whatever that quite means, in patients who received this therapy.

DR. STEVENSON: I just wanted to make sure of that.

DR. HARRINGTON: So, Lynn is comfortable with that, I am comfortable with that interpretation.

Go ahead, Henry.

DR. BLACK: I just want to make one other comment on the guidelines. When we did JNC-7, we were careful not to categorize things in the I, II, or III, or A, B, and C, because it is a false categorization in a lot of ways, and I think it looks the same, and we put it down on our list, and I think I am pleased that we did.

DR. HARRINGTON: Let's go to Question 3. This is not a voting question, but I will read through it quickly here.

Question No. 3. If you believe that there is adequate evidence linking changes in serum phosphate to clinical outcomes in dialysis patients, then the issue is when one should initiate such treatment.

Please evaluate the following risks of early treatment with phosphate binders. Please indicate if you

believe these risks to be product-specific.

Minor GI adverse events. Major GI adverse events. Drug interactions. Interference with absorption of nutrients. Heavy metal accumulation. Development of intolerance to phosphate binder products. Others.

Please describe the incremental benefits of the use of phosphate binders in pre-dialysis patients over use in dialysis patients, and please evaluate the incremental benefits of pre-dialysis use compared with the risks.

Does anyone want to open up here? Susan.

DR. SHURIN: We really didn't discuss that first bullet, particularly the issues of product-specific.

DR. HARRINGTON: We did not discuss issues of product-specific. We had a couple of active comparator trials that we saw. But we did not spend a lot of time--and part of that issue may have been I think one of our speakers, it might have been Dr. McCullough pointed out that because there was a collaboration amongst the three sponsors, there was an intent to not focus on comparative issues.

DR. SHURIN: Right. We saw the data. I don't know what we spent much time evaluating it. I am not sure

this is where we should be weighing in I guess is my comment.

DR. HARRINGTON: Norm, do you want to comment on that?

DR. STOCKBRIDGE: Look, if you think you don't have enough information to answer something, then, that is an answer.

DR. HARRINGTON: Other comments around the table? Lynn, then Jeff.

DR. STEVENSON: I do feel uncomfortable about specifically the lack of information on drug interactions. I think patients very often take things together whether or not they are told to take them separately, and there are a number of vital therapies that they are being given for other things in addition to phosphate. So I am concerned about that.

I am also concerned about the issue of potential calcium loading.

DR. HARRINGTON: Jeffrey.

DR. KOPP: The first part of the question relates to the level of initiating treatment, and I recall one of the early speakers talking about less than 6 would be the

initiating event, and then we have already discussed how the KDOQI guidelines have 5.5 as the target to get below for ESRD, and 4.6 for Stage 4 CKD.

So, I think right there it epitomizes that none of us really know, and somewhere between just over normal or up to 6. I guess reasonable people could disagree. I think most nephrologists probably do initiate at somewhere around 5, but I suspect we don't know, and hence, a trial that might compare I will throw out my version 3 versus 4.5 versus 6, and then we can also talk about achieve versus target is we want to reprise the erythropoietin and hemoglobin story, but we don't.

DR. HARRINGTON: Lynn.

DR. STEVENSON: I would point out it doesn't make sense to me when we are talking about potentially more risks and over a longer period of time in a pre-dialysis population to have a lower threshold for treating those. I am a little uncomfortable with that as a recommendation if we are saying we are aiming for an upper range of 5.5 in the dialysis, I am reluctant to say 4.6 in the pre-dialysis since we don't really have any evidence even of benefit there.

So, I would suggest we at least have the same target for clinical use.

DR. HARRINGTON: Other comments around the table? Specifically, if people could begin to--I, too, felt uncomfortable with the drug interactions. I felt that there was really an insufficient amount of information.

The incremental benefits of phosphate binders in pre-dialysis patients over use in dialysis patients and incremental benefits of pre-dialysis use compared with the risks. I think, Lynn, what you are saying is that a longer period of time of treatment therapy shouldn't be more aggressive in the dialysis patients.

Any other comments on this point, because I think this leads us into the next question? Go ahead.

DR. KOPP: Just briefly, I can see the argument that probably generated that is this concept of getting ahead of the curve before the PTH takes off and may be easier to suppress. There may be data about that, that I don't know, but I suspect that could be a whole separate topic of a presentation.

DR. HARRINGTON: Other comments on the table? Emil.

DR. PAGANINI: If you go down that path, Jeff, then, you get into Bricker's hypothesis or tradeoff hypothesis, which means that you would actually start way back at the beginning, at Phase I, Stage 1, Stage 2, and then you are talking about a significant population and a long duration of therapy in that type of thing.

So, if you are really going to carry that all the way back, then, Bricker says gee whiz, as soon as you go below 60 or 50, then, you start to change, and that has been around for 30-some odd years.

DR. HARRINGTON: Go ahead, Bob.l

DR. TEMPLE: I may have heard it and didn't understand it. I gather there is a belief that the very high parathormone levels that you get if you are on dialysis are ameliorated, and that's good. But did we see data in the pre-dialysis population that there were major effects on parathormone, and I have forgotten them?

DR. HARRINGTON: Did we see that data, and could somebody refresh the panel's memory?

DR. DIAZ-BUXO: One of them, in the Stage 3/4 data from EPIC, I believe it was within normal limits on the treatment group, and I think something on the placebo, but

don't quote me. Let's wait until we get the slide. I believe it was the very last EPIC slide that I requested.

[Slide.]

Yes, it was 141 on the calcium acetate and 233 on the placebo. That was in the control study.

DR. TEERLINK: And this is the study that you haven't done the statistics on, and we don't know the standard deviation, so we don't know whether those numbers are really different.

DR. DIAZ-BUXO: That is correct. They look quite different, but I cannot assure that they are statistically different.

DR. TEERLINK: Or what the baselines were.

DR. HARRINGTON: I think this one where the data were recently available.

DR. DIAZ-BUXO: They are providing me data now. We have something to show you now. Next slide, please. Oh, that is yours.

DR. MENOYO: This is the CKD trial that we conducted in Stage 4 and 5 patients not on dialysis. This was a short-term trial, 8 weeks. You can see here the baseline PTH, median PTH, 341, and the end of treatment is

319. It was statistically significant difference here, PTH from baseline to end of treatment.

I want to point out again this was a short trial, so we probably expect to see a bigger reduction of PTH in the longer trial with sevelamer.

DR. TEMPLE: Just for the Committee, is that the sort of change that everybody was impressed, was the magnitude of change that every was impressed was a big deal in the dialysis setting? It seems small from here, but I don't know these kind of data.

DR. HARRINGTON: That is the question. Let me open it up, Bob. Are these compelling data to people? Emil, you deal with these patients?

DR. PAGANINI: Yes. No, that is not a big change. That is a clinically insignificant change. It is significant, but I think it is a trend, and I think as they brought out, first of all, I don't remember how many patients there were in that--

DR. MENOYO: These are actually 49 patients. These are pre-dialysis patients.

DR. PAGANINI: So, 49 people over the course of how long?

DR. MENOYO: There was a washout period, 8-week treatment, and it was after that.

DR. PAGANINI: So, I mean, you know, you have got a while there.

DR. TEMPLE: It could be that the pre-dialysis people are less deranged, so that the benefit is smaller, which would leave open the question of whether there is a benefit similar to what you see in the dialysis patients.

Am I reading that right?

DR. HARRINGTON: You are reading it right, and like most things in medicine, the less sick you are, the less benefit there usually is associated with the therapy, not always, but usually.

DR. STEVENSON: If you look in the briefing document, on page 31, in the CKD-4, the average PTH is basically only about twice normal, and the phosphate is about 3.8 from this slide, and they are suggesting that it doesn't present a very large target for therapy, at least in the CKD-4 group.

So, it looks like the patients in that study are much, much sicker than the average CKD-4.

DR. DIAZ-BUXO: If you will allow me, I will

present the data I was looking for.

DR. HARRINGTON: Okay.

DR. DIAZ-BUXO: Compared with baseline, please show the slide. Oh, it's slow.

DR. HARRINGTON: While we are waiting, does anybody on the committee have other comments or questions? Go ahead, Kathryn.

DR. WEISE: Two comments. One is to broaden out the concept of benefit beyond biochemical or physiologic benefit, because people have mentioned that allowing this would perhaps allow patients to receive insurance benefits for use of these drugs, which would be a clear benefit to patients, but I am not sure that I would want to cast this group as an advocacy organization for that, and that maybe that advocacy needs to be done, but I don't think this kind of discussion is the place to advocate for that.

DR. TEMPLE: Can I just endorse that? We want to know about evidence whether it meets legal standards for approval. I mean obviously, people care about payment and all kinds of insurance, but that really isn't what we bring things to the Committee.

DR. HARRINGTON: It is a separate discussion.

DR. WEISE: Not the forum. The second point is that coming from a pediatric background, most of what we do is not as evidence based as in the adult world, so, of course, it appeals to me emotionally to be going ahead with this if people are doing that and believe that it is right to do it.

But I think we have to be intellectually very honest as we try to teach our residents to be, that this may not be evidence based, and that we may feel that it is right, but I think it needs to go to a higher standard of analysis.

DR. HARRINGTON: A fair statement along the lines of what Bob had said about voting with emotion.

DR. DIAZ-BUXO: Mr. Chairman, indeed, it was highly significant. We are looking at the change from baseline in the calcium acetate group. It was minus 170 plus or minus 172, and in the placebo it was 28.8 plus or minus 70.7, so that was very significant.

DR. HARRINGTON: Thank you.

Other comments on this Question 3, which is really just getting us to reflect before we vote on Question 4.

So, why don't you put up Question 4, Cathy, and I

will read it. Again, because it's voting, leave your hands up, and we will do the yes votes first.

Question No. 4. Should the indications for phosphate binders extend to use in pre-dialysis patients? Please make any appropriate product-specific qualifications.

So, i will ask to vote yes or no, and then, if you vote yes, we will go around and do the appropriate product-specific qualifications.

DR. STEVENSON: I have one question before we start.

I would actually just like to hear from Emil just a justification or otherwise. Are we allowed to do that?

DR. HARRINGTON: Yes. That is why we have changed the voting structure is my understanding.

DR. STEVENSON: Can I just ask his experience as a nephrologist, can I ask that without asking his vote?

DR. HARRINGTON: Would you like to allow that, Norm?

DR. STEVENSON: I mean he has more experience.

DR. STOCKBRIDGE: Look, the funny rules are not our idea.

DR. STEVENSON: Don't tell me how you are going to

vote, Emil, just tell me what I should take into consideration from the standpoint of a nephrologist.

DR. PAGANINI: On what question?

DR. HARRINGTON: Let me back it up because the way it was described to me, and I think there is some justification for this, is that questions could really be swayed or voting could be swayed by a particularly persuasive person along the way. Can you believe that, Bob?

So, if we were looking at the incremental benefits of pre-dialysis use, which was Question 3, maybe Lynn would like to hear from you as a practicing nephrologist, Emil, as to your sense of the benefits of treating the pre-dialysis patients compared with the risk.

DR. PAGANINI: I think the benefits of treatment here would be again in a complex of different drug interactions or different interactions, one of a mosaic of many interventions to folks focused on calcium phosphorus and PTH levels with their consequence along down the line of what would happen. So what you are trying to do is avoid physiologic changes to abnormal changes in either of these numbers.

To extend it way to the beginning of the CKD-1

would be foolish or anything, frankly, CKD-1 I think is horse hockey. I know I will be crucified when I leave, and that's okay.

But CKD-2 has some substance to it, below 60 GFR, and from CKD-2 to CKD-3, CKD-3 to CKD-4, and CKD-4 to 5, I think as you go down, you become more and more dependent upon external forces to control things rather than internal forces or dietary, or you become more and more dependent upon drug, any combination of drugs that you would use.

I would see that there is a clear extension from dialysis to CKD-5, no question at all, and extension into CKD-4 probable, and extension into CKD-3 and 2 and 1, I don't see anything in 1. I don't see anything in 2, and 3 would be very rare patients.

DR. STEVENSON: In general, in practice, is that something that would be driven by the level of the serum phosphate rather than the stage of kidney disease?

DR. PAGANINI: I think usually, yes, it would be driven by level of serum phosphate, level of calcium, level of PTH, and those are things that you would follows. Again, Bricker's trade-off has said that it is a trade-off hypothesis. What you are doing is trying to control your

phosphorus, trying to control calcium, and your trade-off is an ever increasing level of PTH.

DR. HARRINGTON: Does that help you?

DR. STEVENSON: Yes.

DR. HARRINGTON: Steven, did you have a comment?

MR. FINDLAY: I was seeking clarification on exactly what the sponsors were looking for here. It is not exactly the question that is asked here, but with respect to hyperphosphatemia, I was confused and just would like a clarification on that, because in practical terms, that is what we are voting for.

DR. HARRINGTON: Norm, do you want to clarify?

DR. STOCKBRIDGE: I am sorry, I didn't quite understand.

MR. FINDLAY: Well, I mean the sponsors, all day we have really been talking about extending this benefit to pre-dialysis patients with elevated levels.

DR. TEMPLE: With phosphates of some level.

MR. FINDLAY: Yes.

DR. TEMPLE: I think the question is one of principle. You don't have to exactly figure out which level of the important unless that really matters to you.

MR. FINDLAY: Right.

DR. HARRINGTON: During the day, the sponsor really focused on that sort of top box on that graph that kept coming up on a very specific part of the population. This, I agree with. Norman has a more general question.

MR. FINDLAY: And they mentioned specific ranges of numbers of patients, 80,000 to 100,000. We are not talking about 5 million people here, down into lower levels. That is not in the question per se.

DR. HARRINGTON: Do you want to comment, Norm?

DR. STOCKBRIDGE: Look, there is no barrier to the use in that population now. If the label is more extensive, inclusive of a patient population, who is to say where it gets used.

DR. TEMPLE: But the specific proposal that has been on the table is Stage 4, and it would be if the phosphate is over some value. You know, you could debate what value that should be. If it matters a lot, we can ask them, but is more a question of principle, is there some value, 6.0, 5.5, 7.0, where you should start treating people even though they are not on dialysis.

MR. FINDLAY: So, that goes to the appropriate

product specific qualifications.

DR. STOCKBRIDGE: No, the product-specific part of this was an invitation to say you thought it was perfectly obvious you should extend this indication for two of the three, but the third on, heaven forbid.

DR. HARRINGTON: Does that help you?

John, did you have a comment?

DR. NEYLAN: Just another question and clarification. As I heard the sponsors throughout the day, it was again and again repeated that it was the extension in the patient population with hyperphosphatemia, and if you are in agreement, could that be a friendly amendment to this question.

DR. TEMPLE: Yes, I think that is what they have been--I mean they haven't yet proposed taking people with 4 and getting them to 2.

DR. HARRINGTON: So, maybe, Bob or Norman, the question if you are using John's recommendation, that we specify, the question is should the indications for phosphate binders extend to use in pre-dialysis patients with hyperphosphatemia, is that what you are getting at, John?

DR. NEYLAN: Yes.

DR. HARRINGTON: Norman?

DR. STOCKBRIDGE: That's fine.

DR. HARRINGTON: That is fine, so let's add that to the question.

Again, should the indications for phosphate binders extend to use in pre-dialysis patients with hyperphosphatemia?

Let's have the yes votes raise their hands.

[Show of hands.]

DR. HARRINGTON: Let's start on this side this time. Jeffrey, state your name and your vote.

DR. KOPP: Jeffrey Kopp. Yes.

DR. STEVENSON: Lynn Stevenson. Yes, but not for any lower level than in the dialysis patients.

MS. SCOTT: Malazia Scott. Yes.

DR. SHURIN: Susan Shurin. Yes.

MR. FINDLAY: Steve Findlay. Yes.

DR. BLACK: Henry Black. Yes.

DR. PAGANINI: Emil Paganini. Yes.

DR. FLACK: John Flack. Yes.

DR. HARRINGTON: People voting no, raise your

hands.

[Show of hands.]

DR. HARRINGTON: Are you abstaining, Michael?

DR. PROSCHAN: Yes, I am.

DR. HARRINGTON: We will do those last.

So, the no votes. Mike Lincoff?

DR. LINCOFF: Michael Lincoff. No.

DR. WEISE: Kathryn Weise. No.

DR. HARRINGTON: Robert Harrington. No.

DR. TEERLINK: John Teerlink. No.

DR. HARRINGTON: Those abstaining?

[One hand raised.]

DR. PROSCHAN: I guess I am the only one.

I don't know what that really means. I mean does that mean on the label, it is going to say use this pre-dialysis patients with phosphatemia, or does it mean that it would say there is some evidence that this could be helpful?

DR. HARRINGTON: So, for the record, could we include that you abstained because of lack of certainty around the clarity of the question?

DR. PROSCHAN: Right.

DR. HARRINGTON: Let me take those people who

voted yes and ask if there are appropriate product-specific qualifications. Henry, you have your hand up.

DR. BLACK: I don't think there are appropriate product-specific qualifications, but it would be awfully hard for me to vote against treating someone with a phosphate of 7, which would be hyperphosphatemia or 10 as opposed to 5.6.

I think the question got very fuzzy with that amendment, and I sort of resent that, and I probably should have abstained.

DR. HARRINGTON: Fair comment.

Steven?

MR. FINDLAY: No product-specific. I don't have any comment on that. I don't think we saw enough data.

DR. HARRINGTON: Others who voted yes? Lynn.

DR. STEVENSON: I don't think we saw enough data and furthermore, I think because of the collegiality they were not encouraged to present it in such a way that we could decide, so I don't think we should really be voting on that.

DR. SHURIN: I agree with that.

DR. HARRINGTON: That is a fair statement. I

think there is probably a general sense.

John.

DR. FLACK: I think there are some predictable potential differences that would occur between, say, a calcium carbonate and some of the other non-calcium based products. Adynamic bone disease is one. Hypercalcemia is another. And I think for all of them, irrespective of how they work, there needs to be a commitment to developing a database for monitoring safety that we don't have right now.

I am actually more concerned about that than I am does it work, because these drugs are going to be used really outside the nephrology setting--because I will guarantee you primary-care doctors are going to get targeted with this, because they know where the patients are, and if the patients are going to get treated, many of them are going to have to be treated in a primary care setting.

DR. HARRINGTON: Bob.

DR. TEMPLE: Well, we always need to understand why people tell us what they tell us.

As I understand the votes so far, we have heard that phosphate is unequivocally not a surrogate for clinical benefit and that is the thing that the drug has been shown

to have an effect on in the pre-dialysis patients.

There is no question nobody has established a clinical benefit in pre-dialysis patient. They haven't even studied it. Maybe some of the newer studies are hinting, but so far not.

But a majority of the Committee thinks it should be approved. Any further explanations of what we are going to approve in the absence of a clinical benefit and in the absence of a surrogate, or maybe this turned on very extreme phosphates that really weren't discussed before, and maybe we should have?

DR. BLACK: I don't think there is any way I could legitimately vote to not try to fix an electrolyte where I had a way to fix it before having any evidence. So, I think in some ways maybe we ought to just vote on the question as it was, and then maybe give you some advice, or maybe ask for advice on where that level should be if there is a level.

DR. TEMPLE: Discussion is good.

DR. BLACK: I mean it is really hard as the question was phrased to vote no.

DR. TEMPLE: But again I hope people will address

the fact that you have told us there are no clinical data and there is no surrogate.

DR. HARRINGTON: Henry, let's explore that a bit because we added the term or the phrase "in pre-dialysis patients with hyperphosphatemia," and that made you uncomfortable, and because of that you voted yes.

If that phrase had not been in there?

DR. BLACK: I would have voted no.

DR. HARRINGTON: Because then would you have followed Bob's chain of logic there?

DR. BLACK: Well, I had been up until now, but that particular change at this point in time without much chance to discuss exactly what we meant and where that was, made it sort of a very late entry into what you could decide to do.

DR. HARRINGTON: I think this is important discussion. I think as Bob said, you know, they take our remarks not strictly as you know, by vote, but both by vote and by what the comments are.

So, from your perspective, Henry, and then I want others to weigh in, you would not have voted for phosphate binders in the pre-dialysis patients, but what you were

concerned about is that if there are patients with very high levels of phosphate, you may want to treat those individually.

DR. BLACK: I mean I think we would, I think any of us would. Whether you would put it in a label and approve it is something else, and I don't think--

DR. STOCKBRIDGE: That is the question. The question is about labeling. It is not about what you are going to do in your clinical practice.

DR. BLACK: I don't think we had adequate time to discuss that really, and it was a hasty vote in some ways, and I think what Michael did was the right thing to do, was to abstain, because I really don't know what I would do, if I have more time to think about it.

DR. HARRINGTON: Let's talk about that. It looks like other people have comments.

Michael Lincoff.

DR. LINCOFF: I think this is clearly an issue of is there evidence to support a label that doesn't necessarily mean is there enough clinical experience to support what we do in experience, and I think that is the key differentiation here.

The indication that the drug has now--the drugs we have now were sort of not grandfathered, but an historical level of evidence that didn't necessarily require the same level that we would want for a label to extend the indication.

That doesn't mean we don't necessarily do it in practice, but I think it is an important distinction, and before we change a label, particularly given that it is a change, it implies that now something has come up that would suggest that there is a larger proportion of the population of patients, we have new evidence, we have new something that would suggest a larger population of benefit.

I think that there should be some evidence to support that even if we feel, based upon our experience in the other group of patients, that there is benefit.

DR. HARRINGTON: John Teerlink and then Emil.

DR. TEERLINK: I guess I would like to follow up on what Mike said. In some ways I am concerned about the integrity of the imprimatur of the FDA in terms of this approval process.

If we are going to say that, well, because we think it is right clinically, then, we should approve it, I

can think of a lot of things that I can bring to clinic, bring to the FDA now for approval, and I am not sure I really want to open that up.

You know, the two things that you need to do I think in terms of showing approval are that the drug does what you say it does in the label, so does it lower phosphate. Well, in dialysis patients, it seems to, and the pre-dialysis patients, there is some evidence that it does, so that might be good, but then it also has to demonstrate a benefit.

Now, what that benefit is can be widely debated, but I am not sure that there is any evidence whatsoever to show any benefit from a regulatory standpoint.

The drug is already out there. It is going to be used for these hyperphosphatemic patients who have to come in with phosphates of 10. You are already going to do stuff for them. That is not actually figuring into my calculus here.

What is figuring into my calculus is what kind of precedent are we setting for the approval of drugs where there is no evidence.

DR. HARRINGTON: Emil, then Henry, then John.

DR. PAGANINI: I voted yes with the hyperphosphatemia, but I think the idea of showing no without it and yes with it shows the subjectivity of practice, and that is clearly shown here by someone who says, look, if it wasn't there, I would vote no, but if it is there, I would vote yes. It's subjective, and so that is a gut feeling.

On the other side, the second half of this question says please make appropriate product-specific qualifications to your vote. So, I could say across all classes. That would be a yes if, in fact, there were some sort of studies that were done in that population to show efficacy.

So, I would not out of hand say no, it shouldn't go there, because I practice, yes, it should be there. But I think that there needs to be studies in order to put it on a label.

DR. HARRINGTON: Let's go to Henry, then John Flack.

DR. BLACK: I think there are other issues, as well.

DR. PAGANINI: The second half of the question

said qualify, qualify your vote.

DR. BLACK: I mean do you define hyperphosphatemia once, are you on a diet, have you tried that first? I mean there are a lot of things.

I think if you are strictly talking from the level of evidence that you need to put in a label, I would vote no, however, I just don't know the implications of being asked to not recommend in some way or another, and we have different levels of recommendation.

We are really caught between what we think is good or really necessary practice and what gets in a label. So, I don't think we had enough chance to discuss that.

DR. HARRINGTON: I want to make sure that FDA hears a full discussion. I think that Emil is making an important point, that it points out some of the vagaries both in the wording and what we are being asked to do.

But if you think what we are being asked to do is to vote on an approval for a label. It didn't say what do you do in clinical practice. It says vote an approval on a label.

John.

DR. FLACK: Maybe I missed something. In

extending this to Stage 4 patients, it is only Stage 4 patients who have hyperphosphatemia.

DR. HARRINGTON: That is why we made the addition at John Neylan's recommendation.

DR. FLACK: Because otherwise you can make an extreme case, but it doesn't really make much sense to me to extend it to people who are not hyperphosphatemic, in Stage 4. Again, I will go back to the fact that you really have to manage--I think you have to manage these individuals, and it is going to be part of a multi-tiered sort of strategy in it.

I mean heck, even PTH is affected by multiple things. A lot of African-Americans have secondary hyperparathyroidism with non-depressed kidney function because of obesity and vitamin D deficiency and probably low calcium intake.

All this stuff is not clean, you know, push a button X and you get Y. But if you are hyperphosphatemic and you are pre-dialysis Stage 4, and you can manage their hyperphosphatemia, I don't know how we don't really go down that road, and it seems to me that the benefit--I am concerned about the risk, the risk of hyperphosphatemia,

some of those risks are not necessarily well studied in clinical trials anyway.

You don't need to be a brain surgeon to know you get calcifications and metastatic stuff, and all, and so I think we are being, I don't know, maybe a little bit too stringent here, because hyperphosphatemia in itself, and it is linked to bone disease, I think is reasonably well established, to me is enough.

All the other stuff they have got presented there, I am not convinced by, but for hyperphosphatemia itself, metastatic calcification, and bone disease, I think it is a real hard stretch to say the stuff doesn't help.

DR. HARRINGTON: Kathryn.

DR. WEISE: This is probably just repetitious, but I don't think we are saying that it doesn't help. I think we are just looking for the bar that we have to reach to say that the label should be changed.

DR. HARRINGTON: Michael.

DR. PROSCHAN: Is it possible to have a wishy-washy label that says, you know, in pre-dialysis patients it lowers phosphate, which may or may not have a net benefit in the patient?

DR. HARRINGTON: Ask the label writers.

DR. TEMPLE: Well, these matters are probably judgment, but first of all, the drug has to do what it says it is going to do, so it does lower phosphate, but we also have to conclude that that is a useful thing to do and that there is some subjectivity in that, and that is part of what the discussion is.

But to say we don't know if it's good for you or bad for you, I think would be at odds for what we expect.

DR. KOPP: I have two comments. My vote was driven in part by the idea of extreme hyperphosphatemia, so I guess if it is labeled for that, I would hope some statement about that would be made.

I don't know if you can put a numerical number on it greater than 6, greater than 7, but I also would hope that we could go back to the idea of urging the companies, if it is under subpart H, or whatever is required, to define which level of hyperphosphatemia in the pre-dialysis patients are associated with important clinical benefits.

DR. STOCKBRIDGE: Can you clarify for me what your sense of urgency is about a serum phosphorus of, what did you say, 6, 6.5?

DR. KOPP: Right, and by itself it is meaningless, somebody with acute renal failure, who is going to get better, I know we are not going to treat that patient, so it is the context of chronicity and the level of PTH that has not responded to other therapies, so it is not an easy answer. It is not an easy label to write as I am proposing.

DR. STOCKBRIDGE: Part of this has to do with establishing what the incremental benefit of early intervention is. So, you know, that somebody may eventually progress to a point where they get something we would call a clinical endpoint as a result of their elevation in serum phosphorus, that's fine, but does that mean you can wait until their visit a week from now, or do you call them back into the emergency room and get them started on phosphate binder?

I mean I am trying to figure out why, in fact, it is worth doing this in a patient who is short of dialysis.

DR. KOPP: I think you can wait. It has taken months to get to a phosphorus of 7 or 8 or 9, but by the same token, other therapies are less likely to have a favorable effect. Putting somebody on calcium when their phosphorus is 9 may be problematic, because of a dramatic

increase in the calcium-phosphorus product.

So, I would say with very high levels that have been achieved chronically, this sort of a therapeutic approach does make clinical sense. Whether to construct a label around that argument, that is what I have been wrestling with in this vote.

DR. HARRINGTON: Steven.

MR. FINDLAY: Just for the record, I thought the sponsors--I voted yes--I thought the sponsors made a strong, a relatively strong circumstantial case for the benefit in this narrow group of patients.

I also think that we agreed throughout the day that the studies presented were not sufficient and that--just to restate what was discussed throughout the day--that further randomized, controlled clinical trials and other studied needed to be done on that population, dialysis population.

DR. HARRINGTON: Go ahead, Lynn.

DR. STEVENSON: I think we should clarify that like all these things with precedence, there are thing that make this one different from all the ones before and all the ones that come next, which is that we are jumping on a bus

that is already moving.

So, it would be one thing to talk about shifting it from park into first gear. We are just talking about shifting it from third into fourth gear. This bus is already moving for reasons, you know, before any of us were involved, and I think that makes the situation a little different.

DR. HARRINGTON: Norm, you were reaching for the microphone.

DR. STOCKBRIDGE: I was going to say that is not data either, that some action has been taken, that that is not clinical data either.

DR. HARRINGTON: Bob.

DR. TEMPLE: Steven, your last comment, I am not sure I understand. You said we several times before said one thing, mostly in the direction of no, but that you voted yes. Are you still comfortable with both of those two things, and how do they fit?

MR. FINDLAY: I am comfortable with my vote, but I do, I am admitting it is based on circumstantial evidence. I agree with John's point about the very difficult situation we all find ourselves in when we get this kind of evidence,

and you are having to make a decision that affects real people.

On balance, I think the sponsor has presented enough evidence to suggest, and I agree it's a train already that has left the station, but that shouldn't factor in perhaps, that they made a compelling case that there is benefit for this range of patients.

DR. TEMPLE: Is the group you are talking about people with very high, to be defined--very high and--

MR. FINDLAY: Yes, and forgive me, I am not a--

DR. TEMPLE: And some degree of calcification or some degree of something else, that is, people who are manifesting things?

MR. FINDLAY: I can't speak to those specifics. I have to leave that to others.

DR. PAGANINI: Bob, I think maybe the metabolic bone disease classification will allow us to classify these folks.

So, if you move along that track of MBD and the CKD, and you go to the four subgroups, and then take each of those subgroups and see whether or not there is an outcome related benefit to phosphate control in each of those

subgroups, whether that be for entry to dialysis, length of time, laboratory data, different significant entry to dialysis laboratory data, vascular calcifications, coronary calcifications, time to, at entry of dialysis when they finally get down there, bone dysfunction of some sort whether it be biopsy related or not, according to those groups that they have, in fact, defined them as subgroups of folks either with or without vascular calcification, with or without bone disease, and seeing whether or not control of phosphorus within those groups are important, you will have defined your subgroup, your population.

I don't think that has been defined yet.

DR. TEMPLE: So, those are things that would make it reasonable to treat? I am not sure, how would you use that information?

MR. FINDLAY: Those are the studies that would allow you to categorize the patients that would benefit from.

DR. TEMPLE: Oh, no, we definitely want more studies. I was more interested in this vote where more than half of you said yes in the face of previous statements that we don't have a surrogate, and I was trying to figure out

what made people feel they knew enough to treat some defined population.

It sounds like the population is people with very high phosphates, and I am just trying to figure out their further characteristics, like do they already have calcified vessels or they have already got coronary artery disease or what.

MR. FINDLAY: If we continue with the analogy where we are putting it out of park, we are in third or something, we are in a 4 by 4 and we are off-roading it right now, wouldn't it be nice to have a road somewhere.

DR. TEMPLE: Oh, we all agree we want more data. These questions go to whether there is something you could actually say now, before there is any more data, and the vote suggested that people feel with varying degrees of assurance, as we have just been discussing, that there might be something that could go in the label now without more data. That is what you told us.

DR. HARRINGTON: Yes, so let's go down that path, Bob, because what I have been hearing is that for the people who voted yes, that they there is at least two camps within the room. There is the camp I think expressed by both Henry

and Jeffrey that very clearly said that they were driven to vote yes by the notion that there were very high levels of phosphate that they didn't want the clinicians to ignore.

I think that there are others who have voted yes, because there is a more general belief that in the Stage 4 patients, that they should be offered treatment because hyperphosphatemia is associated with bad things down the road and while it may not reach the level of surrogacy, there is enough bad stuff going on that the treatment is a good thing.

Those are the two camps I am hearing. I don't know if there is a third camp within the yes vote. So, I don't think this yes vote is as clear as just a numeric counting of it might suggest.

Is that a fair interpretation from the Committee? Go ahead, Jeffrey.

DR. KOPP: If I could elaborate in response, to me the definition would include some level of PTH, which is refractory to other therapies, or the other therapies cannot be initiated, and again I would defer to my colleagues in this area. I don't know, is it 3 times, 4 times elevated, but that is where I would be going with the labeling.

DR. HARRINGTON: Other comments? Go ahead, Henry.

DR. BLACK: No, I agree with how you put it. It is just very hard not to suggest treating people who have a level that I think we have pretty good evidence is risky and where we couldn't probably do a trial.

DR. HARRINGTON: It may have been my fault in terms of how we parse to the vote, but I voted no, because I blocked out of my brain the high phosphates, because I said, well, this therapy is available, if something was really high, someone is going to treat them anyway. But I understand your point as to how that may have driven you to vote one way or another, so I apologize if I drove you in that direction.

So, part of the other follow-up question here, and this is part of a discussion we have had all day, what are the data would support establishing a claim for use, and this said if you voted no, but I think everyone around the table has said that they would like to see more data.

Let me see if I can at least put down some of the things I think we have heard today, Bob. The placebo control would be ideal although people recognize some of the complexities of placebo control in this population, that a

dose-ranging study or a dose strategy study or level strategy study might be a reasonable thing to do, active controls with all three drugs would be a reasonable thing to do.

Other thoughts, comments?

DR. TEMPLE: Active control only if you beat something.

DR. HARRINGTON: Active control to me is only a useful one if there is a dose ranging associated with it or some level.

DR. TEMPLE: Evidence of dose-response.

DR. HARRINGTON: Right. The other thing is presumably is you push the starting phosphate down some, you get more possible to do a placebo, because there is less certainty that you are in that dangerous category.

DR. SHURIN: I think the key issue is that we need clinical outcomes. I mean it is fine to do the coronary calcium, but if you don't have some measure of cardiovascular disease, it is a meaningless study. The same thing is true with a bone disease. If you don't have some measure of whether or not people are getting fractures, I mean it has got to be a clinical outcome.

DR. HARRINGTON: So, clinical outcomes. Other comments? Go ahead, John.

DR. NEYLAN: Actually, it is a question to the Committee. We all agree that clinical outcomes would be the final best arbiter of success or failure, but what sort of clinical outcomes are we talking about given again the rather small number of patients and the rather short duration of their time in this period, which just precedes the institution of renal replacement therapy.

DR. HARRINGTON: John Teerlink.

DR. TEERLINK: I think I would try to offer it up to the sponsors here, say okay, let's forget about pre-dialysis, you come up with folks. Just say hyperphosphatemia, and that would extend your--you know, you want to talk about extending it to 11 million, go ahead, you know, if you can show the outcomes.

I know, but I am just saying this is an area where I don't think we are bound by this pre-dialysis unnecessarily group.

I think it can be extended to Stage 3, Stage 4 patients with hyperphosphatemia, and, Lynn, look at outcomes, and then in terms of which outcomes you choose, I

think there are two very tempting outcomes, one being in the cardiovascular arena and the other is in the metabolic bone disease.

I don't think anything I have said certainly has tried to negate that those aren't very important. If anything, what I have said today has tried to raise the level of the importance of those things.

I am saying those are what is really counting the patients, and if there are ways to get at clinical outcomes within those arenas, I think that is important to do, and that would be within the Stage 3/Stage 4 patients, which would give them an expanded indication and a much greater group of folks.

Now, there may be other reasons why they may not want to pursue that strategy, but I think there are creative ways to try to approach that.

DR. HARRINGTON: Other comments around the table?

Go ahead, Emil.

DR. PAGANINI: Just to make sure that the prospective studies are done in a complex of metabolic disease. So, in other words, not just a single entity, but in a complex of things that might be beneficial.

Do you follow what I am trying to say?

DR. TEERLINK: Yes, of course.

DR. HARRINGTON: Are you advocating, I think it was Dr. McCullough that was talking about a strategy of metabolic control versus less intense metabolic control, something similar to, say, for example, ACCORD?

DR. PAGANINI: I do.

DR. HARRINGTON: Which would be another type of study, a strategy study as opposed to an A versus B drug study?

DR. PAGANINI: Correct.

DR. HARRINGTON: John Neylan, did you have another comment?

DR. NEYLAN: A very specific one. I was just wondering again to the Committee, the endpoint of coronary calcification came up several times today, and while we all recognize that this doesn't rise to the level of a validated surrogate, nonetheless, I heard some opinions around this table suggesting that they indeed give it a lot of clinical import, so given that as a fairly discrete and accessible endpoint for studies like this, would the Committee feel that that would be an appropriate design for the sponsors?

DR. HARRINGTON: I will weigh in. I actually don't. I think you have to understand as people live longer, feel better, or avoid bad things like going onto dialysis or having heart attacks or having heart failure or getting rehospitalized, or not breaking their bones, but I don't see--you know, I disagree with Mike on this.

I think that coronary calcification is an important research tool and perhaps it is an important diagnostic tool in managing some patients, but I don't see it as an endpoint, but that is prospective.

DR. BLACK: I want to agree with that. If this is such a high risk group, there ought to be no paucity of events that we could count that matter.

DR. HARRINGTON: We heard all day how sick they were

John Flack and then Mike Lincoff.

DR. FLACK: I totally agree. I participated in an NIH planning committee about these subclinical endpoints, coronary calcification is one of them and. while the patients are at high risk, you really don't know what the heck to do with them, and you don't know if you change it, if you are going to get risk reductions, you might or you

might not. So I think it is tantalizing, but I don't think it is ready for prime time as an endpoint for a study.

It seems to me that the place where the evidence is very likely to be positive and the strongest is bone disease, and if I were in their shoes, I would basically fixate on bone disease and do studies related to bone disease and some of this other stuff is more speculative and out there. But it seems to me that is where you get the biggest probability of making a bang in a reasonable period of time.

DR. HARRINGTON: We now have a randomized clinical trial that says if you treat people with zoledronic acid after hip fracture, you reduce mortality, so there is at least some precedent out there that might suggest bone disease is the appropriate way to go.

DR. FLACK: Maybe if you stumble into mortality, that's great, but I don't think that you have to target mortality.

DR. HARRINGTON: No, my point was that people going after it as an endpoint was a reasonable thing to do.

Susan, did you have a comment?

DR. SHURIN: No, I just want to emphasize I think

that from the standpoint of NHLBI, that there would be no enthusiasm for coronary calcification as a surrogate endpoint, it would have to be a clinical endpoint.

DR. HARRINGTON: So, that means that NHLBI would have interest in a potential collaboration with industry on tackling this tough problem on hyperphosphatemia?

DR. SHURIN: We will look at anything that is sent to us.

DR. HARRINGTON: Michael.

DR. LINCOFF: Just for the record, although I said I felt coronary calcification was an endpoint that was at least reassuring they had some clinical or near clinical data, I did vote against this as a surrogate, so I wouldn't look at that as an endpoint for a prospectively designed trial.

DR. HARRINGTON: So, you want to see the cardiac events?

DR. LINCOFF: Or just show me something that says it works.

DR. HARRINGTON: Other comments from the Committee? Norm and Bob, have you gotten what you need today?

DR. STOCKBRIDGE: Yes, I think that is pretty helpful. What I heard was most of the people who voted yes on the last question on 4, qualified that by saying they still wanted to see some kind of real clinical outcome study before things got approved. Did I get that right?

DR. HARRINGTON: Let's ask the people who voted yes.

Say that again, Norm?

DR. STOCKBRIDGE: That people who voted yes on Question 4 still wanted to see a clinical outcome study before an approval got granted.

MR. FINDLAY: No.

DR. KOPP: I am a no on that.

MR. FINDLAY: I am a no on that. That is a very clear-cut statement that I don't think we voted, at least some of us didn't vote. I think we went with the fuzziness.

DR. STEVENSON: I, for one, wanted a study to be a condition of approval, which I think could be a dose-ranging study. It doesn't necessarily have to be placebo-controlled, but it has to be more than just a comparison of two active agents, and you have to have some idea if the strategy actually is working.

DR. TEMPLE: Well, I probably should shut up, but if what I hear people saying--and that is not to say we have concluded that we should necessarily do this--they think there are phosphates so high that realistically, you need to treat them even if the person isn't on dialysis yet, but that maybe if we ever decided to approve that, a condition of approval might be a requirement to study lower phosphates, you know, 5.5 or something probably doesn't meet Henry's criterion, in more formal studies to see if that is a good thing to do, too, to stave off problems in the longer run.

There are ways we can require such things.

DR. BLACK: In other arenas, I am very much in favor of treating very early with safe drugs that we have pretty good evidence for, so I would be a little bit hard pressed to not like that here, but I think the evidence of what I want to do is much stronger than what we have now, and we still need trials even in that area to show it works.

DR. HARRINGTON: Other comments? Norm, do you have any closing? Bob?

DR. STOCKBRIDGE: No.

DR. TEMPLE: Interesting, difficult discussion,

and we appreciate it.

DR. HARRINGTON: We want to thank the Committee and we will adjourn the meeting.

[Whereupon, at 4:40 p.m., the meeting was adjourned.]