phosphorus, parathyroid hormone. Exclusion criteria included symptomatic coronary disease, past myocardial infarction, or diabetes mellitus.

Patients were randomized either to a low phosphate diet alone or a low phosphate diet with either calcium carbonate or sevelamer. Note that calcium carbonate is not an approved binder, but as I said previously, is used widely.

There were no significant differences in any of the baseline biochemical values between the three groups including parathyroid hormone.

Eighty-four of the 90 patients completed the two-year study. At the end of the study, GFR was lower in the sevelamer arm compared to its initial value. Phosphaturia increased in the controls and fell in those receiving calcium carbonate and in those receiving sevelamer indicating the efficacy of the binders.

The binders bind intestinal calcium, do not allow it to be absorbed, and thus lower urinary excretion. However, there were no changes in serum phosphorus between the initial and final values in any of the groups.

[Slide.]

The final total calcium score was significantly greater than the initial total calcium score in controls and in calcium treated subjects. In contrast, the final total calcium score was not significantly different from the initial total calcium score in the patients receiving sevelamer.

The goal of this meeting is to allow nephrologists to use phosphate binders on label in these very patients studied by Russo and colleagues. We would like to, hopefully, eliminate the progression of coronary calcification as did Russo. This calcification is, as you have seen, killing our patients, not only those on dialysis, but those approaching dialysis, as well.

[Slide.]

In a publication of Kidney International, Block et al. randomized 129 patients new to hemodialysis to receive either calcium-containing phosphate binders, a combination of calcium carbonate and calcium acetate, or sevelamer hydrochloride.

Subjects underwent EBCT scanning at entry to the study and again at 6, 12, and 18 months. Subjects with a coronary artery calcification score of greater than 30 at

baseline had progressive increases in coronary calcification in both treatment arms. however, subjects treated with calcium-containing phosphate binders showed more rapid and more severe increases in coronary artery calcification when compared to those receiving sevelamer.

Thus, the use of phosphate binders in patients new to dialysis can also delay progression of coronary calcification.

[Slide.]

Let us think about the risks of hyperphosphatemia and progression of renal disease. We will now review the studies listed below.

[Slide.]

In a publication in NDT, Voormolen and colleagues studied incident patients with CKD 4-5 who were referred to the outpatient clinics of eight hospitals and followed for a mean of 337 days.

The mean initial glomerular filtration rate was 13 mL/min and the mean serum phosphorus was 4.7 mg/dL. During follow-up, almost one-third of the patients started dialysis. Hyperphosphatemia was found in 48 percent of the patients, hypophosphatemia in only 2 percent of the

patients.

The level of plasma phosphate was associated with baseline glomerular filtration rate. Plasma phosphate was significantly associated with a decline in renal function. Each 1 mg/mL higher phosphate was associated with a 0.15 mL/min/month steeper decline in renal function.

When the rate of decline was adjusted for known risk factors for faster decline, the higher phosphate remained independently associated with a more rapid rate of decline.

[Slide.]

In a publication in the Clinical Journal of the American Society of Nephrology, Schwarz and colleagues studied 985 male U.S. veterans with chronic kidney disease, Stages 1 to 5.

Unadjusted and multivariate adjusted relative risks for progressive CKD, as defined by doubling of serum creatinine, were calculated for serum phosphorus, calcium, and the calcium-phosphorus product using Cox proportional hazards model.

The hazard ratio of the composite endpoint by quartiles of serum phosphorus in the unadjusted Cox model is

shown in the upper line. The hazard ratio after adjustment for 15 variables including age, race, blood pressure, both systolic and diastolic, diabetes and proteinuria is shown on the bottom line.

A baseline serum phosphorus of greater than 4.3 mg/dL was associated with the highest hazard ratio for the composite endpoint of doubling of the serum creatinine in both the unadjusted and the adjusted models.

[Slide.]

Finally, in a publication in the Journal of the American Society of Nephrology, Norris and colleagues examined the factors in African-American patients with chronic kidney disease that predict increased risk for adverse renal outcome.

Again, Cox regression analysis was performed to assess the potential of 38 baseline factors to predict the clinical renal composite outcome of a 50 percent decline or 25 mL/min decline, or of end-stage renal disease in more than 1,000 patients with hypertensive nephrosclerosis. The mean follow-up was 3.9 years.

In univariate analysis, the renal composite outcomes was strongly associated with higher baseline

urinary protein excretion throughout the full range of proteinuria.

A total of 15 risk factors reached statistical significance with and without adjustment for baseline proteinuria. Factors that were significantly associated for an increased risk for the renal composite outcome after adjustment for baseline GFR, age and gender, both with and without adjustment for baseline proteinuria, again included serum phosphorus.

[Slide.]

Finally, phosphate binder use in CKD patients not on dialysis.

[Slide.]

Let us review how practicing nephrologists are addressing the use of phosphate binders in patients with CKD. As we reviewed, the NKF recommends that phosphate binders be used in conjunction with moderate phosphorus restriction to control phosphorus in patients with CKD 2, 3, and 4.

Nephrologists are well aware of these recommendations. They are also well aware of the data that you saw this morning linking the hyperphosphatemia to

mortality in our dialysis patients.

In this survey of 100 nephrologists performed in June of '07, these kidney specialists had placed 16.6 percent of patients with Stage 3 CKD on phosphate binders and 39.9 percent of patients with Stage 4 CKD on phosphate binders, which is consistent with the prevalence of hyperphosphatemia in these stages of kidney dysfunction.

In this survey, all of the nephrologists say they would prescribe phosphate binders to hyperphosphatemic patients in Stage 4 CKD. Clearly, the vast majority of patients with Stage 5 CKD are treated with phosphate binders.

The goal of this presentation is to allow us to utilize these phosphate binders as we are already doing, but now in compliance with their label.

[Slide.]

So, now, let us conclude.

Serum phosphate increases with decreased kidney function.

The elevated serum phosphorus is associated with cardiovascular calcification and accelerated progression of CKD.

Calcification and increased mortality are early complications of CKD.

Interventional studies have shown that phosphate binders can retard the progression of vascular calcification.

Adverse events associated with phosphate binder treatment are mild and mostly related to the GI tract.

[Slide.]

It is important to address calcification and increased mortality early in part by decreasing phosphorus absorption with phosphate binders.

Pre-dialysis patients do not even have the benefit of dialysis itself to remove phosphorus. A week before patients go on dialysis, they don't have the dialysis treatment which in general removes about 800 mg of phosphorus with each treatment.

So, the week before they start dialysis, they are facing this phosphate burden without even the benefit of dialysis.

Given the risks associated with hyperphosphatemia, the favorable safety profile which we reviewed, the risk-benefit ratio clearly favors I think this treatment in CKD

Stages 4 and 5.

Thank you for your attention.

I would now like to introduce Dr. Jose Diaz-Buxo.

DR. HARRINGTON: Actually, why don't we hold on because we are scheduled for a break. Why don't we take a break until 10:30 and then we will come back. We will hear the wrap-up and then we will hear the open public speakers.

[Break.]

DR. HARRINGTON: I would ask the sponsor to come up to the podium and present the conclusion, and then we will go to the public hearing, and then we will return for questions before lunch.

Phosphate Binders for the Treatment of Hyperphosphatemia in Patients with Chronic Kidney Disease Conclusions

DR. DIAZ-BUXO: Dr. Harrington, Dr. Stockbridge, distinguished members of the panel, it is my pleasure to summarize the information presented today on behalf of Genzyme, Shire, and Fresenius Medical Care by our experts.

[Slide.]

First, let me summarize the key points made by the experts.

Dr. Hruska told us about the biological plausibility that hyperphosphatemia is a determinant for vascular calcification. This is perhaps the strongest and most direct evidence hyperphosphatemia is a state of phosphorus homeostasis. Phosphorus is a signaling molecule in the pathogenesis of vascular calcification.

Control of hyperphosphatemia diminishes vascular calcification and prevents cardiac hypertrophy.

Dr. McCullough reviewed the significant data regarding the cardiovascular consequences of chronic kidney disease. In the 14 studies where there was an aggregate of more than 200,000 patients including CKD 4 and 5 patients, there was a strong correlation between serum phosphorus and clinical outcomes.

Seven observational studies in pre-dialysis patients including some with normal renal function have demonstrated an unfavorable association between serum phosphorus increments and clinical outcomes.

Dr. Bushinsky showed us that approximately two-thirds of the CKD patients have coronary artery calcification at the start of dialysis. The magnitude of vascular calcification correlates with adverse clinical

outcomes, and phosphate binder therapy attentuates vascular calcification in CKD Stage 4 and 5 patients who are pre-dialysis.

[Slide.]

Chronic renal disease is a significant public health problem and is expected to increase in the future. The various stages of classification introduced by the National Kidney Foundation KDOQI guidelines are convenient in the study of this condition, but should not be construed as concrete and isolated stages, but rather they are a continuum and CKD is a progressive disease of decreasing renal function.

[Slide.]

The Food and Drug Administration has posed a number of relevant questions to be answered based on the information presented here today.

The first one is: For what clinical outcomes is serum phosphate plausibly part of the pathogenesis in pre-dialysis patients?

Dr. Hruska has shown that the molecular and physiologic basis in which hyperphosphatemia is itself instrumental is the pathogenesis of several complications.

Subsequently, we have demonstrated that this includes vascular calcification, cardiovascular morbidity and mortality, the progression of renal failure, and bone disorders.

[Slide.]

The FDA has also asked you to consider the variability related to the natural history of the disease. A key question is for which clinical outcomes has serum phosphate been shown to be predictive of risk in pre-dialysis patients.

The data certainly indicate that vascular calcification, coronary artery calcification progression, cardiovascular events, decline in renal function, and patient mortality are associated with plasma phosphorus levels in patients with CKD, not on dialysis.

[Slide.]

The FDA asks: For which clinical outcomes have interventions targeting serum phosphorus in the pre-dialysis setting been shown to alter risk in the manner predicted by the change in phosphate?

While there is a large body of evidence in the dialysis population that support interventions in serum

phosphorus, that serum phosphorus alters risk, while there are no prospective placebo-controlled clinical trials in pre-dialysis patients showing a direct correlation between lowering serum phosphorus and clinical outcomes, a recent publication by Russo showed that pre-dialysis patients treated with low phosphorus diet and phosphate binders had lower total calcium scores compared to those pre-dialysis patients on the low phosphorus diet alone.

Furthermore, the progression of coronary calcification was also slowed down. These results suggest that reducing phosphate burden above that reduced by dietary restriction may impact the development of calcification.

The study suggests that interventions before dialysis may lead to important outcome benefits if started early.

[Slide.]

Is serum phosphate a valid surrogate in dialysis patients?

The FDA has accepted control of serum phosphorus as an endpoint in dialysis patients in Stage 5.

From the pathophysiologic perspective, there are no relevant differences in the role of phosphorus between

the dialysis and the pre-dialysis patients.

Once patients reach dialysis, the magnitude of hyperphosphatemia and the associated multi-organ dysfunction are amplified and possibly become irreversible.

Thus, it is important to start to treat hyperphosphatemia in CKD Stage 4 and 5 pre-dialysis.

[Slide.]

For which clinical outcomes have interventions targeting serum phosphate in the dialysis setting been shown to alter the risk in the manner predicted by the change in phosphate?

There are no randomized placebo-controlled trials demonstrating the reduction in serum phosphorus, reducing the rate of meaningful clinical outcomes in CKD patients on or off dialysis.

There are strong correlations, however, between serum phosphorus levels and meaningful outcomes, such as vascular calcification, myocardial infarction, the development of heart failure, progression of renal failure, and mortality.

However, because of the multiple variance including morbidity and other difficulties with chronic

renal failure, it will be necessary to have a non-treatment group in a controlled trial, which may be considered unattractive by most practicing physicians and perhaps unethical by some.

Perhaps with CKD Stage 4, patients with CKD Stage 4 have been treated for more than 40 years with phosphate binders. Treatment of patients with Stage 4 for hyperphosphatemia is the standard of the renal community, therefore, patient recruitment into clinical trials with a no-treatment arm would be problematic.

Hyperphosphatemia, on the other hand, has been found to increase the relative risk of death in Stage 5 patients in multiple publications.

[Slide.]

The FDA has asked all of you to review the risks in general and to consider any product-specific risks.

Specifically, minor gastrointestinal adverse effects are generally similar among the three products and are frequently known to be present in CKD patients.

Major gastrointestinal adverse effects, well, we have seen that all products have had rare major serious GI adverse effects.

There are a few drug-drug interactions, but they are pretty well characterized in the product package inserts.

In reference to interference with absorption of nutrients, there are no clinically significant product-specific differences to our knowledge.

There is minimal metal accumulation and no detrimental effects that have been reported.

The intolerance profiles are well defined; patients switch products for a variety of reasons. However, if intolerance to one binder occurs, the patients can, and do, switch from one to another binder and continue managing their phosphorus levels.

[Slide.]

Regarding the incremental benefits of using phosphate binders in pre-dialysis patients, I would like to make three main points.

First, as presented by the experts today, it is clear that increases in serum phosphorus above normal have significant clinical consequences.

Two, controlling serum phosphorus may delay the clinical sequelae associated with CKD progression.

Finally, the use of phosphate binders in pre-dialysis patients may reduce progression of renal disease, vascular calcification, cardiovascular events, and mortality.

[Slide.]

The safety profile of the phosphate binders on the market today are well established. Adverse effects are mostly mild and limited to the gastrointestinal tract.

In studies conducted to date, the safety profiles are similar in dialysis and pre-dialysis patients. In fact, the phosphorus burden in pre-dialysis patients becomes progressively worse due to the failure of the homeostatic mechanisms, and treatment in CKD Stage 4 and 5 pre-dialysis patients will help maintain that phosphorus balance.

[Slide.]

In summary, hyperphosphatemia is a key component in CKD mineral and bone disorder. Hyperphosphatemia presents before CKD has progressed to the point at which renal replacement therapy is required, and is considered by many, by most renal physicians, as an independent risk factor for cardiovascular morbidity and mortality.

The current KDOQI guidelines recommend early

detection and intervention of hyperphosphatemia.

[Slide.]

Today, physicians face the dilemma of attempting to be compliant with current guidelines even though it means using the medications off label.

Dialysis should not be the determining factor in the treatment of hyperphosphatemia. This patient population should not have to wait for outcome trials that may require years to accomplish, if, in fact, that can be accomplished.

This delay could result in substantial morbidity and mortality in patients for whom this treatment is withheld. Clinical trials with long-term outcomes and endpoints should not be a prerequisite for expansion of the indication for the use of phosphate binders.

[Slide.]

Given the pressing need to treat these patients, if this committee decides that further evidence to validate phosphorus as a surrogate is necessary, the following studies could be considered post-approval.

First, a Phase IV commitment by all three companies to long-term follow-up of patients with CKD in clinical studies.

Another option would be an NIH-sponsored clinical trial or trials.

We could also develop a registry with participation of all three sponsors.

[Slide.]

Is the evidence perfect? No, but we have shown a chain of logic in evidence to support the expansion of the current labels to Stage 4 patients with hyperphosphatemia and Stage 5 pre-dialysis patients.

Label expansion would allow for the FDA-approved treatment of hyperphosphatemia in CKD patients prior to and following initiation of dialysis.

[Slide.]

Thank you so much for your consideration and representatives of all three companies and the expert physicians who presented today are available to answer questions whenever you deem necessary.

DR. HARRINGTON: Thank you very much.

I would like to invite the public presenter to come forward.

Open Public Hearing

DR. HARRINGTON: If you could just identify

yourself.

MS. LeBEAU: My name is Kathe LeBeau and I have lived with kidney disease for the last four years, acquired as a result of primary hyperparathyroidism that produced a calcification of my kidneys.

I have been on home hemodialysis since April of this year and I am on the kidney transplant waiting list.

I also work with the Renal Support Network, a patient-run, patient-driven organization dedicated to helping improve the lives of people with chronic kidney disease and providing hope to fellow patients.

I am here today to share with you from the patient's perspective, some reasons that the use of phosphate binders should be extended to those in earlier stages of chronic kidney disease and the impact that could have in the lives of those patients based on my experience and that of other individuals that I know with kidney disease.

I see every day and understand all too well what it means to live with those things that result when treatment is delayed.

The Renal Support Network agrees with, and

supports, the National Kidney Foundation's KDOQI guidelines on the use of phosphate binders in Stage 3 and 4 CKD patients. If phosphorus or intact PTH levels cannot be controlled within the target range despite dietary phosphorus restriction, then, phosphate binders effective in lowering serum phosphorus levels should be prescribed.

As any renal nutritionist will tell you, dietary phosphorus is all too common in the every-day foods that we eat, such as dairy products and cheeses, dried beans and peas, colas, chocolate, but it is hard to control, not only because of the food that it occurs naturally in, which can at least be identified and excluded from the diet, but rather it is more because of the use of phosphates in preserving and processing foods, harder to discern as it does not appear by quantity on any food product at this time.

Even reading food labels closely is not always foolproof as you have to look carefully for phosphate in its many forms in the ingredient section. Finding the words that mean phosphorus, such as phosphoric acid, diet calcium phosphate, monocalcium phosphate, pyrophosphates, hexametaphosphate, polyphosphates, sodium phosphates, and so

on.

Complicating the situation, these ingredients used as preservatives may be more easily absorbed than phosphorus from natural food sources, so it is often difficult to reduce in the every-day diet.

Further, the very nature of some CKD cohort and causal conditions can result in an acceleration of the disease and the buildup of phosphorus in the body. With kidneys failing, their ability to regulate the delicate calcium-phosphorus balance is impaired early in the disease process before any symptoms of this appear.

Therefore, the damage begins long before any treatment is considered or started. Patients in earlier stages of CKD should be afforded the option of treatment for regulating phosphorus to prevent the advancement of symptoms prior to starting dialysis.

Because kidney disease and its effects differ from patient to patient, the decision should be based on the total medical perspective of an individual patient's health, and not on the arbitrary delineation of the start of dialysis.

With the anticipated burgeoning of the CKD

population doubling by 2010, these patients can benefit from the lessons learned from the existing end-stage renal disease patients who often suffer with irreversible conditions for the very reason that treatment was not started prior to the initiation of dialysis.

For example, my own calcium buildup as a result of the imbalance due to hyperparathyroidism resulted in not only the calcification of my kidneys and the start of the disease process, but it also left me with the painful problem of kidney stones.

A fellow patient, Bill Dant, of Utah, suffers from an even more marked difficulty as a result of too little, too late phosphate binder treatment. Not only is his vascular calcification so extensive that his blood vessels show up on an x-ray, but he lives with painful bone thinning and damage, as well as neuropathy in his extremities that has impaired his healing ability.

Other friends who are patients have lived with an increased risk of fractures, extreme weakness and fatigue, debilitating aches and pains, soft tissue calcification in their eyes and other organs, and coronary artery calcification that leads to a greater risk of cardiovascular

event and, as been pointed out this morning, we die.

The increasingly routine blood tests that screen for a wide range of CKD-related conditions, including out-of-balance calcium, phosphorus, and PTH levels are alerting doctors to people who have forms of this disorder even though they may be symptom-free and in the earlier stages of kidney disease.

Along with the Renal Support Network, I urge the Committee to embrace the current practice by many physicians and allow the use of phosphate binders earlier in the disease progression to manage the problems and complications that result from high phosphorus levels and therefore, hopefully, minimize life-long and debilitating conditions for these fellow patients.

Thank you.

DR. HARRINGTON: Thank you.

I have been reminded that I was remiss, that before that I was supposed to read the open public hearing script, so I will do so now, so I hope you will bear with me.

Both the FDA and the public believe in a transparent process for information gathering and

decisionmaking. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you have had with the sponsor, its product, and, if it is known, its direct competitors. For example, this information might include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting.

Likewise, the FDA encourages you at the beginning of your statement to advise the committee if you do not have such financial relationships. If you choose not to address this issue of financial relationships, it will not preclude you from speaking.

The FDA and this committee place great importance on the open public hearing process. The insights and comments provided can help the Agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics,

there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect.

Therefore, please speak only when recognized and thank you for your cooperation.

I apologize to the speaker for not having read that first, but do you want to declare any conflicts?

MS. LeBEAU: No.

DR. HARRINGTON: Okay. So, the speaker has declared no conflicts.

If there are no other speakers, I will read the concluding statement that the open public hearing portion of this meeting is now concluded and we will no longer take comments from the audience.

Questions to Presenters for Fresenius Medical Care, Genzyme Corporation, and Shire, Incorporated

DR. HARRINGTON: The Committee will now turn its attention to address the task at hand, the careful consideration of the data before the Committee, as well as those comments we heard from the public speaker.

In thinking about the time management issues, we

have an hour before we are scheduled to break at lunch, so what I would like to do is to move the section where it says "Questions" to now, and see if we can get our questions in before lunch.

If we can't, we certainly have sufficient time after lunch. We can address questions to any of the speakers from this morning. I, throughout the morning, have been taking notes and I have identified at least eight areas of general questioning that would include the following.

Discussion of the guidelines from the National Kidney Foundation, addressing the issue of what it means to define something as a surrogate, the appropriateness of randomized clinical trials in this arena, the feasibility of randomized clinical trials in this arena, issues related to practice variations, what the actual trials of phosphate binders in dialysis have shown us and taught us, what is the evidence for clinical outcome benefit with these therapies, and finally, perhaps as important as any of the other issues, what are the policy issues that we will be addressing.

We are talking about a specific issue, but as many of the times when we are addressing things with this

committee, there are broader policy issues to consider.

Since I am the Chair, I will take the liberty of throwing out the first series of questions. If I could ask Dr. Willis to come to the microphone, that would be fine, and maybe the Committee, we could concentrate first, if you have questions for Dr. Willis, and I will start.

In your presentation where you begin the discussion about guidelines, you note that you follow the AHRQ guideline process in terms of the methodology of developing guidelines.

I am not familiar with the Kidney Foundation guidelines as a cardiologist, but I am very familiar with the ACCHA guideline process. In our guidelines, we give recommendations, a class of recommendations, Class I being something we ought to do, Class III being something we ought not to do, and Class II being those indications for which there is uncertainty and gives practitioners some flexibility.

We also weigh all of our recommendations, weight of evidence A largely meaning that things come from randomized clinical trials, B observational data, and C expert consensus. I think you called it opinion during one

of your remarks.

Can you help me understand the NKF guidelines generally, and more specifically, can you give me what the guideline recommendations are specifically for the Class III/Class IV pre-dialysis patients with regard to the treatment of phosphate binders and hyperphosphatemia?

DR. WILLIS: Yes. First of all, as I mentioned, we have been developing clinical practice guidelines since 1995, and I would say that with each one we have struggled with, there is just a general paucity of evidence especially in the dialysis population.

We have always used an AHRQ center to help us develop our guidelines, but early on and through 2003, we used only two levels of guidelines, if you will, or strength of guidelines, and those were evidence or opinion.

So, I think that it would be fair to say that these are less stringent criteria than actually we have subsequently adopted. You know, we have used--well, we are now using strong, moderate, and weak--we have used A, B, and C, but our subsequent guidelines are actually stratified in that way and classified according to strength of evidence.

With respect to the bone guidelines, when we say

that something is evidence based, I think that you could construe that as generally speaking of a strong or moderate level of evidence, but the workgroup didn't delineate it that way.

When we say that something is an opinion, it is a recommendation that has been developed from examining the evidence, but I often have said that I wish we had called that "inference" instead of "opinion."

In other words, like, for example, when in Stage 3 and 4 chronic kidney disease, our workgroup recommended essentially maintaining a normal serum phosphorus level, I would say that the inference is drawn, and again I mean, you know, we have records of the discussion, but one thing that was inferred was that high phosphorus is definitely associated with bad outcome.

It is also associated with the development of secondary hyperparathyroidism, so given how deleterious these things are, we recommend keeping it normal, but there really were no, in other words, no randomized trials that spoke directly to that.

DR. HARRINGTON: So, let me just try to clarify this a bit more. In the context of the NKF guidelines, you

provide the practitioner some sense of how strongly you are recommending that they do something.

DR. WILLIS: Exactly.

DR. HARRINGTON: And how strongly is it recommended that phosphate binders be used for the treatment of hyperphosphatemia in this population?

DR. WILLIS: Actually, if you don't mind, I am going to turn to the actual guidelines.

DR. HARRINGTON: Data is always good.

DR. WILLIS: Well, as I said earlier, the statements themselves--I will read the statement for Stage 3 and 4 CKD.

DR. HARRINGTON: Thank you.

DR. WILLIS: In CKD patients Stages 3 and 4, the serum level of phosphorus should be maintained at or above 2.7 mg/dL, and that is an evidence-based statement, and no higher than 4.6 mg/dL, and that is opinion. So, it is the higher level that is opinion.

So, as I said, we did not couch the statements in terms of, you know, must, should, and should consider, but basically, we provide a rationale statement that helps practitioners assess how strongly they should consider doing

this depending on their patient's general condition.

DR. HARRINGTON: Other questions? Let me go to Emil, John, and then Mike.

DR. PAGANINI: It is going to sound a little bit foolish, but nonetheless, I would like to have these questions answered, if you could.

The first is who sponsored this particular guideline, was that NKF, and was that directly sponsored by industry?

DR. WILLIS: This guidelines development was supported by educational grants. The primary sponsor was Abbott Renal Care. We received additional contributions from Genzyme and Amgen.

DR. PAGANINI: Did any of these people sit on the panel at all, or have representatives on that panel?

DR. WILLIS: No. Actually, and I didn't have time in my presentation to go into this, but we have a fairly elaborate process for ensuring the independence of our workgroups. You know, people employed by industry are never permitted to sit on workgroups, and didn't in this case.

The workgroup members--although it is not a strict secret, the workgroup members are not informed who the

sponsors of a given guideline are, and the sponsors are never permitted access to any document or deliberation until the document is sent out for public review.

DR. PAGANINI: If I can keep going here.

DR. HARRINGTON: Absolutely.

DR. PAGANINI: CKD 3 and 4 were the recommended target audiences for control of phosphorus based on an opinion of the high phosphorus.

That opens up a population of 7.7 million to 11, whatever million people as a recommendation for some sort of intervention, possibly drug intervention in that population, and that is based on opinion.

Is there absolutely no evidence at all that there is any help in outcome from lowering the phosphorus as a direct association, as a direct effect as opposed to just an association?

DR. WILLIS: Again, I am sort of an expert on our guidelines, not specifically mineral metabolism, so some of the things, some of the later evidence was discussed this morning by the experts in the guidelines what is directly referred to in terms of controlling phosphorus in Stage 3 and 4 CKD is all related to control of PTH, and, you know,

secondary hyperparathyroidism.

DR. HARRINGTON: Emil, maybe what we can do is finish questions to Dr. Willis and then you can reask that question to the industry sponsors. So, John and then Mike.

DR. TEERLINK: Hi.

DR. WILLIS: Hi.

DR. TEERLINK: I was interested, I actually did read through the guidelines and I found them very interesting, at least the 2003 ones, I didn't get through the whole panoply of them.

I was interested to see that in 2003, the recommendation from the panel was to say that longitudinal studies evaluating phosphate binders and their efficacy side effects and impact on morbidity and mortality are needed, and that was 2003.

My cognitive dissidence warning signal has been flashing during this, because I hear that trials, on the one hand, that this is a very common disease with very high incidence of event rate and bad outcomes, but on the other hands, trials can't be done, and we have a major recommendation from a major body recommending that these trials be done.

It is now four years later and nothing has been done, so can you speak to that? I want to obviously ask others to speak to that issue, as well, but it seems a bit--and then I have a second question, as well.

DR. WILLIS: I can speculate that--I mean these trials are difficult to design, and there have been some attempts to, for example, intervene in one complication, in what is a very complex patient population, and trying to look at some hard endpoint, and those have, some surprisingly, turned out to be negative, and people say that, well, people speculate that that is because by improving one variable, you may not be able to improve, for example, survival on its own.

So, again, I mean more data is always better, but I am not in a position to say what would be the right study to do.

DR. TEERLINK: So, you were saying, for example, altering a single factor like phosphate hasn't been shown to actually have any beneficial effect even when looked at in a consistent manner.

The other question was is it your belief that there is actually a class effect to these agents? Do you

really believe we should be talking about--even in the guidelines, they begin to try to sort out a little bit between the agents--I am not trying to sow discord amongst the sponsors here.

But I think we are kind of stuck with this making a general recommendation for three different agents that have a bit different mechanisms of action or different molecules. From the guidelines standpoint, there seems to be a drift towards saying, hey, there may be differences between these agents.

From your position on the guidelines, what is your position on class effect for phosphate binders?

DR. WILLIS: You know, I have to say that the workgroup didn't really take a position on that, and I don't feel comfortable doing that. I mean it is discussed that some binders might be better for certain patients.

DR. HARRINGTON: So, John, that obviously is a question we will come back to with the sponsors. I want to make sure everyone gets in with Dr. Willis.

Jeff.

DR. KOPP: Thanks. By the way, KDOQI I think did an excellent job and it is widely appreciated in the

nephrology community, so I should begin with that statement.

DR. WILLIS: Thank you.

DR. KOPP: My question pertains to the rationale for having a different phosphate target for Stage 3 and 4 versus Stage 5, so just to restate that. For Stage 3 and 4, it is 2.7 to 4.6, and more liberal target, if you will, for Stage 5, of 3.5 to 5.5.

Is that based on less importance to achieve the lower level in Stage 5, or it's a matter of practicality or something else?

DR. WILLIS: This is actually discussed in sort of the clinical applications and limitations section of that guidelines, but it is basically that at the time that these were written, I mean since then a lot more data has accumulated suggesting that people should work even harder to get phosphate levels down, but at the time, 3.5 to 5.5 was considered a very stringent level, and sort of the lowest that the workgroup felt they could maintain, because you then get into with some patients severe dietary restriction and things like that.

Even in an evidenced-based recommendation, I guess I should just emphasize that there is judgment that goes

into it and that was the judgment, that basically, 5.5, the higher level, was below the lowest phosphate level that at that time had been shown to be associated with bad outcome, so that is how it got to be that way.

DR. HARRINGTON: Do you have a follow-up, Jeff? Okay. John.

DR. FLACK: Kerry, is it fair to infer that since studies, long-term studies were called for, even for morbidity and mortality, that the workgroup did not feel that Stage 3 to 4 patients were too difficult to study as a group?

That is one thing I kind of struggled with here. There is a huge plausible convincing argument about phosphate and animal data, a little bit of human data, but then there is this notion that they can't be studied because there is too many things going on.

I was just curious from the KDOQI perspective if you remember any deliberations by the workgroup about that issue.

DR. WILLIS: To be honest, what I remember, I mean they definitely did. I mean one of the things that we consider very important about the guidelines is that they

have stimulated research, and actually what I remember was the workgroup talking about that it would be very difficult to do a study looking at mortality and speculating on what various surrogate endpoints might be that they could look at.

But I--honestly, I would tell you if I did, but I don't remember what they were. As I said, I am sort of a guideline developer, not --.

DR. HARRINGTON: Michael.

DR. PROSCHAN: There have been some celebrated failures of surrogate outcome trials like the cardiac arrhythmia suppression trial, you know, showing that certain drugs not only didn't help, that suppressed arrhythmias, not only didn't reduce sudden death and cardiac arrest, but increased it.

That would not have been known had that trial not been done. I think a lot, just like in this situation, there was a lot of sentiment that it could only be beneficial to reduce arrhythmias.

So, what assurance do we have that the same thing isn't going to happen with phosphate binders?

DR. WILLIS: Well, I mean I think a positive

assurance in the absence of data is hard to come by. I mean essentially, you know, again I am really not here to speak about trial design. It is simply that it is our position that hyperphosphatemia needs to be treated.

DR. HARRINGTON: So, Michael, I think that you have hit one of the key questions that obviously we are going to come back to. What Dr. Willis' real specialty is in developing guidelines, and I want to make sure that we ask all the questions on the guidelines, and then we will get into this other.

I do have another question for you, Dr. Willis. One of the comments has been that everybody is using it anyways, so if everybody is using it anyways, you know, number one, why should you study it, and number two, how should you study it.

But the only piece of data I saw on that is 100 nephrology survey that said that 39 percent of them were using it or something like that.

I am curious. Does the NKF have more data on this? What is the actual use of phosphate binders in the group of patients that we are interested in? In other words, is there equipoise in the community, or is everybody

doing it?

DR. WILLIS: I am sorry, I really--we don't have more data and I don't know of more.

DR. HARRINGTON: Okay. Nelson.

DR. WATTS: I think that slide said that it was being used in 39 percent of patients, but 100 percent of nephrologists use it.

DR. HARRINGTON: One hundred percent, an industry survey of 100 nephrologists.

DR. WATTS: One hundred percent do it when appropriate and of their patients, if I remember the slide right, 39 percent were getting it. So, I doesn't seem like there is a disagreement among nephrologists.

DR. HARRINGTON: Jeffrey.

DR. KOPP: I was going to put this question off for later, but maybe I should ask it now.

A related issue is would approval for this indication expand the use? In other words, are there individuals who nephrologists would like to provide it to, but cannot for reimbursement issues?

I think Dr. Diaz-Buxo inferred something along those lines or at least made me think of that question. We

could hold that question for later, or you could address it.

DR. WILLIS: I actually have--I was contacted by a couple of nephrologists who had heard about this hearing to say that very thing, that if the indication were expanded, they could get it, you know, for patients who otherwise did not have access, but that is purely anecdotal.

DR. HARRINGTON: Michael.

DR. PROSCHAN: It seems like some of the arguments for earlier phosphate binder use would also apply to earlier stages than Stage 4, and I am wondering whether the guidelines considered earlier use.

I guess related to that is this might be a slippery slope and if you allow this without clinical trials in Stage 4, then, the next step might be to allow it without clinical trials in Stage 3, and I am wondering if the committee considered that and talked about it.

DR. WILLIS: Well, just to be clear, our committee really didn't talk about, you know, much about the label, certainly expanding indications, but in the slide that I showed, that showed the increasing prevalence, the prevalence of hyperphosphatemia is relatively low in Stage 3, so I don't think that that is much of a worry.

DR. HARRINGTON: Along those lines, you point out that part of the guideline development process is the implementation phase.

Does NKF actually measure the impact of guidelines? In other words, has the treatment of hyperphosphatemia changed over the four years since these guidelines were issued? Do we know that?

DR. WILLIS: Actually, we don't do it ourselves, but for dialysis patients, we have the U.S. Renal Data System, and, yes, markedly more patients have controlled calcium and phosphorus since our guidelines were issued.

DR. HARRINGTON: In that dialysis population.

DR. WILLIS: Yes.

DR. HARRINGTON: From the Committee, any more questions for Dr. Willis? Bob.

DR. TEMPLE: We didn't see the results of many trials, successful or unsuccessful. You seemed to refer to a number of trials that have attempted to modify phosphate, and have not--

DR. WILLIS: Oh, no. I wasn't talking about phosphate. I was talking about trials in later stage kidney patients.

DR TEMPLE: Okay. So, there really aren't any negative trials we didn't see, there just aren't new trials.

DR. WILLIS: Right. Sorry, I should have made that clear. I was talking about just the general principle.

DR. TEMPLE: I should also mention that Tom Bigger, one of the principal investigators for CAST, likes to tell everybody that when he went to places to tell people about doing the study, he was accused of grossly unethical behavior for denying people that critical therapy.

DR. HARRINGTON: The similar one is that when we launched the HERS trial, with hormonal replacement therapy, we were roundly criticized by the ob-gyn community for exposing women to the risk of no hormonal therapy.

Other questions of Dr. Willis before we allow her to sit back down?

[No response.]

DR. HARRINGTON: Thank you, Dr. Willis.

Go ahead, Emil.

DR. PAGANINI: I just have a practical question. If an indication on a product insert is stated on that product insert, does that open that indication up for advertising?

DR. TEMPLE: It sure does, and if it is not there, you are not allowed to promote it.

DR. HARRINGTON: Henry.

DR. BLACK: Yes. I didn't think it was fair to ask Dr. Willis to answer some of the questions I have, so I have been waiting for some of the others who might know more.

DR. HARRINGTON: As a matter of procedure, then, who from the sponsor group is going to direct the questions? Is there a single person?

MS. WILLIAMSON: I will.

DR. HARRINGTON: Perfect. We will start with Dr. Black since he jumped right in there and let him. Go ahead, Henry.

DR. BLACK: These are general questions and I don't know whom to address them to exactly, but we saw information from observational studies which make us think that everybody's phosphate should be below 2.5. That is a little hard for me to appreciate.

We saw some issues about the other end where we are talking about how well dialysis patients do when their phosphate is controlled without any appreciation really of

what you used to call the quality of dialysis and how well you are dialyzing somebody, whether that is, in fact, what we are seeing by the phosphate being well controlled.

I would like that answered. I also didn't see any of the studies that adjusted for diet. Now, they may have been there, but I didn't see those, and we need no better example of how clinical trials change practice than not only HERS, but the Women's Health Initiative, which is going to be the marker of why we need to do some things like this.

DR. HARRINGTON: Let me stop you there and let them answer those two.

So, the first--let me make sure I have it right, Henry--that you are interested in the question of has the quality of dialysis has improved, does that explain the reduction in phosphate?

DR. BLACK: Right, not necessarily how well you dialyze somebody, but within the groups that were dialyzed and had good phosphate, were there any other measures of quality of dialysis.

DR. HARRINGTON: And then the second question, you want to know, in all these analyses showing the effects of the phosphate binders, are they adjusted for diet.

DR. BLACK: Or the risk of high phosphate.

DR. HARRINGTON: Right.

DR. BUSHINSKY: Thank you for asking what is going to be an interesting morning I can tell. Clearly, dialysis adequacy is now measured very carefully. We have measures of dialysis adequacy, so called KT/V, and it is monitored monthly at least in virtually every dialysis unit.

It is clear that dialysis adequacy has improved over the years, but it is also clear that it really hasn't made any difference. There was a big study sponsored by the NIH, and I think it is one of the studies that Kerry was referring to that was negative, referred to as the HEMO study within the nephrology community.

The HEMO study tried more intensive dialysis against less intensive dialysis. There were small differences, but basically it was a negative study.

If we can get into dialysis and phosphorus, so we consume about a gram of phosphorus a day, absorb about 60 percent of it, so 600 mg of phosphorus are absorbed on a daily basis. We will do this by week. Multiply that by 7 and you have 4,200 mg of phosphorus that are net absorbed on a weekly basis.

Our dialysis patients, with each dialysis treatment, lose approximately 800 mg of phosphorus, so 800 times 3 is 2,400. You do the subtraction, if I can do that right, it is about 1,600 mg of phosphorus that must be bound on a weekly basis to prevent phosphorus retention. That is where the phosphate binders come in.

The people we are talking about now, the pre-dialysis patients have that 4,200 mg of phosphorus coming in every week, but don't have the dialysis to take it away. So, where does it go? So, diet, while it might make a little difference, you heard from our patient it is impossible to really restrict dietary phosphorus, get adequate protein, and so it is impossible to maintain balance.

DR. BLACK: That is not exactly my question.

DR. BUSHINSKY: Okay.

DR. BLACK: My question really is, in the people where we use this, and where it is indicated, and where keeping phosphorus under control seems to be beneficial, is there any way to say that people whose phosphate is well controlled are getting dialyzed better, not that all those things were going on?

DR. BUSHINSKY: There is no evidence that you are dialyzed better or worse, because the majority of phosphorus is removed in the first two or three hours of dialysis. Further dialysis removes much smaller amounts of phosphorus, so unless you are dialyzed six days a week, you can't remove the phosphorus.

DR. HARRINGTON: Henry, did you have another question?

DR. BLACK: About the effect of diet on people who are not on dialysis and whether that has been addressed.

DR. HARRINGTON: Are you going to add to Henry's question? Okay. Then, we will go John, John, Lynn, we will go around.

DR. HRUSKA: I would just like to go back to the science a little bit and amplify on this independence of dialysis quality and phosphate control.

The problem is that the exchangeable pool is slow, and so you bring the phosphorus down very quickly during dialysis, but then as soon as dialysis is over, the exchangeable pool continues to equilibrate and hyperphosphatemia reoccurs, so that it is almost impossible for a dialysis patient to be in balance unless he is

completely compliant to binders.

Now, if you lengthen the time of dialysis, then, you can control, so that you lengthen the time, so that the exchangeable pool kinetics work, then, you can control phosphorus.

In regards to the pre-dialysis situation where you were questioning that we should bring phosphorus down below 2.5, clearly, that is the point where you start reversing efficacy.

DR. BLACK: I wasn't recommending that. I was just looking at the Framingham data, which seemed to show that was the best phosphorus to have.

DR. HARRINGTON: Let me go to John Flack, then John Neylan, and then we will start with Lynn and go down on this side.

DR. FLACK: What about trials in this patient population that maybe are ongoing, not necessarily already published, is there a body of work ongoing looking at both safety and potential benefits, not necessarily on morbidity and mortality, but some of the things that you have been talking about today in regards to vascular function, pulse wave velocity, et cetera?

I am actually struck by how compelling the case is physiologically and logically and how these fall off the cliff with virtually nothing experimental in this population.

DR. HARRINGTON: So, are you asking, John, if there are ongoing trials that we have not yet heard about?

DR. FLACK: Right.

MS. WILLIAMSON: The answer to that would be yes. All three companies have looked at the use of their product in the pre-dialysis patient populations. We are at various stages of the clinical development programs, but all of the companies do have some data on use in this patient population. We look forward to being able to share those data with the Agency as part of our normal process for discussion around labeling.

We can say in terms of top line, most of these data have not yet been fully vetted for publication, which is why in addition we don't have an application in front of you that we are going through all of the details of these data.

But what we have seen, at least I can speak on behalf of Genzyme, is that in terms of top line results, in

terms of the endpoints that we have looked at traditionally with respect to lowering of phosphorus, we are not seeing anything significantly different than what we would have expected based on current clinical experience.

DR. HARRINGTON: Now you have got my curiosity up. Could you maybe describe what those clinical trials are that I think that John wisely asked about?

MS. WILLIAMSON: I am going to introduce you now to Dr. Jose Menoyo, and he is with the Genzyme clinical development program.

DR. MENOYO: Hi. Good morning. I am Jose Minoyo.

From the perspective of Genzyme, I am speaking only on behalf of Genzyme at this point. We have conducted an open label, multicenter trial looking at patients and CKD that are hyperphosphatemic, Stage 4 and 5, where they use sevelamer in these particular patients, and looking at the control of phosphorus.

We have demonstrated that you can basically bring a mean phosphorus around 6 mg/dL to a mean phosphorus through the KDOQI guidelines that Dr. Willis was presenting for Stage 4, lower than 4.6, 4.7.

DR. HARRINGTON: Are these randomized clinical

trials or are these open label, no control group?

DR. MENOYO: This particular trial was open label.

DR. HARRINGTON: Was there a control group?

DR. MENOYO: No.

DR. HARRINGTON: So, maybe we could hear from the other sponsors.

DR. PRATT: Yes, I am Dr. Pratt from Shire Pharmaceuticals.

[Slide.]

We have actually conducted an exploratory Phase II randomized clinical trial in CKD Stage 4 patients. This was a double blind, placebo-controlled, 8-week study in which we took patients with hyperphosphatemia and ran them in for a few weeks after appropriate dietary counseling to make sure that they actually remained hyperphosphatemic and that it wasn't just effect of diet that we were looking at.

It was, as I said, a small preliminary study. They were randomized either to receive active therapy with Fosrenol or placebo. There was a 4-week titration phase and a 4-week maintenance phase.

Efficacy, again, I am not going to show any real numbers, because we have just gotten these results in, they

haven't been through our quality process yet, so while the results we are going to report we believe to be accurate, we can't guarantee absolutely until we actually finish going through our QA process.

We saw statistically significant reduction in serum phosphate from baseline in the active group compared to placebo. The patients had mean phosphate values in the 5.1 to 5.3 range at baseline and these dropped to approximately 4.7 in the active group after 8 weeks of therapy.

We also saw reduction in urinary phosphorus excretion from baseline in this active group compared to placebo, as well as we did see modest reductions in parathyroid hormone levels.

[Slide.]

With regard to the safety profile in this patient population, again, there were 78 patients in the Fosrenol group, 41 in the placebo group. This was a placebo-controlled trial. Again, there was a high incidence of adverse events although not quite so high as we see in the dialysis population in similar clinical studies.

Again, the most common adverse events observed in

this study were GI events, and the only one that really stands out, in the Fosrenol treatment group compared to the placebo group is vomiting in which there was about 6 percent of the patients in the Fosrenol group experienced vomiting, whereas, only 2 percent in the placebo group.

As you can see for the rest of the abnormalities, they were pretty much the same in placebo, as well as in the active arm of the study. It was just a very small preliminary study as a basis for moving forward, but this is a randomized, placebo-controlled trial.

DR. HARRINGTON: I think there is probably a third sponsor that wants to weigh in.

DR. DIAZ-BUXO: Slide.

[Slide.]

Similarly, we have conducted some studies and I am presenting here the calcium acetate efficacy, which is a prospective multicenter randomized, double-blind, placebo-controlled, parallel arm study for 6 months.

That is why when we say that it is very difficult to recruit these people, we are not talking out of school. Many doctors really have very strong feelings about the size, they don't want to really bring patients, and it is

very difficult to gather the number of patients that we have gathered for this study.

The study population was adults with hyperphosphatemia with a serum phosphorus more than 4.6 and chronic kidney disease Stage 4, pre-dialysis, with GFR less than 30 mL/min. So, they were treated, the comparison was between calcium acetate versus placebo, and the dose was based upon the phosphorus level at the end of the washout.

The primary endpoint was a serum phosphorus target of 2.7 to 4.5, in other words, what we generally know as normal. The secondary endpoints, serum PTH, target of 70 to 110 consistent with the usual guidelines, and calcium-phosphorus product of 23 to 44.

[Slide.]

These are the subject demographics. As you can see, there were no significant differences. The GFR was within the parameters described.

[Slide.]

It was 46 patients, by the way, on the placebo side and 64 on the calcium acetate arm. Here, we have the average serum phosphorus, calcium-acetate treated subjects were 4.5 times more likely to achieve the target serum of

phosphorus than those receiving the placebo during the treatment, and that was highly significant.

[Slide.]

These was the common GI effect profile, and we have from two different studies. On the first one we have placebo versus PhosLo or calcium acetate. On the other one we have the data we have previously presented, but on the study I was just referring to, as you can see, nausea, vomiting, diarrhea, constipation was relatively similar or lower than what we have shown later on.

But the most important thing is that in some of those, the placebo arm actually had more nausea than the ones from the PhosLo, so it was pretty low.

Do we have another slide? No.

Thank you.

DR. HARRINGTON: Go ahead, John.

DR. FLACK: Did you allow use of vitamin D analogs in this study, and do you have any data on PTH suppression?

DR. DIAZ-BUXO: Yes.

[Slide.]

This is very preliminary. This has not gone through peer review, and, in fact, I have not reviewed these

data for statistical analysis. But the PTH data we have here on the pre-dialysis patients, as we can see, with the calcium acetate, it was clinically, definitely lower than on the placebo, 141 to 233, and certainly out of range.

The calcium-phosphorus product was essentially the same, and with regards to the vitamin D--do you have the data on vitamin D? They were very similar with regards to these two groups anyway, but I don't believe that parameter was controlled. I don't have the data actually.

DR. HARRINGTON: Did the other sponsor want to make a comment?

DR. MENOYO: Yes, I just want to correct something. Our study, we had a washout period, patients with hyperphosphatemia, there was a washout period where the patients basically the phosphates rise. After that, the patients were treated for 8 weeks and then discontinued the phosphorus again, and we saw the phosphorus basically coming up again.

[Slide.]

The patients basically treated with sevelamer achieved a significant reduction in calcium-phosphorus product and the LDL cholesterol, and the safety profile, if

I can have the slide, please.

[Slide.]

You can see calcium here, to your questions, the calcium at baseline was 8.5, at the end of treatment was 8.8. The PTH was 341 at baseline with a significant change at the end of treatment with a PTH mean of 319.

[Slide.]

As you can see here, patients at baseline vitamin D levels was 28.9. Patients were treated with 400 international units of supplement vitamin D every day, and the mean vitamin D levels at the end of treatment was 31.1.

[Slide.]

As you can see here, adverse events, nausea, constipation, diarrhea, vomiting are presented here, were very similar to what we have seen in the dialysis experience.

DR. HARRINGTON: Thank you.

I think one more sponsor and then I am going to move down to John Neylan.

DR. PRATT: Just a comment concerning the vitamin D. In our short trial, we did not use vitamin D supplementation. However, we did get vitamin D levels at

baseline in this patient population, and we found that 92 percent of the patients were either vitamin-D insufficient or deficient.

We did not replace it during the course of this therapy, but that was a finding just from the screening of the patients there, which I think indicates the importance of vitamin D status in these patients as well.

DR. HARRINGTON: Let me come down to John Neylan.

DR. NEYLAN: Thanks. I want to make two comments and then a question. The first comment. Regarding KDOQI guidelines and their call for additional long-term studies, I think it would be unusual to find in clinical practice guidelines today statements that didn't call for such.

I mean it is just sort of a natural request that we need longer term follow-up, and that goes to the need for further study, but not necessarily a requirement for such to achieve a threshold for a level of evidence for an indication.

The second, that John opened up, are there indeed any studies that industry is doing right now in this area Again, one might, in the earlier conversation, have taken the conclusion that nothing is being done, that there is an

absolute paucity of data, and, in fact, I think we are hearing now that there is actually a very active clinical research activity going on, on the part of all three sponsors.

I think that brings up the point number two that I wanted to make, was that when industry achieves a label and an indication, that doesn't mean that all clinical research stops and halts from that point on.

I would ask the sponsors if they, in their given labels now, with an indication for phosphate binder use in the dialysis population, if any of them are actually doing studies in that population now or if they all walked away, and I think I can guess the answer to that.

DR. HARRINGTON: Why don't we rapidly go through the three sponsors.

DR. PRATT: On behalf of Shire, yes, we still continue to do studies in the dialysis population. Again, the CKD not on dialysis population is an area of active research interest, as well.

DR. HARRINGTON: Before you sit down, I appreciate John's point about ongoing research, can you tell us if you are doing any studies looking at actual clinical outcomes?

DR. PRATT: We are not doing any long-term clinical outcome studies in dialysis patients at this time.

DR. DIAZ-BUXO: We are doing efficacy and safety studies, we continue doing them, but we are not doing any long-term clinical outcomes.

MS. WILLIAMSON: Genzyme continues to study our products both in the dialysis and the pre-dialysis patient population. Today, we are here because we believe that sufficient evidence exists to use within the context of the label of these products in the pre-dialysis population without the requirement of long-term outcome studies, because we believe there is a serious need for these patients to be treated if they are hyperphosphatemic.

DR. HARRINGTON: John, did you have a follow-up?

DR. NEYLAN: One, but maybe I will save it for later discussion, that has to do with the practical duration of follow-up in studies of this sort. One doesn't do randomized, placebo-controlled trials of the safety and efficacy of parachutes. There are similar issues at play here.

DR. HARRINGTON: Yes. We are going to have a whole discussion I suspect this afternoon on what kind of

trials, if any, could be done in this area. I appreciate your point.

I guess we have to let you jump in, Bob.

DR. TEMPLE: No, you don't, you are the Chair. You might want to come back, of course.

Just to pin it down, it sounds to me like the answer to John's question was that in the place where there is an existing claim, presumably based on perceptions, there are no ongoing outcome trials and there aren't likely to be any, because no one wants to do it.

So, you could take that as some implication that putting something in the labeling could affect the likelihood of conducting outcome trials. You can still do small trials of minor things, but our experience is I think that once something is in the label, it isn't easy to do an outcome trial.

In oncology, where we have approved a lot of drugs under subpart H, the follow-on trial to confirm benefit has often been in a somewhat different stage of the disease when not yet approved, so it is a real problem I think.

DR. HARRINGTON: Fair statement. I know people over here are waiting, but I am going to go down the row

here starting with Lynn and then we will come to Mike and Mike.

DR. STEVENSON: Thank you very much. I want to thank the presenters for a very elegant coordination of their presentations this morning, and we really do appreciate the precedent of your collaboration.

I have two questions related to the assessment of renal function if we put aside for a moment the issue of the mineral and bone disorders and talk about the vascular calcification issues and cardiovascular mortality.

You have certainly convinced us I think that high phosphate is bad and that very high phosphate is very bad, but we know a lot about the limitations of the estimates of renal function and I am wondering the degree to which high phosphate, if you adjust for PTH, is actually reflecting worse renal disease and if that is one of the reasons it is so strongly correlated with bad outcomes.

That is the first question is whether we are just looking at worse renal function rather than something specific about high phosphate.

The second question is if this high phosphate is so deleterious, why are we basically lumping it with our GFR

calculations, which we know are particularly inaccurate once you get lower, rather than saying that anyone who has renal disease, we want to treat these high phosphates.

Dr. Bushinsky showed this morning in Slide 81, in fact, that there are phosphates in the same level really throughout the range of kidney disease and why wouldn't we be just as concerned about a phosphate of 5.5 in somebody whose creatinine clearance is 55, for instance.

Those are my two questions.

DR. BUSHINSKY: Thank you for those questions.

[Slide.]

It is clear that, as you say, as kidney function deteriorates, there is an increase in phosphate. This is a quintile, so it is a fifth of the patients, are hyperphosphatemic virtually at any GFR.

We are concentrating on these patients because those are the patients that the pathophysiology supports, the fact that the phosphorus is absorbed, and not excreted, and that there is phosphorus retention.

Why someone with a basically normal or close to normal GFR is hyperphosphatemic could be related to some other disease such as a disorder of vitamin D metabolism, a

disorder of FGF-23, so I am not sure these patients need treatment as much, but as the kidney fails, and as we know that the hyperphosphatemia is part of the failure of the homeostatic mechanisms to excrete that phosphorus and deal with the phosphorus, it seems this is the ideal group to begin treatment.

If you say would you treat these patients, nephrologists clearly are.

DR. STEVENSON: And then my previous question, is the reason that it is related to cardiovascular mortality just because maybe it is a more sensitive indicator of renal dysfunction as you are moving down below 50?

DR. BUSHINSKY: If I could have the Kestenbaum data. It was corrected. This is a table under the figure for degree of renal function. In my presentation, I tried to say that corrected for degree or renal function. So, they removed renal function.

[Slide.]

This is uncorrected. Right below it there is a table in which they correct it on the paper.

DR. STEVENSON: I guess my question is how do we know how we are actually correcting it, because creatinine

clearance isn't necessarily all that precise for renal dysfunction as we get into the lower levels.

So, in fact, does it just mean that there is more renal dysfunction when you have the higher phosphate rather than, in fact, the phosphate itself is the only bad actor?

DR. BUSHINSKY: Clearly, more renal dysfunction causes more hyperphosphatemia.

[Slide.]

To the extent that they could statistically correct for the decline in the renal function, you can see after the adjusted, and that includes C, which is age, gender, primary kidney disease, baseline GFR, blood pressure, proteinuria, hemoglobin, and serum creatinine, there is still a good correction.

That is the best data there is that I am aware of, that it is an independent effect of phosphorus, not a fall in GFR.

DR. HARRINGTON: But you are getting into the key issue that I am sure that Michael down here can help us with, is how does one move biomarkers to the issue of surrogacy because a lot of other stuff is at play here, and if you believe, you know, the classic DeMetz paper, you

know, is it a straight line from the biomarker to the clinical outcome, or, in fact, are there multiple other ways that the clinical outcome gets achieved.

I think that you are getting right to that point.

DR. McCULLOUGH: Lynn, I will just adjust the cardiovascular data that I showed. I was really careful to show just adjusted hazard ratios and everything I showed was adjusted for the baseline estimated GFR.

But when you look at the literature in general that is linked reduced estimated GFR to adverse outcomes, the big unmeasured confounders in most of those data sets are phosphorus and PTH.

So, for instance, in some of the valvular literature, and valvular calcification, we say we saw a relationship between CKD and valvular disease, but we didn't measure phosphorus or PTH.

So far those are more likely to be missing. For instance, in Framingham, in this study, they didn't have those data in the studies. It is more of an unmeasured confounder in the overall global. There are thousands of papers now showing estimated GFR and adverse outcomes.

So, everything I showed you, I attempted to be

really tight and say, okay, in the ones where they have gone to measure PTH and phosphorus, they always have the estimated GFR.

DR. HRUSKA: I think perhaps a good way to approach your question is to consider other hyperphosphatemic syndromes and question whether or not hyperphosphatemia in those syndromes has the same outcome.

I think a good example of this would be to consider FGF-23 deficiency. We now know that there is a human disease associated with FGF-23 deficiency in an animal mouse model. So, the phenotype is hyperphosphatemia and there is heterotopic ossification in the mouse model simply correcting the serum phosphorus reverses the heterotopic ossification.

The phenotype of the human deficiency is hyperphosphatemia and a syndrome called tumoral calcinosis where not only is there some vascular calcification, but there is tremendous periarticular accumulation that is very painful.

DR. KOPP: I would like to ask the presenters a couple of questions about toxicity. We have been told that these agents are very safe, and I suspect in general that is

true.

Could we have Slide CC-100 up, and I think Dr. McCullough may have been the presenter for this slide or whoever want to address it, but the point was made during the presentation that only with sevelamer therapy did GFR fall.

Any comments about that, if I am reading that correctly?

DR. BUSHINSKY: No, I just presented the data as it is. I think the fall of GFR of 26.3 to 24.1, while it was significant in the paper, is not a very impressive number.

DR. KOPP: Would you remind us the time, is this a 6-month study?

DR. BUSHINSKY: This was a 2-year study.

DR. KOPP: It is striking, then, that the other groups didn't change over a 2-year period, but I guess the question in general is, is that a signal that has been seen in any other sevelamer studies, or is that unique to this one.

DR. BUSHINSKY: No, that I am aware of. Perhaps the sponsor can address it.

DR. MENOYO: No, we haven't seen a decrease in GFR secondary to sevelamer use in patients on either dialysis or CKD.

DR. KOPP: My other question was about lanthanum accumulation. I have to say I know nothing about this, but I do notice that levels accumulate in liver and bone, and the question at least needs to be asked and hopefully answered, if we expand the indication to the additional 10 million people that I think if we took it to Stage 3 and Stage 4, and treated them, not for a few years since we know that the dialysis survival is so much shorter, but for 10 or 20 years, are we putting those patients at any kind of risk.

DR. PRATT: First of all, before we go into the lanthanum issue, just sort of a correction on the prevalence. While there may be that many patients who are in that stage, approximately, only a small proportion of them at the moment are hyperphosphatemic, which is the point that we are getting to.

[Slide.]

With regard to lanthanum accumulation, it is true that a small fraction of each dose of lanthanum or Fosrenol is absorbed, it is less than 2,000th of 1 percent of a dose,

and when it is absorbed it is highly protein bound and it is cleared predominantly by the hepatobiliary route. Urinary excretion is not a major route of elimination of lanthanum, so it is not surprising that you actually see lanthanum in the liver, because that is its major source of excretion.

With regard to the liver effects there, the lanthanum that is circulating in the plasma and cleared through the hepatobiliary system is cleared predominantly by an endosomal/lysosomal route. We have demonstrated this in animal models, we haven't done it in humans, because of the high endogenous fecal lanthanum content that you get under normal circumstances.

Lanthanum is present in your diet, and because of the small amounts that are present, you can't really do a mass balance study in humans with this. However, in animals, where we have been able to saturate the mechanism, you can actually follow the lanthanum through the endosomes into the lysosomes and into the biliary tract and see that it is going. You never see any location of lanthanum extralysosomal in these animals.

We have also looked in clinical patients, and we have studied--Fosrenol has been one of the most extensively

studied phosphate binders prior to registration. We had over 2,250 patients enrolled in our clinical studies, which went from--we have got studies of 6 month, 1 year, 2 years. We have got follow-up of patients between 3 and 6 years of follow-up.

In that group of patients, we have not seen any evidence of effects on liver synthetic function, on acute hepatic injury, or on expiatory functions that have been noted.

The same thing in our animal models, even in our toxicology studies, which were quite extensive, we have seen no effects of lanthanum in the toxicology models.

Now, bone, again because lanthanum is very similar to calcium in its chemistry, it actually is not surprising that it does deposit in bone. As part of our clinical program, we have done extensive bone biopsies. We had over 500 bone biopsies that we have done in patients, many of them with baseline and 1 year and 2 year.

We have done a subset of patients who have been treated continuously with lanthanum for 4.5 to 5 years, who has a small number of biopsies, but nonetheless, we were able to do that, and we have also looked at patients who

were treated with lanthanum for a period of time and then withdrawn from therapy.

We basically show no evidence of adverse effects on either static or dynamic bone parameters compared to standard phosphate binder therapies, which included predominantly calcium based, but however included also some patients with sevelamer.

Lanthanum can be slowly cleared from bone after discontinuation of therapy.

[Slide.]

This is just an example of the clinical data that we have. Again, in the comparator arm is patients who have not been treated with lanthanum, and then the boxes are lanthanum carbonate patients.

You can see that there is a small accumulation of lanthanum over a period of time. If you take that regression line and you look at the 15-year prediction, with the highest bioavailability that we have observed in any human, and assuming that you get no clearance, you get a value that could be, after 15 years, as high as 46 mcg/gram.

In contrast, in our toxicology studies, where we have actually been looking for adverse effects, and we have

not seen any in bone, but the highest levels we have ever been able to achieve in animals have been up about 94 mcg/gram in toxicity studies with no effects on osteoblasts, osteoclasts, or other functions.

Go back to the previous slide, please.

[Slide.]

One other last little bit about accumulation. Again, because lanthanum itself is a very fine powder, and we are dealing with very, very low levels, you have to be very careful about contamination in your studies.

All of our studies that are done to GLP quality, are done administering lanthanum orally as gavage, so as to avoid the contamination of skin.

There is no evidence that lanthanum crosses the blood-brain barrier, and we have done a cognitive study in patients on dialysis where we have actually followed cognitive function in these patients for two years, and we have not seen any difference from patients who were treated with all the other phosphate binders in a cohort that was followed at the same time.

So, we believe that we have extensive evidence that extending the use to this patient population would

certainly confer no additional risk over the time that we are studying. We do continue to follow patients long term and we are trying to follow patients for now we have got some approaching 7 years.

Thank you.

DR. HARRINGTON: It is 4 minutes to 12:00. We will come back at 4 minutes of 1:00 and get started. Nelson, we will start with you for questions, go around the table, and then Michael and Michael.

[Whereupon, at 11:56 a.m., the proceedings were recessed, to be resumed at 12:56 p.m.]

AFTERNOON PROCEEDINGS

[1:00 p.m.]

DR. HARRINGTON: So we are going to pick up where we were before lunch which was with the Committee able to ask questions to the sponsor or other speakers from the morning. I want to make sure that I pay attention--I know everybody has questions that they want to address.

Again, I will ask somebody from the sponsor group to coordinate that.

We are going to start with Nelson, go down to John and then we are going to go around the table. We will also ask Ms. Scott if she has any comments that she would like to make along the way.

So, Nelson, we will start with you.

DR. WATTS: I have two questions unrelated. One is the actual prevalence of the problem and what is being done about it. So how many patients are there out there with Stage 3 and Stage 4 CKD who have, and how many of those have hyperphosphatemia and how many of those are currently receiving off-label treatment with phosphate binders?

The second has to do with pathophysiology. You focused on phosphate which is, for obvious reasons, but you

mentioned that parathyroid hormone and calcium are also important. I haven't seen anything to try to dissect out other ways of controlling PTD, for example, with vitamen D analogues or calcium-receptor agonists and that influence on calcification and vascular-disease mortality.

DR. HARRINGTON: So a pathophys question and a prevalence question.

DR. HRUSKA: So, with regards to the prevalence, several speakers could speak to that but, because of the pathophysiology, perhaps I will answer the first question. So it is 11 million in Stage 3 and 4. The incidence of hyperphosphatemia in the Stage 4 population where the total number now drops to about 400,000, the prevalence, or the incidence, of hyperphosphatemia in that group varies between studies between 8 and 20 percent.

So the estimates, then, of the population that, or the cohort

DR. HRUSKA: So the cohort that we are proposing to treat is between 80,000 and 120,000 patients.

DR. WATTS: Do you know how many of those are on treatment now off-label?

DR. HRUSKA: The estimates from that small survey

was that about 50 percent of those patients, well, it is actually less than 50 percent, about 40 percent of those patients are being treated.

DR. HARRINGTON: While you are on the subject, can I just ask, from the nephrology perspective, if 40 percent are being treated, why aren't the other 60? Is there something about the patients that people have decided they shouldn't be treated, or is it a lack of education in the nephrology community about treating these folks?

DR. HRUSKA: I will put that back to you. How come after a heart attack, patients don't get prescribed ACE inhibitors or afterload reduction or beta blockers?

DR. HARRINGTON: It is a series of issues, as you well know, and so I am assuming that your answer is that there is a series of reasons that have to do with medical contraindications, education of the clinicians, compliance of the patients, et cetera. Is it that same?

DR. HRUSKA: The two big issues are compliance of the patients and education of the physicians. So, again, most of these patient now pre-dialysis are not in the care of nephrologists. And secondly, because the drugs are not labeled, there is probably a decrease in usage.

What Dr. Willis was able to tell you is that as an effect of the KDOQI guidelines, there has been a change in practice, and so the number of patients pre-KDOQI that met guidelines for hyperphosphatemia were less than 20 percent, but with guidelines, it is only up to about 40 percent, this in terms of phosphate control. So, we have an extreme way to go here.

DR. WATTS: Before we leave that let's bring up CC-108, which is this Biotrends. I am not sure that is the best source of data, but I think I understand this differently from the way others have described it.

So, the way I understand this is that, in the little footnote, it says 100 percent of the nephrologists say they prescribe phosphate binders for Stage 4 patients who have hyperphosphatemia, and then my reading of the middle bar is that in their practices right now, 39.1 percent of patients are being treated.

So, maybe there is a selection bias, they are getting a higher percentage of Stage 4 patients who have hyperphosphatemia if the true prevalence is somewhere between 8 percent and 20 percent, but I don't think that says that they are not treated.

DR. HRUSKA: Just because every nephrologist says that he prescribes, it doesn't mean that his entire practice is on therapy, and that is where the discrepancy comes.

DR. WATTS: Correct, and it doesn't mean that all patients with Stage 4 or Stage 3 disease have hyperphosphatemia, so I don't think this tells us anything about the --

DR. HRUSKA: No, it is just the hyperphosphatemic patients, right, it is just the hyperphosphatemic patients.

So, could I get to your pathophysiology question, then, Dr. Watts.

[Slide.]

Your points are very well taken that this is a multifactorial problem, and, in fact, our initial target, parathyroid hormone, which has been approved for the endpoint for reduction in serum phosphorus prior to the expansion of the pathophysiology has shown itself actually not to be extremely well correlated.

So, patients, for instance, with low turnover osteodystrophy, who have very low parathyroid hormone levels, still tremendously vascular calcify. The role of parathyroid hormone in the cell in question is very complex,

because as you know, and the cardiologists on the panel well know, is that part of your constitutive vasodilatation is due to PTHrP.

So, this shares the same receptor with PTH, so in hyperparathyroidism, one of the actions of the disease, of excess PTH levels, is to disable the action of PTHrP by receptor downregulation. So, as you get continued high levels of PTH, you lose the PTH receptor, but the effect in the vasculature is that now you have lost tonic vasodilatation or a component of it.

So, how much of the action of PTH is reversed by the lack of activity of PTHrP? The bottom line is that PTH does not correlate very well. Calcium is an important components, but surprisingly, calcium phosphorus product has not withstood the initial concepts that it was actually the big problem, that just elevated products would lead to passive precipitation.

That has not held out, and in fact, calcium phosphorus product is weaker than the serum phosphorus alone even though calcium is a potential player. So, you can see that in the work from Giacelli here, she has shown that phosphorus is an obvious regulator through Pit-1, but

elevated calcium actually, so hypercalcemia is also a problem.

Hypercalcemia would rank below serum phosphorus, PTH would rank below the two of them.

DR. HARRINGTON: Are you satisfied, Nelson?

DR. WATTS: Yes.

DR. HARRINGTON: John.

DR. TEERLINK: I have three groups of questions.

The first is in regards to the risk-benefit profile of this. When we are asked to look at a surrogate, there are two kind of traps you can fall into. One is that the relationship between the surrogate and what you think is the ultimate endpoint is not really a straight line which has been already alluded to, and I am not sure we have actually convincingly demonstrated there is such a straight line there.

The other problem is that even if there is this straight line with the surrogate to the outcome, that along the way, there may be things that these agents do that you didn't plan on, and so there may be safety concerns that outweigh that.

Now, in a hemodialysis patient where you have a

higher risk in a high-risk patient, some of those can be mitigated. You are accepting a higher level of risk.

When you go to lower risk patients, the question is, first of all, has that risk really been evaluated. So, when I looked through the package inserts, I saw, for calcium acetate, there is major concern over hypercalcemia, the lanthanum.

We talked about the increasing bone levels, and one of the comments in the package insert at least is it is saying that no steady-state had been achieved in up to 4.5 years of lanthanum. I know you have data out further, and I appreciate you showing that still.

The comparison to the dog data seems a little concerning because that is four weeks up to 194 mcg per whatever the unit was. That is 4 weeks of exposure. I don't think we understand what occurs over greater amounts of time as you have 15, 20 years of exposure.

Then, for also lanthanum, there is an 8-fold increase in dialysis graft occlusion, raising the question of an increased incidence of thrombosis in that area, is there some interaction that may actually increase thrombotic events that we aren't seeing in the high-risk patients, but

in the low-risk patients those events could be important.

Then, sevelamer also has a 2-fold increase in hypertension, and we have had recent experience with drugs that one of their side effects may be the increase in blood pressure, reducing their beneficial effect on a surrogate.

So, taken in totality, I have concerns about these safety issues, and I am interested in knowing what your experience is in the pre-dialysis patient group for long-term follow-up for safety outcomes. I am talking about safety, not just adverse events, but myocardial infarction, thrombotic events, these kind of issues, and what actually the event rates have been.

MS. WILLIAMSON: As we consider how to answer that question, one piece that I could address is your question on the long-term follow-up for the pre-dialysis patients. Given the fact that the products are not labeled for pre-dialysis patients, we are not in a situation where we have the access to long-term follow-up for those patients.

That is certainly something that we are interested in looking at in terms of options, but I am going to have Dr. Malluche answer.

DR. TEERLINK: I am sorry, so the implication is

that you need to have labeling to follow up on those patients?

MS. WILLIAMSON: No, we don't have access to those patients in a long-term study, so we don't have data, hard data in that patient population.

DR. MALLUCHE: Let me address the topics that we have in discussion here. Of course, you have heard all these elegant data regarding the signal molecule, the calcifications, all this. All these things happen when the patient starts to lose, let's say, 50 percent of the kidney function all the way down to about a GFR of 25 or so.

During these times, the patient is not hyperphosphatemic. The kidney works overtime to avoid hyperphosphatemia by increasing the fraction excretion of phosphorus. That is what you see when you look at the GFR of about 50.

Serum phosphorus levels don't go up, but fraction excretion of phosphorus goes up, and goes up at the expense of increased FGF-23, which then lowers 125, and you have 125 deficiency, and you also have increased levels of parathyroid hormone.

These are all compensatory mechanisms that

obviously have negative effects by itself, but what we are talking here about is the hyperphosphatemic patient, which is way further down the road. Those patients are in Stage 4 or in Stage 5, as you have heard, and their expectancy, the duration from them to reach dialysis requirements is somewhere, let's say a year, year and a half.

So, in consideration for safety, when you compare it with dialysis patients, you may add a year or a year and a half of treatment, but not many, many years as it might appear from the way I understood you.

If you look at the safety profile, for example, with lanthanum, actually, initially, lanthanum was shown not to be absorbed at all. It was found that the heavily uremic intestine is somewhat leaky, and that is how lanthanum makes it into the circulation at all. Before, it is practically non-absorbable.

The amounts in bone even though you are correct it is not a steady-state, but if you project it, you would have to be a 14 years before you are at 40 percent of those toxic ranges. So, definitely, I think we are in a time period where toxicity is highly unlikely.

DR. PRATT: Just with regard to that, that was our

human data with the bone biopsies that we did obtain. In our animal toxicology studies, that was the highest levels that we could achieve, you know, looking for toxicity completely.

However, we do have full life carcinogenicity studies in animals with various doses, and there are no effects that you see on bone structure or any abnormalities in bone in those animals, and we have done the full analyses of all those bones in two species, full-life, with no effects at high doses.

DR. DIAZ-BUXO: With regards to calcium, I want to bring two things. First of all, I think Dr. Malluche made a very practical point, and that is, we are talking about 1, 1.5 year, that we are asking for extension of the indication. So, it is not really a long time.

When you consider that we have something like three-quarters of a million patient years with calcium acetate on dialysis patients, should we really expect to really have more problems in the pre-dialysis patients?

Well, the answer is these people are getting a serum calcium with practically every single visit or every single follow-up, yet hypercalcemia not only is well known,

and it could be related to the additional amount of phosphorus.

The guidelines make it very clear that we should not exceed a certain amount of the total calcium absorption from both dietary and from the phosphate binder plus we have some guidelines out there.

Thirdly, it is correctable, and there are some disciplines to do so by reducing the dose, anyway We feel pretty confident anyway that 1 to 1.5 year of the potential increase in the small fraction of patients who may have some problems, you know, it is minimal compared with what we feel are the clinical benefits.

DR. HARRINGTON: Before you sit down, though, the group here this morning has heard about this is a relatively small group, but it is part of a much larger group with Class III and Class IV, Stage 3 and 4 chronic kidney disease, and in that group, we know, as has been mentioned by Dr. McCullough and others, high prevalence of coronary disease.

We also heard just a few minutes ago that one of the challenges is that it is not nephrologists caring for this earlier group of patients, and it is also not a group

that is covered under the End-Stage Renal Disease program, and so their access to care may be different, et cetera.

So, I actually am worried about extending something to a, quote "less sick" population in whom at least from what I have heard I don't have confidence that I understand how the effects of aspirin interacting with this class of drugs. I have not heard about ADP blockades or drugs like clopidogrel. I have not heard what happens to statins.

So, I think to say that there aren't other questions in a less sick group of patients whose care may not be as regular as the dialysis population for whom it is paid for, I think it is trivializing the fact that a lot of these people are going to be out there and not get the kind of adequate follow-up, the regular blood draws, et cetera.

DR. DIAZ-BUXO: I cannot argue with the common sense and the good question that you are really asking. Obviously, you know that I don't have any answers, none of us have answers, those studies have not been done.

However, I might bring another argument, and that is because those patients don't have access to care, because their insurance company may not pay for an acceptable and

FDA-approved phosphate binder.

What are they on? They are generally on calcium carbonate. Just to go back to the calcium issue, where the absorption is twice as much, where efficacy per pill is half as much, for hyperglycemia, may be more absorption is higher we know that much, that it can be definitive.

So, the alternatives are not really any better. So, once again, it would be wonderful to really have all the knowledge, it would be fantastic. The question is, is this a real high priority to do that, or are we talking about a very small population for a short period of time. We are not talking here about 11 million patients. We are not talking here about an immense amount of money.

We are talking here mostly about being consistent with the intention of treatment, and I know that there may be many flaws from the scientific point of view to these arguments. I think that most of the appeals that we are making are to clinical sense rather than high scientific level studies anyway.

DR. HARRINGTON: You know, the number of times that clinical sense has led us down the wrong path is legendary, so let's be careful about that.

DR. DIAZ-BUXO: You are perfectly right. However, when we are talking about many of the examples that the FDA have used, it is quite different from really something that, you know, active ingredients is considered generally safe.

DR. HARRINGTON: Jeff and then John. I guess, John, you had the mike, I am sorry, so go ahead.

DR. TEERLINK: The point is, though, that we really don't have much safety experience in this patient population group, and we don't know what is going to happen, and it may be safe, it may not be.

Do you have a response to my other question?

MS. WILLIAMSON: On behalf of the sevelamer question, we would like to at least answer your question.

DR. HAAS: You referred to the label and a difference in the frequency of adverse events in hypertension, of hypertension and Renagel and comparator, and I just did want to address that, because we have considerable data on pre- and post-treatment, beginning of study and end of study by patient information, and while the adverse event reports, that is 4 patients difference, there was nothing to support in any of our studies a difference in hypertension or blood pressure levels.

It was just the illusion that there is a hidden problem.

DR. TEERLINK: Well, the flip side of that is that the number of patients that that is based on is a very small patient database, so we don't know I think is the point I am bringing up, and on the evidence that I have in front of me, you see a 2-fold increase in hypertension in patients with a high incidence of cardiovascular disease without a control group, you know, for subsequent studies I don't know how to deal with that data.

DR. HAAS: I understand your point. It is just that you have to look at the actual numbers of the blood pressure readings, and there was nothing that supports that. That is an adverse event table, and those are very subject to considerable variability. There is better evidence in those same trials.

DR. TEERLINK: So, that was a bit of the safety thing. One of the other issues along with safety is--I am sorry, I didn't want to cut you off.

DR. MENOYO: I just have one other issue. We showed the data on CKD on the 8-week trial, and we didn't see any increase in hypertension in that particular trial,

8-week treatment. It is not a long-term follow-up, we are asking the CKD population.

DR. TEERLINK: And that comparator was?

DR. MENOYO: There was no comparator in that particular trial, so baseline information.

DR. TEERLINK: Which we know that blood pressures usually go down during patients when they are treated in trials because they get better care and usually other medications are adjusted.

DR. MENOYO: I agree with you, but we also --

DR. TEERLINK: Again, with our control group, I just don't know how to interpret it.

DR. MENOYO: We also know that one of the major causes of CKD that is typically seen in this patient population is hypertension, as well.

DR. TEERLINK: One of the other issues that has been kind of glossed over is the issue of the drug-drug interactions just because, okay, you can just delay when you give the drug, you know, you wait two hours for one drug, and Lynn had actually brought this up, as well, potentially, and I think, you know, for these patients who are on multi-drug regimens for hypertension and diabetes, delaying a drug

by two to three hours and having to do that with every dose of your medication is not an inconsequential aspect of your medication therapy.

So, that is pretty much my issues on the safety. In terms of the beneficial side, as I mentioned, I am not sure that we have actually seen any kind of data to support a coherent beneficial type, but I would like to bring up Slide CC-101, because this is the one study that was actually brought up.

This is the Russo study that was brought up, and this study was presented by at least two people and referred to by a number of people during this discussion as showing a beneficial effect. It is falling into a common statistical trap.

The trap is that if controls are different over time, and sevelamer is not different over time, therefore, sevelamer is different than the controls, and I was shocked. I said, well, gee, that is not right, you can't do that. Surely, they must have looked at that the right way, which is to compare between the groups.

Sure enough, luckily, they did in the study, and they actually showed that there was no difference between

control, sevelamer, or calcium carbonate in terms of your total calcium score, and that is figure 3 on page, whatever it is, of this actual article.

So, I was a little disheartened perhaps that this slide was presented at least twice.

DR. BUSHINSKY: Slide on.

[Slide.]

DR. TEERLINK: Yes, this is the slide that I am referring to, and there is absolutely no difference between these. There may be a trend, we don't know, but you can't present based on 29, 28, and 27 patients that there is a difference in total calcium score here. It is not significant. There is no difference, and those are standard error bars, as you will refer to.

DR. BUSHINSKY: Yes.

DR. TEERLINK: I think the one trial that we had, that showed maybe--a randomized trial that showed maybe there was a beneficial effect actually did not, and I want to give you the chance to clarify that or at least agree with my point.

DR. BUSHINSKY: My presentation on the previous slide was reading directly, was copied directly from the

text of the paper.

DR. TEERLINK: Yes, that is figure 2, which is right next to the figure.

DR. BUSHINSKY: Right, which is right next to the figure, and they say that the total calcium score significantly increased in patients on the low phosphorus diet alone, to a lesser extent in calcium carbonate-treated patients, and not at all in sevelamer-treated patients.

DR. TEERLINK: And then they go on to say there is no significant difference in the mean, absolute, and annualized absolute values of the total calcium score between any groups.

DR. BUSHINSKY: Right. Okay.

DR. TEERLINK: So, there is no difference between these groups, and that is not an appropriate statistic to look at the question.

DR. BUSHINSKY: Thank you.

DR. TEERLINK: The other issue in terms of the data, from the 1998 package insert, there is a statement in the Indication Section saying the safety and efficacy of an agent in chronic kidney disease patients who are not on hemodialysis have not been studied.

I think we have seen here that since 1998, that statement is still true, and that is concerning to me. I hear then when I get the packet, I get these reasons, there are three reasons given for why we can't do a clinical trial.

First, is that an outcomes trial would entail a complex design where you have to balance all these confounding variables. Well, that is what usually a randomized trial is for, and those usually are balanced by randomization.

The second point is that it would require a large number of patients and a long follow-up time. Well, yes, that is perhaps true, but that is similar to every other cardiovascular trial we have ever had to do.

Third, that it would require evaluation of normalizing serum phosphorus and all this, but it is assumed that all you need to look at is phosphorus, and there is no real mention of an outcomes analysis here, and I think the message for me at least is loud and clear that if we are going to expand this use, I would want to see real outcomes and real safety signal in terms of what happens.

We have given the examples of estrogen replacement

therapy and multiple other things that have shown that we can't just extend these and can't just use surrogate markers.

I don't know if there is any response to that, but I think it is silly to say that you can't do these trials. We have done them. We have done them in many other areas.

DR. HARRINGTON: Do you want to respond to that?

Are you going to address the issue of can you do a clinical trial?

DR. McCULLOUGH: Yes, just a word about the clinical trial, and I love those comments, John. Because this is a circumstance, in a randomized trial, randomization will balance independent factors quite well.

We have tried to demonstrate to you that these factors are all biologically interrelated, so if you squash down phosphorus, then, PTH comes down, but if you give a calcium-based binder, then, calcium in some patients can go up, but if you give a non-calcium-based binder, it can go low, and some others.

The circumstance that exists is that some of the vitamin D products are actually approved for use in pre-ESRD CKD, so they are already approved for use to treat part of

this CKD-MBD problem on the hyperparathyroidism aspect of things.

So, in my view, what the clinical trial would need to be is not singular product versus placebo, but probably metabolic control of the problem with multiple agents, and then looking at some type of intermediate variable like calcification and then the binary outcomes in the future.

In my view, that is kind of the ideal clinical trial, but they are caught in a funny situation, the sponsors are, because part of the therapy for CK-MBD is already approved and in use, and in the guidelines. Part of it is recommended by the guidelines, but not approved, and that is the segment being discussed today, so it's a funny circumstance.

Clearly, a clinical trial needs to be done, but as you can see, it won't be a single sponsor trial--it will be a single sponsor trial, but have to leverage multiple different agents or be NIH sponsored.

DR. TEERLINK: Then, on circulatory committees, we make a distinction between effectiveness versus efficacy. I am sorry.

DR. MENOYO: I am sorry, if I could go back to the