremia. I am particularly bothered by the small number of patients less than 130. There are only 189 of them, and there is very little data on the long-term follow-up. My understanding now is that in chronic hyponatremia the majority of these patients will be treated long term, and I think we are making assumptions on very little empirical evidence.

Finally, the bleeding in the cirrhotic patients I think is a concern and if we are talking about long-term therapy, particularly among heart failure patients, we are going to have patients on aspirin, clopidagrel, etc., and I just don't think we have seen enough of that information to

exclude there being a problem.

DR. HIATT: Bob?

DR. TEMPLE: As I said before, the heart failure study must have a lot of interaction data in it. It must. All those people are heavily treated with everything under the sun. I don't know whether it has been looked at but if we haven=t looked at it yet, that certainly can and needs to be looked at.

The other observation I would make is that for the very sick people who were excluded here, they were excluded because there was a no treatment group. We don't really need a no treatment group anymore to distinguish an effect of this drug from the effect of placebo.

So, I don't see any reason why very sick people couldn't be studied within a single-arm study. When that will happen we will talk about among ourselves. But that actually can be obtained, even though I think it is still very hard to do a placebo-controlled trial in those people. But you could certainly see what the consequence of rapid rise is and other things like that in those people. There is no impediment to that.

DR. HIATT: Do you have quick comments on that?

DR. WARNER STEVENSON: Yes, I just want to raise one issue that at some point I think needs to be addressed, which is that patients should probably be hospitalized when this is initiated. We didn't really discuss that but, in fact, they were for this study and that does concern me and we need to think about that.

DR. WOLFE: A follow-up on that point, which is that all these patients were in the hospital for the first day and the scenario we are talking about in terms of efficacy or safety is people not in the hospital in most cases being treated by people who are not as knowledgeable as the people who treated the people in this trial. That is the real world as opposed to the experimental world.

DR. HIATT: That is fair enough.

DR. KASKEL: I was wondering if there will be some plans developed by the sponsor for how this will be managed as outpatient. Will there be daily weights or every other day weights? How often will they come into the outpatient setting to be monitored? I think that is important.

DR. HIATT: Sure. That brings us to the last question. This is sort of trying to I think judge risk and benefit and ask whether you would approve this drug. Again,

the challenge I think in asking this question is how you see the data influencing your decision. Is it a clean signal in serum sodium or is it a clinical benefit?

To do this-BI am just trying to think of the process now. We have to start at this end of the room now. I suppose we can go around the room and make comments or we can just go around the room and vote and see what people think. Dr. Harrington?

DR. HARRINGTON: Vote or comments?

DR. HIATT: I think you should vote.

DR. HARRINGTON: Don't we vote simultaneously?

DR. TEMPLE: You vote simultaneously. You can just ask and see if anybody has additional comments.

DR. HARRINGTON: I have no additional comments.

DR. HIATT: Then why don't those who vote on question 7.1--

DR. TEMPLE: Wait. Somebody else might have an additional comment.

DR. HIATT: Oh, I am sorry.

DR. TEMPLE: He is great but he is not everybody!

DR. HIATT: Sorry.

DR. FLACK: What I would throw out is, given that

we don't have much in the way of long-term follow-up data, that there be a time limitation for approving how long you can be on it, and after that it is basically a decision. I wouldn't sanction just unlimited use of the drug right now. We don't have enough follow-up data so I would qualify approving it to not really get outside of where we have data where we feel comfortable.

DR. HIATT: Before we take this vote are there any other comments? Michael?

DR. LINCOFF: Do we want to discuss as part of the vote or afterward which of the two alternative labels because that is an important distinction I think.

DR. HIATT: Certainly there are more points that we can clarify. I mean, if you vote yes, then that obviously implies that there is more study and there are labeling issues. If you vote no, there is just more study.

DR. FOX: Can I just clarify? Is the agency asking this panel to give them guidance on labeling or is that a topic for discussion between the agency and the sponsor?

DR. STOCKBRIDGE: Well, I think 7.1 gives you an opportunity to say what you want about conditions for approval.

DR. HIATT: Any clarifications about this question? Paul? Paul is the patient representative.

DR. ZANETTI: A yes vote is no restraint for future follow-up. Is there any halfway mark?

DR. HIATT: Well, let=s assume that if you vote yes there will be lots of discussion about what that means.

DR. HARRINGTON: I just conferred with Norm and 7.1 gives you the opportunity to clarify what your yes vote might include.

DR. HIATT: Any other clarification?

DR. TEMPLE: Actually, unless anybody thinks it violates anything, I would like the no votes to be able to comment too. I think they might want to be able to say who it should be restricted to also.

DR. HIATT: Are we ready to vote? All those in favor of approval, please raise your hand.

[Show of hands]

MS. FERGUSON: We have to go around and everybody has to speak into their microphone and say their name.

DR. HIATT: It is the same.

MS. FERGUSON: They still need to say it into the mike.

DR. HIATT: So, all those voting yes, starting with Paul, please turn the mike on and say yes.

DR. ZANETTI: Paul Zanetti. Yes.

DR. PAGANINI: Paganini. Yes.

DR. ROBINSON: Alan Robinson. Yes.

DR. FLACK: John Flack. Yes.

DR. NEATON: Jim Neaton. Yes.

DR. LINCOFF: Mike Lincoff. Yes.

DR. WARNER STEVENSON: Lynn Stevenson. Yes.

DR. KASKEL: Rick Kaskel. Yes.

DR. HIATT: Now we will take the no votes.

DR. HARRINGTON: Robert Harrington. No.

DR. WOLFE: Sid Wolfe. No.

DR. HIATT: William Hiatt. No. So, eight and three.

If you voted affirmatively and I guess we would all like to comment on any restrictions beyond those that we mentioned, we could go around the room and clarify any other things that haven=t been said about what we think should be restricted. Just go around the room perhaps and make any individual comments. If you don't have any comments, that is fine.

DR. FOX: I heard some sensitivity on the panel around wanting some long-term data. Even though it wasn't in the briefing materials that I had access to, which was limited, I imagine that the sponsor either has or is developing a patient risk management plan and that sort of thing can certainly be incorporated. I think the technologies and the methodologies exist today to do better postmarketing surveillance and safety monitoring than was perhaps available in the past. And, I suspect the sponsor will collaborate on that with the agency.

As far as the higher risk groups that were not studied, I am sympathetic to the views expressed by some of the clinical experts that came to the microphone today. Really the long laundry list of symptoms and signs that could be attributable to hyponatremia, the only way to prove that is to pick those you think are due to hyponatremia, treat the sodium, watch them go away or not, and then let the sodium back down and watch them come back. Then, really for Koch=s postulates to all be fulfilled you would raise sodium again and watch them go away again. Now, I don't think we are going to do that.

DR. KASKEL: As we discussed, I think there is some

subset of patients here that need to be looked at. I would like to see the sponsor develop plans to look at patients who are on all the interfering agents with renin-angiotensin aldosterone system and, again, the safety measures for weight. Some of these patients may not have to come back into an outpatient setting. They can be followed at home with appropriate follow up. And, I think we need some oversight as to the long-term outcome.

DR. WARNER STEVENSON: I would strongly favor hospitalization for initiation of this therapy because I suspect other medications are going to have to be adjusted and it is very difficult to do in an outpatient setting. And, I would suggest postmarketing surveillance of the chronic therapy.

DR. LINCOFF: Those last two thoughts are mine exactly, concerns about how do you start it and some sort of long-term follow-up.

DR. NEATON: In addition to those, I think a follow-up study for people with low sodiums, longer term, and some restrictions I think need to be placed on the patients with cirrhosis in terms of the risk of bleeding. I don't know what those are but that would be a concern that I

would have. Then, I think a randomized trial is needed for people with higher sodiums, levels between 130-135, looking at cognitive function.

DR. FLACK: Robust exploration of the current database that the sponsor has in regards to other drug therapies to make sure there is not something that looks like a signal buried in the haystack in people on certain drugs that may promote bleeding, or problematic for where they are metabolized, to look at some of these subgroups.

DR. HIATT: If the drug is approved I would echo all those thoughts and add that I would probably restrict the label to symptomatic, less than 130, short term, whatever that definition is, and then ask for a Phase 4 commitment to further explore the various subpopulation questions.

DR. ROBINSON: I think it goes without saying that we haven=t discussed a contraindication of the most common cause of hyponatremia, which is pregnancy. So, I think, you know, it certainly shouldn't be used in pregnant women.

I don't know about hospitalization. I certainly would agreeB-in terms of osmotic demyelination, I think the data is that unless you are down below 120, or something--I

guess you could say 125, the chances of getting osmotic demyelination are slim. So, there might be a cutoff where you would say below 120 or if you want to be safe below 125 you have to start the therapy in the hospital. I don't know that you have to be hospitalized for every case. But I wouldn't object to that.

DR. PAGANINI: I would agree that hospitalization is plus or minus and really depends on the severity of presenting illness, but I would also mirror what you said, Bill, and that is that 130 or greater asymptomatic probably shouldn't be treated but 130 and below with symptoms probably should.

DR. WOLFE: I agree with the three or four people who have said that this really has to be started in the hospital, both in terms of making it much more likely that other causes, such as drug-induced hyponatremia, are excluded; making it much more likely that this is actually euvolemic or hypervolemic hyponatremia; and making it much more likely that one can detect and follow the changes in serum sodium and intervene quickly. I mean, those things are much less likely to happen. Each of them and collectively, I think they make it much more dangerous for

this drug to be started on an outpatient basis.

DR. HARRINGTON: My sense is that the drug was studied in a very controlled situation. Patients were in the hospital setting for the first 24 hours. They were studied by experts, mostly in renal disease. So, what we are talking about is a very, very different situation getting out to the general. So, if approved I would want to see it be a fairly narrow indication with a lot of the caveats, which I think are good ones, that were brought up.

Can I morph into question 7.2 since the no votes are on this side of the table?

DR. HIATT: Yes, please do because the three of us who voted no need to make one final comment.

DR. HARRINGTON: My comment and why I voted no is that I just think there is not enough information about this particular drug to sort of let the genie out of the bottle for the broad population of patients who, I am concerned, may be treated without a lot of the caveats of people around the table.

So, going forward, do I believe it raises sodium and that is probably a good thing? Absolutely. I would want to see the patients with mild to moderate symptoms in

that range of 130-135 range. I would like to see the sites that are used expanded to the outpatient setting, to different types of docs other than just the renal/endocrine experts. So, start to do the Phase 3 trials with larger numbers of patients that more begin to mimic how it will actually be incorporated into practice before it is in practice.

DR. WOLFE: Just to repeat some of the things I said before, the data that should be required is as in the question, adequate evidence of clinical benefit. We just do not have that right now. And, given the small database of risks, this is a risky benefit/risk situation, so to speak. So, I think that it is absolutely critical to come up with data which don't exist at all now, which is clinical evidence of benefit with this drug.

DR. HIATT: I guess as my closing comment, I think this was a really robust development program. I think the sponsor did a fantastic job in their trials, including their experts.

My no vote, to explain that, is that I too am uncomfortable going from this surrogate with this single development program to believing that this safety meets my

criteria for other surrogates that we have discussed, like blood pressure and LDL cholesterol. Because it is not there yet, I wasn't convinced that there was clinical benefit to treating this surrogate. That is my primary reservation.

DR. FLACK: I would like to see the company get really good guidance in that area so they don't come in here and experience what we had today because I am not sure that they got their guidance. And, the issue of this not being a surrogate, sodium not being a surrogate and meeting the clinical effectiveness, it didn't sound to me like something that had really been pushed early on, back in the development stage.

DR. HIATT: So, in closing this meeting, this has been an incredible five years for me personally and for other people on this committee. On that last comment, John, that is exactly what Cardiorenal does. I do think we try to hold to very high standards here and this process I think has been terribly robust. So, I thank all of you for the privilege of serving. And, I would like to close the meting. Thank you.

[Applause]

[Whereupon, at 4:55 p.m., the meeting was

adjourned.]