FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE (CRDAC) MEETING

Virtual Meeting

Wednesday, November 16, 2022

9:30 a.m. to 4:24 p.m.

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

LaToya Bonner, PharmD

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Jacqueline D. Alikhaani, BA

(Consumer Representative)

Volunteer and Advocate

American Heart Association

Los Angeles, California

C. Noel Bairey Merz, MD, FACC, FAHA, FESC

Director

Barbra Streisand Women's Heart Center

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Distinguished Professor of Medicine
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(Chairperson)

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Nashville, Tennessee

Christopher M. O'Connor, MD, MACC,

FESC, FHFA, FHFSA

Professor of Medicine, Duke University

President and Executive Director

Inova Heart and Vascular Institute

Falls Church, Virginia

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(Non-Voting)

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(Acting Industry Representative)

Global Head of Cardiovascular, Renal &

Metabolism Development

Novartis Pharmaceuticals Corporation

East Hanover, New Jersey

TEMPORARY MEMBERS (Voting)

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(Patient Representative)

Chair, Policy & Global Affairs

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(9:30 a.m.)

Call to Order

DR. LEWIS: Good morning, and welcome. I would first like to remind everyone to please mute your line when you are not speaking. For media and press, the FDA contact is Chanapa Tantibanchachai. Her email and phone number are currently displayed.

My name is Julia Lewis. I will be chairing this meeting. I will now call the November 16, 2022 Cardiovascular and Renal Drugs Advisory Committee meeting to order. Commander LaToya. Bonner is the acting designated federal officer for this meeting and will begin with introductions.

Introduction of Committee

CDR BONNER: Thank you, ma'am.

Good morning. My name is LaToya Bonner, and I am the acting designated federal officer for this meeting. When I call your name, please introduce yourself by stating your name and affiliation.

We'll start with Ms. Alikhaani.

MS. ALIKHAANI: Good morning. I'm

Jacqueline Alikhaani, and I live in Los Angeles. I am a heart survivor, heart patient, and citizen scientist. I'm a long time volunteer with the American Heart Association, and I also serve as an ambassador for PCORI, the Patient-Centered Outcomes Research Institute; wonderful to be here this morning.

CDR BONNER: Thank you, ma'am.

Next, we have Dr Merz.

DR. BAIREY MERZ: Welcome. Noel Bairey Merz, clinical investigative cardiology, Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, California.

CDR BONNER: Thank you.

Next is Dr. Butler. Please introduce yourself for the record.

DR. BUTLER: Hi. Javed Butler. I'm a cardiologist at Baylor Scott and White Health in Dallas, Texas.

CDR BONNER: Thank you.

Dr. Cook?

DR. COOK: Thomas Cook, Department of

Biostatistics and Medical Informatics at the University of Wisconsin-Madison. Thank you.

CDR BONNER: Thank you.

Dr. Kasper?

DR. KASPER: Ed Kasper, heart failure cardiologist, Johns Hopkins, Baltimore, Maryland.

CDR BONNER: Thank you, sir.

And our chair, Dr. Lewis?

DR. LEWIS: Julia Lewis, nephrologist, Vanderbilt University Medical Center.

CDR BONNER: Thank you.

Dr. O'Connor?

DR. O'CONNOR: Christopher O'Connor. I'm a heart failure cardiologist and president of the Inova Heart and Vascular Institute.

CDR BONNER: Thank you, sir.

We'll continue with Dr. Fried.

DR. FRIED: Good morning. Linda Fried, nephrologist, Pittsburgh VA and University of Pittsburgh.

CDR BONNER: Thank you, ma'am.

Mr. Conway?

MR. CONWAY: Good morning. Paul Conway. I'm a 42-year kidney patient, 3 years on dialysis, 25 years out on a transplant. I serve as chair of Policy & Global Affairs for the American Association of Kidney Patients. Thank you.

CDR BONNER: Thank you.

Next is Dr. de Boer.

DR. DE BOER: Ian de Boer. I'm a nephrologist and an epidemiologist at the University of Washington in Seattle, and I direct our Kidney Research Institute and have a clinical practice at the Puget Sound VA Medical Center.

CDR BONNER: Next is Dr. Emerson.

DR. EMERSON: Scott Emerson. I'm a professor emeritus of biostatistics at the University of Washington in Seattle.

CDR BONNER: Thank you.

Dr. Mendley?

DR. MENDLEY: Good morning. I'm Susan Mendley. I'm a nephrologist and program officer at the National Institute of Diabetes and Digestive and Kidney Diseases of the NIH.

CDR BONNER: Thank you.

Dr. Nachman?

DR. NACHMAN: Patrick Nachman. I'm a nephrologist and director of the Division of Nephrology and Hypertension at the University of Minnesota. Thank you.

CDR BONNER: Thank you, sir.

Next is our acting industry representative, Dr. Soergel.

DR. SOERGEL: David Soergel, head of cardiovascular renal metabolism drug development at Novartis. Thank you.

CDR BONNER: Thank you.

Now I will introduce to you our FDA participants, starting with Dr. Joffe.

DR. JOFFE: Hi. This is Hylton Joffe. I'm the director of the Office of Cardiology, Hematology, Endocrinology and Nephrology at FDA.

CDR BONNER: Thank you.

Dr. Stockbridge?

DR. STOCKBRIDGE: Good morning. I'm Norman Stockbridge. I'm the director of the Division of

Cardiology and Nephrology at FDA.

CDR BONNER: Thank you.

Dr. Thompson?

DR. THOMPSON: Good morning. My name is Aliza Thompson, and I am the deputy director of the Division of Cardiology and Nephrology at the FDA.

CDR BONNER: Dr. DeConti?

DR. DeCONTI: Good morning. This is Selena De Conti. I'm the safety analyst for the application.

CDR BONNER: Thank you.

Next is Dr. Chen.

DR. CHEN: Good morning. This is Ling-Wan Chen. I'm the biometrics reviewer from the Division of Biometrics II at the FDA.

CDR BONNER: Thank you.

I will now turn this meeting back over to our chair.

Dr. Lewis?

DR. LEWIS: For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite

strongly held. Our goal is that this meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings; however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topics during breaks or lunches. Thank you.

Commander LaToya Bonner will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

CDR BONNER: Thank you.

The Food and Drug Administration, FDA, is convening today's meeting of the Cardiovascular and Renal Drugs Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208,

Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interests of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves the discussion of

new drug application, NDA, 213931, for tenapanor hydrochloride tablets, submitted by Ardelyx, Incorporated, for the control of serum phosphorus levels in adults with chronic kidney disease on dialysis. The committee will be asked to comment on whether the size of the treatment effect on serum phosphorus is clinically meaningful and whether tenapanor's benefits outweigh its risks.

This is a particular matters meeting during which specific matters related to Ardelyx's NDA will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. David Soergel is participating in this meeting

as a non-voting industry representative acting on behalf of regulated industry. Dr. Soergel's role at this meeting is to represent industry in general and not any particular company. Dr. Soergel is employed by Novartis.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. LEWIS: For today's meeting, the meeting DFO will read a statement on the formal dispute resolution request.

LaToya Bonner, please proceed.

CDR BONNER: Thank you.

Statement of Formal Dispute Resolution

request.

During the course of review of a new drug application, a wide variety of important scientific and medical issues are considered that are central to product development, including issues related to a product's safety and efficacy. Sometimes an applicant may disagree with the agency on a matter, and a dispute arises. These disputes often involve complex scientific and medical matters. Formal dispute resolution, FDR, is a pathway in CDER by which applicants may seek to resolve scientific and medical disputes that cannot be resolved at the division level.

FDR provides a mechanism for an applicant to obtain formal review of a decision by raising the matter with the next management level in the center chain of command above the level at which the decision being appealed was made. The deciding authority during review of an FDR request may determine that additional input is needed from an appropriate advisory committee before making a determination regarding the dispute.

Today's CRDAC meeting was requested by Dr. Peter Stein, the director of the Office of New Drugs, who is the deciding authority for the FDR request submitted by Ardelyx, Incorporated, regarding the complete response letter issued by the Division of Cardiology and Nephrology for tenapanor hydrochloride tablets, NDA 213931.

Dr. Stein requested the advisory committee meeting in order to seek additional input on scientific and medical issues relevant for the dispute. The CRDAC committee members will be asked to consider and vote on questions related to the medical and scientific issues to be discussed in detail today.

The advisory committee members will not be asked to vote on whether the FDR request should be granted or denied. Dr. Stein will carefully consider the advice of the CRDAC committee members on these medical and scientific issues when reaching a decision regarding the formal dispute resolution request. Thank you.

DR. LEWIS: We will proceed with FDA

introductory remarks from Dr. Aliza Thompson.

FDA Opening Remarks - Aliza Thompson

DR. THOMPSON: Thank you, Dr. Lewis.

As Dr. Lewis noted, my name is Aliza Thompson, and I will be giving FDA's opening remarks.

Good morning, everyone, and thanks in advance to our committee members for your participation in today's meeting. The purpose of today's meeting is to discuss the marketing application for tenapanor, for the control of serum phosphorus level in adults with chronic kidney disease on dialysis.

Hyperphosphatemia is a common complication in this population, and in most patients, thrice-weekly intermittent hemodialysis and dietary restriction of foods and drinks high in phosphorus are not sufficient control levels. Hence, gastrointestinal phosphate binders are widely used.

To date, four major classes of phosphate binders have been approved to control serum phosphorus in this population; however,

gastrointestinal side effects such as constipation, diarrhea, and nausea are common. The pill burden can be high and adherence can be challenging. As such, there is unmet need for well-tolerated treatments that effectively control serum phosphorus. Ideally, such treatment would have a low pill burden.

As you will hear today, to support the efficacy of tenapanor as monotherapy for reducing serum phosphorus in adults with chronic kidney disease on dialysis, the applicant conducted two studies. The applicant also submitted the results of a third study to support use in combination with existing phosphate binder treatment. These studies met their prespecified primary endpoint, which assessed effects on serum phosphorus, nevertheless, the Division of Cardiology and Nephrology did not approve tenapanor for the proposed indications, citing concerns about the magnitude of the treatment effect.

The division further indicated that to address this issue, the applicant would need to

conduct an additional adequate and well-controlled trial, demonstrating a clinically relevant treatment effect on serum phosphorus or an effect on a clinical outcome thought to be caused by hyperphosphatemia in this population.

The division also noted that, in principle, it may be possible to individualize treatment based on a patient's early response to a drug that lowered serum phosphorus levels; in other words, assess for a response at some early time point and only continue treatment in patients who have a clinically relevant response. However, the division indicated that such a strategy would need to be prospectively tested and would also likely need to be based on multiple measurements of serum phosphorus over time, given the variability in serum phosphorus measurements seen in patients.

As a backdrop to today's discussion, I would like to briefly discuss serum phosphorus as a surrogate for clinical outcomes in patients with chronic kidney disease on dialysis. First, I want to emphasize that FDA has accepted serum phosphorus

as a valid surrogate endpoint and basis for approval of products intended to treat hyperphosphatemia in patients with chronic kidney disease on dialysis. I also want to emphasize that our decision to accept serum phosphorus as a valid surrogate endpoint is not being revisited today.

In epidemiologic studies, elevated serum phosphorus levels have been associated with an increased risk of secondary hyperparathyroidism, vascular, valvular, and other soft-tissue calcification and cardiovascular disease in patients with chronic kidney disease. In patients on dialysis, higher serum phosphorus levels have also been associated with increased mortality.

We believe such epidemiologic data, as well as biologic plausibility, suggest that treatment effects on serum phosphorus could improve patient outcomes; however, we also acknowledge that data from randomized-controlled trials demonstrating that treatments that lower serum phosphorus improve patient outcomes are lacking.

The second point I want to make is that

although the division has not stipulated that applicants demonstrate a treatment effect on serum phosphorus larger than some threshold, we have indicated that the magnitude of the treatment effect should be clinically relevant. We have also stated that if the magnitude of the effect is significantly smaller than that of currently approved products, then applicants should address the clinical relevance.

In the studies that established the efficacy and safety of products currently approved for the control of serum phosphorus, these therapies lowered serum phosphorus levels by approximately 1.5 to 2.2 milligrams per deciliter. The division also believes that being much less effective than existing medications means that use of such a treatment in lieu of existing treatment could delay or possibly prevent patients from reaching their target level.

We believe this may be particularly true in settings in which the treatment effect is modest and the variable of interest, in this case, serum

phosphorus levels, displays significant measurement-to-measurement variability. In such a setting, we believe that it may be hard for clinicians to discern whether an individual patient is experiencing the desired response.

With that as background, I would like to turn to the topics we would like the committee to address.

The applicant's development program evaluated tenapanor's effect on serum phosphorus when administered, one, as monotherapy, and two, in combination with existing phosphate binder treatment. In the first question, we ask you to discuss the magnitude and clinical meaningfulness of tenapanor's treatment effect on serum phosphorus when administered as monotherapy. In the second, we ask you the same question, but in the context of administration with phosphate binder treatment.

The next topic we would like the committee to discuss is tenapanor's safety and tolerability. Diarrhea was the most common adverse reaction in clinical trials of tenapanor patients with chronic

kidney disease on dialysis. We would like you to discuss this risk from a safety and tolerability perspective.

Finally, we ask the committee to vote on two questions. The first voting question asks whether tenapanor's benefit outweighs its risk for the control of serum phosphorus in adults with chronic kidney disease on dialysis when administered as monotherapy. The second asks whether tenapanor's benefit outweighs its risk for the control of serum phosphorus in adults with chronic kidney disease on dialysis when administered in combination with phosphate binder treatment.

Although we are interested in how you vote, I want to emphasize that we are particularly interested in the rationale behind your votes. And if you vote no to a question, we also ask that you provide recommendations for additional data and/or analyses that may support a positive benefit-risk assessment for tenapanor in that setting.

With that, I will turn the program back to Dr. Lewis, our committee chair. Thank you again

for your time and help with this application.

DR. LEWIS: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships that they may have with the applicant, such as consulting fees, travel expenses, honoraria, and interest in the applicant, including equity interests and those based on the outcome of the meeting.

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

speaking.

We will now proceed with Ardelyx's presentations.

Applicant Presentation - Laura Williams

DR. WILLIAMS: Good morning, Dr. Stein, Dr. Lewis, members of the Cardiovascular and Renal Drugs Advisory Committee, and the FDA. I'm Dr. Laura Williams, chief medical officer at Ardelyx. Thank you for the opportunity to share our data supporting the clinically meaningful serum phosphate lowering effect of tenapanor in adult patients with hyperphosphatemia on maintenance dialysis. Let's start with some background.

Tenapanor was approved for the treatment of irritable bowel syndrome with constipation in adults in September 2019 and is currently marketed as Isbrela at a 50-milligram, twice daily dose. After submitting the NDA for the control of serum phosphorus in June 2020, the sponsor received a complete response letter from FDA in July 2020, based on their view that the magnitude of the treatment effect was small and of unclear clinical

significance.

We appealed the division's decision through two formal dispute resolution requests and received an interim response in April of this year from the Office of New Drugs offering Ardelyx the opportunity to present the data package to this committee, which brings us to today's meeting.

The FDA and Ardelyx agree on the following. Hyperphosphatemia is a serious common complication in patients on maintenance dialysis. Based on biological plausibility and existing observational data, FDA has accepted serum phosphate as a valid surrogate, which forms the basis for treatment guidelines and clinical practice in the FDA approval of all phosphate binders, and we all agree that there is a real unmet need for safe and effective therapies that lower pill burden and allow more patients to achieve guideline-directed treatment goals, a milestone that most patients on maintenance dialysis are currently unable to consistently achieve despite widespread use of phosphate binders.

While there is some discussion around which analysis population provides the best estimate of tenapanor's effect on serum phosphate reduction, there is no disagreement around our clinical trial designs, study conduct, and results from the three registration trials in our clinical development program.

In the CRL, the agency agreed that the submitted data provides substantial evidence that tenapanor is effective in reducing serum phosphate in CKD patients on dialysis, and in the FDA's briefing document, they note that except for diarrhea and related tolerability issues, their safety analyses did not raise significant concerns.

I will first provide a brief synopsis of the results from our three phase 3 registration trials to provide context for today's discussion. Please note, all three studies were successful, meeting their prespecified primary efficacy endpoint. These forest plots show mean treatment differences in serum phosphate reductions between tenapanor and placebo at a minus 1.4- and minus 0.8-milligram per

deciliter level for the larger and smaller monotherapy studies 301 and 201, respectively.

These studies employed a randomized withdrawal design consistent with the FDA guidance on enrichment strategies. The bottom row shows the mean treatment difference in the combination study, where tenapanor was added to patients on maintenance dialysis whose serum phosphate remained inadequately controlled despite treatment on a stable dose of phosphate binder therapy.

As such, the treatment difference was not surprisingly smaller, but still statistically significant and clinically meaningful, as a greater proportion of patients on combination therapy were able to achieve target serum phosphate goals than those on phosphate binders alone.

There are two key questions FDA is asking you to consider today as you evaluate the clinical relevance of tenapanor's effect on serum phosphate lowering. These two questions are separated by two related discussion points as we evaluate the overall benefit-risk assessment. Let's address the

first key question.

What is the magnitude of serum phosphorus reduction achieved with tenapanor, and is it clinically meaningful? As monotherapy in combination with phosphate binder, as I shared, the mean treatment differences were minus 1.4 and minus 0.8 milligrams per deciliter for the primary efficacy analysis in the two monotherapy studies and minus 0.7 in the combination therapy study.

When using the analysis that includes both responders and non-responders, as FDA now suggests, the mean serum phosphate reduction was minus 0.7 milligrams per deciliter. While prospective data directly linking a specific level of serum phosphate reduction that improves clinical outcomes is clearly preferable, that data simply do not exist. It did not exist when evaluating approval of phosphate binders, and it does not exist now as we evaluate tenapanor.

So the true answer to this question is left to biological plausibility, the strong correlations in observational studies and, frankly, subjective

clinical judgment, which has been the basis for approval of all phosphate binders as FDA states in their briefing document. Thus, when attempting to answer this question, it is imperative that we examine all the data.

In addition to the primary efficacy endpoint data from Study 301 that I just highlighted, data from the 26-week randomized treatment period, or enrichment phase, demonstrated that a meaningful number of patients achieved serum phosphate reduction and reached target treatment goals within the range historically referenced for phosphate binders. This treatment phase included an active phosphate binder as a safety comparator, which also serves as a conservative positive control further confirming the treatment effect seen with tenapanor.

Additionally, the novel mechanism of action and simplified dosing regimen, with one small pill taken twice a day, provide another treatment option for serum phosphate lowering. We will review all the evidence supporting the clinically meaningful

serum phosphate reduction seen with tenapanor as monotherapy and in combination with phosphate binders, and we have asked expert nephrologists, like those of you on the panel who currently manage these patients, to share their perspective with you today.

Moving now to the two related discussion points, FDA expressed interest in identifying a population where the drug effect could be quickly identified to support the utility, the clinical utility of tenapanor. Specifically, FDA suggested analyses that might help discern if early response to tenapanor was predictive of continued response.

Post hoc analyses from Study 301 confirmed this premise, that early response, or non-response, to tenapanor predicted continued response or non-response, which in turn should allow nephrologists to assess and optimize patient benefit. We will share that analysis, which applies FDA's suggestions on minimizing serum phosphate variability and explains the difference between the FDA and sponsor's results of this

analysis.

The standard clinical practice of monitoring serum phosphate monthly, at a minimum, allows effective management of patients as is currently done with phosphate binders. Those who tolerate therapy and are likely to receive the most benefit from continued treatment can remain on therapy, while others can be discontinued. Like any medication, tenapanor should be discontinued in those patients who do not experience a clinically meaningful benefit, and we support labeling to that effect.

Next, diarrhea was the most common adverse reaction in the tenapanor clinical trials. Careful review of the data suggests that this is more of a tolerability issue that can be managed as opposed to a significant safety concern. That said, we of course looked for potentially more worrisome issues related to diarrhea, especially in this patient population. Mechanistically, we know tenapanor blocks dietary sodium absorption, resulting in increased intestinal sodium content and water

retention. As such, softer stool consistency and diarrhea are expected pharmacodynamic effects that have been observed in all tenapanor clinical studies and have been appropriately managed in nearly all patients. Data included in the long-term safety studies show that potential downstream consequences of diarrhea were rarely observed. Together, these data demonstrate that the overall safety and tolerability profile for tenapanor is acceptable.

And now and perhaps the most important question, do the benefits of control of serum phosphate with tenapanor in CKD patients on maintenance dialysis outweigh its risk? As monotherapy, in combination with existing prostate binder treatment, based on our data, the answer is yes.

Tenapanor is a first-in-class phosphate absorption inhibitor that has demonstrated requisite safety and efficacy in reducing serum phosphate in patients on maintenance dialysis, and has a more simplified dosing regimen with fewer

smaller pills dosed as a single pill twice daily. Not only did we meet the prespecified efficacy endpoint in all three well-controlled registration studies, with statistically significant and clinically meaningful mean treatment differences versus placebo, also, many patients achieved clinically meaningful reductions in serum phosphate that align with those referenced for phosphate binders, done in the setting of a positive control.

Early response predicted continued response, concentrating the benefits of tenapanor in responders. Across our clinical development program, diarrhea tended to be more of a tolerability issue that was appropriately managed as opposed to a significant safety concern, and the overall safety and tolerability profile was acceptable. When evaluating all the data, the benefits of this new treatment option to lower serum phosphate outweigh the risks of potential downstream consequences of diarrhea, thus yielding a positive benefit-risk assessment.

Let's now turn to tenapanor's mechanism of

action, which is distinct from phosphate binders. As previously noted, tenapanor is a small molecule that inhibits NHE3, and it is minimally absorbed. This schematic, without tenapanor, shows phosphate moving between cells via the paracellular pathway, the primary pathway of phosphate absorption in the GI tract, from the apical surface of the intestinal lumen to the bloodstream. On the right, now you see tenapanor acting locally to block that paracellular absorption of dietary phosphate.

Typically, no one class of therapy is expected to work for all patients. Across most therapeutic areas, the availability of multiple agents that work differently on a common target -- for example, viral load, A1C, blood pressure, and ejection fraction -- has advanced our ability to treat patients, and this strategic approach remains essential.

Tenapanor provides a new treatment option with a distinct and targeted mechanistic approach to managing serum phosphate. Will it work for everyone? No, as is true for most drugs, including

phosphate binders, but for those who derive benefit, it has the potential to address real unmet need.

With that, here's the agenda for the remainder of the presentation. We also have additional external experts with us today. All external experts have been compensated for their time and travel associated with today's meeting. Thank you. I'll now pass the presentation to Dr. Chertow.

Applicant Presentation - Glenn Chertow

DR. CHERTOW: Thank you, Dr. Williams.

Good morning. My name is Dr. Glenn Chertow. I am professor of Medicine, and by courtesy, professor of Epidemiology and Population Health at Stanford University School of Medicine. I previously served as chief of the Division of Nephrology for more than 13 years. I have been caring for patients with kidney disease for more than three decades and have been particularly interested in the manifestations and management of disorders of mineral metabolism in advanced chronic

kidney disease, including hyperphosphatemia. I am honored to be here today as an advocate for our patients and my colleagues to address the unmet need for a new and complementary approach to controlling serum phosphate.

Hyperphosphatemia matters to patients and the clinicians who care for them. It is a condition with tremendous clinical consequences, and its burden is compounded by its high prevalence in patients receiving maintenance dialysis. Hyperphosphatemia leads to worsening secondary hyperparathyroidism, increases the risk of fracture, contributes to vascular and heart valve calcification, and calciphylaxis.

Unfortunately, phosphorus is not efficiently removed with conventional thrice-weekly hemodialysis. The risks associated with hyperphosphatemia are on a continuum and not anchored to a specific threshold of serum phosphate. Although serum phosphate is an accepted surrogate for clinical outcomes, the FDA has raised the issue of how to assess clinical significance

based on the magnitude of the serum phosphate lowering effect. Ideally, we would rely on data from large randomized-controlled trials to identify the amount of lowering of serum phosphate to improve clinical outcomes, but there are no such trials.

Clinical practice guidelines, standards of care and practice, and FDA approval of phosphate binders have been based on evidence derived from observational studies. My colleagues and I have conducted several population-based studies, which have helped to understand the implications of uncontrolled hyperphosphatemia.

This graph is adapted from a manuscript we published in 2004 in the Journal of the American Society of Nephrology and shows statistically significant and clinically meaningful increases in the risk of death associated with serum phosphate concentrations above the reference range of 4-to-5 milligram per deciliter. As you can see, even modestly higher serum phosphate concentrations, averaged over 3 months and shown

here in 1-milligram per deciliter increments, are associated with higher adjusted risks of death in this population. Additional studies conducted by other investigators have shown similar results.

Our treatment goal for patients with hyperphosphatemia is to lower serum phosphate toward the population reference range, which is generally defined as a serum phosphate 2.5-to-4.5 milligram per deciliter. For most patients, maintaining serum phosphate within this range is unattainable. Recognizing that a small fraction of patients consistently achieve serum phosphate concentrations within the population reference range, earlier clinical practice guidelines and dialysis facility quality assurance protocols have typically aimed for a compromised target of below 5.5 milligram per deciliter.

In clinical practice, we employ several approaches to help control serum phosphate in patients receiving dialysis. First, we advise patients to reduce dietary phosphate intake by restricting the intake of processed foods, which

contain inorganic phosphates used as preservatives and additives, as well as dairy products and other sources of organic phosphates. These restrictions are often difficult for patients, especially those with limited resources, and can complicate other dietary restrictions imposed because of concomitant diabetes, hypertension, and hyperlipidemia.

Frequent or extended duration hemodialysis can help to control hyperphosphatemia but add to the immense burden of dialysis already experienced by patients. As you've heard, the vast majority of patients on maintenance dialysis are prescribed phosphate binders that work by binding phosphate in the intestinal lumen, allowing a larger fraction of ingested phosphates to be eliminated in the stool.

Phosphate binders need to be taken in conjunction with or just after meals. Most of my patients take three or more tablets or capsules with each meal, and additional tablets or capsules with snacks without achieving targets. About half require two different phosphate binders in order to get closer to goal and to mitigate adverse effects,

including hypercalcemia.

The high pill burden obligated by phosphate binder therapy should not be taken lightly, particularly in a patient population with multiple comorbidities. The images you see here do not account for other medications these patients frequently require for conditions such as type 2 diabetes, hypertension, ischemic heart disease, atrial fibrillation, and heart failure. We ask patients every day to take what I refer to as a fistful of pills. As you may know, the median daily pill burden for patients receiving dialysis has been reported to be 19, and one-quarter of patients exceeded 25 pills per day with about half being phosphate binders.

Patients and providers need additional treatment options for hyperphosphatemia, particularly treatments that can be safely used in conjunction with phosphate binders that can lower serum phosphate through alternative mechanisms. More than three-quarters of patients do not consistently achieve target serum phosphate

concentrations over a 6-month period. Current binder options are inadequate.

I care for several patients who have tried every single commercially available phosphate binder, often in combination, and have not achieved control. These patients have developed complications of hyperphosphatemia that may have been prevented, even with modest improvements in serum phosphate concentrations.

With respect to the issue of a clinically meaningful response, recall that these mean values represent a range of responses in some serum phosphate reduction. Mean values in this range, including the low end of the range, are clinically meaningful to physicians and to patients. In clinical practice, we only maintain patients on therapies that exert a clinically meaningful benefit and are well tolerated, otherwise, we stop them.

Cardiologists and nephrologists are accustomed to using multiple agents with different mechanisms of action to help our patients achieve

treatment goals. For example, we use ACE inhibitors or ARBs, beta blockers, MRAs, and SGLT2 inhibitors to treat heart failure, and for hypertension we utilize multiple agents to bring systolic blood pressures toward 120 millimeters of mercury.

Patients and physicians want to control hyperphosphatemia and need strategies other than dietary restriction, longer or more frequent hemodialysis sessions, and/or large quantities of phosphate binders. We need more options to manage serum phosphate to help more patients achieve the target serum phosphate concentrations recommended by our clinical practice guidelines.

We need therapies with alternative mechanisms of action that can be used alone or in combination with phosphate binders. Patients would benefit from a therapy with a simplified dosing regimen, meaning fewer pills, smaller pills, and less frequent dosing, and of course we need treatment with a favorable safety and tolerability profile.

As you will hear in the following presentations, tenapanor is a minimally absorbed safe and efficacious agent that can improve control of hyperphosphatemia in patients receiving dialysis. In my view, the demonstrated benefits in terms of average productions in serum phosphate concentrations, as well as the proportion of patients achieving serum phosphate targets, are clinically meaningful and could materially improve management.

Thank you for your time and attention. I will turn the presentation to Dr. Connor.

Applicant Presentation - Jason Conner

DR. CONNER: Thank you, Dr. Chertow.

I'm Jason Conner. I'm the president of ConfluenceStat and an assistant professor of medical education at the University of Central Florida's College of Medicine. I focus my career in biostatistics on helping both sponsors and the FDA identify appropriate study design and evaluate data for approval recommendation. I've been asked by the sponsor to speak about the design

considerations for the tenapanor clinical development program.

Their program relied on the FDA guidance in designing their trial. Specifically, the sponsor used an enrichment type of trial called a randomized withdrawal design, which is discussed in detail in FDA's Guidance for Enrichment Strategies for Clinical Trials to Support the Determination of Effectiveness of Human Drugs and Biological Products. Although this is an established approach, this design might be new to some of you, so I'd like to describe how a randomized withdrawal design works.

In a randomized withdrawal trial, first, all patients are provided with the active treatment. This is known as the enrichment phase. During this period, patients are identified who both tolerate the drug and meet the predefined responder threshold, shown here in blue and labeled "responders." Patients who do not complete this period, or who do not respond, are shown here as non-responders in white. Typically, non-responders

exit the trial at this point.

Only responders are then randomized to either continue on active treatment or switch to a placebo. These patients comprise the primary analysis population in nearly all randomized withdrawal trials. The rest of today, you'll hear this population referred to as the efficacy analysis set. The expectation for a treatment with a true effect is that patients randomized to remain on therapy will show sustained improvement, while patients randomized to a placebo will experience a loss of efficacy.

The primary endpoint measured this way, using data of the responders from the enrichment phase, along with the while-on-treatment strategy described in the ICH E9 guidance, is the ideal estimand for a chronic disease under a randomized withdrawal design. What we want to know, and what this trial is asking is, for patients who tolerate and take the treatment habitually, how much different would their serum phosphate be if they went off treatment?

The primary analysis population, or EAS, shown here yellow, the primary analysis population described in the FDA guidance, and in any textbook describing randomized withdrawal trials, is precisely the way Studies 201 and 301 were prospectively defined to be conducted.

You'll hear from the FDA that the ITT of the randomized withdrawal periods from sponsor's Studies 201 and 301 may perhaps provide the best estimate of the average treatment effect with tenapanor. This difference of opinion you'll hear today is due to a slight difference in the conduct of Ardelyx's randomized withdrawal trials.

Instead of non-responders exiting the trial, as is standard in a randomized withdrawal trial, both responders and non-responders were kept in the trial and randomized. This was done to increase the blinded placebo-controlled safety database. All the safety data you'll see comes from all randomized patients.

Even though the non-responders were made, the sponsor's prospective analysis plan specified

that only those who met the responder definition would be included in the efficacy analysis set, shown here in yellow, and all sample size calculations were based upon this EAS; however, the FDA is suggesting that all randomized patients be included in the primary analysis set. What was a good faith effort to increase the safety database for this novel treatment has led to FDA suggesting an analysis that is contrary to the way randomized withdrawal trials were intended to be analyzed.

As a final point, randomized withdrawal trials using a responder population as intended have a long history of adequate and well-controlled trials supporting the FDA approval of drug. Here is a more recent subset of the 25-plus randomized withdrawal trials used to support agreement.

Importantly, when we look to the precedent established from other randomized withdrawal studies of approved product, we see a range in the proportion of patients who completed the enrichment period and responded to therapy, and therefore were included in their efficacy analysis set. This

indicates that some approved product had lower response rates but still had clear treatment effects in those responders.

If populations, including non-responders as FDA has suggested, would have been used, treatment effects would have been attenuated, and treatments like Veltassa and Lyrica may never have been approved. These concepts should be kept in mind when evaluating the clinical meaningfulness of the treatment effect and assessing the benefit-risk of tenapanor. Thank you, and I'd like to turn the presentation back to the sponsor.

Applicant Presentation - David Spiegel

DR. SPIEGEL: Good morning. I'm Dr. David Spiegel, vice president of nephrology at Ardelyx. Before joining industry, I was professor of medicine at the University of Colorado, where for over 25 years I served as a clinical director of the dialysis program, caring for hundreds of patients suffering from kidney failure, requiring maintenance dialysis.

Today, I'm pleased to present data from the

tenapanor clinical studies that support the efficacy and the clinical meaningfulness of tenapanor. I'd like to briefly cover our phase 2b dose-finding study, which was a double-blind, randomized, placebo-controlled trial.

The phase 2 study demonstrated that the 30-milligram BID dose had the most pronounced serum phosphate lowering effect, and the placebo corrected serum phosphate reduction with a 30-milligram BID dose of tenapanor was 1.4 milligrams per deciliter. Therefore, we chose to proceed with a 30-milligram dose for our phase 3 program.

In the phase 3 program, our two monotherapy studies utilized a randomized withdrawal study approach. Study 201 was a 12-week study that included a 4-week randomized withdrawal period. Patients completed a phosphate binder washout and were randomized to tenapanor 3, 10, or 30 milligrams BID. Patients who completed the open-label treatment period were re-randomized to either remain on their current dose of tenapanor or

receive a matching placebo. Non-responders were not exited from the trial.

For the purpose of defining a responder for the statistical analysis plan, we and the agency agreed patients who've entered the randomized withdrawal period with a serum phosphate reduction of at least 1.2 milligrams per deciliter, at the end of the treatment period, were the predefined efficacy analysis set and analyzed for the primary endpoint.

This plot shows the mean serum phosphate reduction for the subgroup defined as the efficacy analysis set by having a serum phosphate reduction of at least 1.2 at the completion of the randomized treatment period. During the 8-week treatment period, approximately 50 percent of patients who completed met the predefined responder definition, and that group achieved a mean serum phosphate reduction of 2.6, from 8.1 to 5.5 milligrams per deciliter. As seen, the patients demonstrated a response early, evident at week 1, that persisted over the 8-week treatment period.

The figure on the right shows the predefined efficacy analysis set during the randomized withdrawal period. Those randomized to placebo had a mean increase in serum phosphate of 1.4, and those continuing on tenapanor demonstrated an increase of 0.6, representing some regression to the mean. The primary endpoint was met with a statistically significant treatment difference of 0.8 milligrams per deciliter.

Study 301 was our long-term monotherapy study with tenapanor. The core design elements were similar to Study 201, but Study 301 was larger and had a longer duration in both the treatment period and the randomized withdrawal period to help eliminate any potential carryover effect in the placebo group.

Study 301 started all patients on the proposed dose of one 30-milligram tablet taken twice daily. In addition, we and the agency agreed that Study 301 should include an active safety control arm in which patients were treated for 52 weeks with sevelamer to compare adverse events

in patients on maintenance dialysis, a population known to have a high event rate.

Let's look specifically at the 301 design. After washout of phosphate binders, patients were randomized 3 to 1 to receive either tenapanor 30 milligrams twice daily or sevelamer carbonate with labeled dosing during the 26-week randomized treatment period. Investigators were permitted to decrease the dose of tenapanor in 10-milligram increments, based on serum phosphate concentrations and GI tolerability.

Sevelamer was dosed by standard care practice using the the label as guidance, which allowed for incremental adjustments in dose. At the end of the 26-week treatment period, all patients in the tenapanor group, irrespective of the serum phosphate response, were re-randomized 1 to 1, to either remain on the tenapanor dose or receive placebo during the 12-week randomized withdrawal period or RWP.

The primary endpoint was the same as in Study 201, the mean change in serum phosphate from

the randomized withdrawal period baseline to the end of the randomized withdrawal period in the responder population for the efficacy analysis set. As with Study 201, non-responders were not exited and remained in the study, although they were not included in the primary endpoint. All patients who were randomized to tenapanor at the study start were eligible to enroll in the open-label safety extension period and receive tenapanor for an additional 14 weeks.

Turning to the results, we again see the decrease in serum phosphate during the 26-week randomized treatment period for patients who had at least a 1.2-milligram per deciliter decrease from baseline at completion of the RTP, the efficacy analysis set. Similar to study 201, approximately 50 percent of patients who completed the randomized treatment period met the responder definition and were included in the efficacy analysis set. The mean serum phosphate, again, decreased by 2.6 from a baseline of 77 to 5.1 milligrams per deciliter at the end of the randomized treatment period.

The right graph shows the mean serum phosphate during the randomized withdrawal period, plotted over time for patients re-randomized to tenapanor and to placebo. This is the predefined responder population used to evaluate the primary endpoint at the end of the randomized withdrawal period. By the end of this period, serum phosphate increased by a mean of 1.8 in the placebo group and by 0.4 in the tenapanor group, with a statistically significant difference of minus 1.4 milligrams per deciliter, meeting the primary efficacy endpoint.

This forest plot shows the importance of using a responder population in a randomized withdrawal study. The top row shows the primary endpoint I just reviewed. The second row shows the same analysis for those defined as non-responders at period entry, confirming that when tenapanor is withdrawn or continued from patients who are non-responders, there is no change in their serum phosphate.

For the responders plus non-responders for randomized withdrawal period intent to treat, we

saw a treatment difference of minus 0.66 milligrams per deciliter that was also statistically significant. Please note that an all-comers population, as discussed by Dr. Conner, is not typically used in randomized withdrawal trials, and it would be atypical to use that population for evaluating tenapanor's treatment effect.

Now let's turn to the efficacy results from Study 202, which showed tenapanor's efficacy as combination therapy with phosphate binders in patients poorly controlled. In this double-blind, parallel group study, tenapanor or placebo was added to a stable phosphate binder regimen in a resistant population of patients. The serum phosphate remained uncontrolled at the time of screening and study entry, despite treatment with binder therapy.

In this study, we observed a serum phosphate reduction of 0.65 milligrams per deciliter for tenapanor plus binder compared to placebo plus binder at week 4, meeting the prespecified primary endpoint, and we see almost twice as many patients

achieved the target serum phosphate goal of less than 5.5 in the tenapanor plus binder arm versus the placebo plus binder arm.

The agency has questioned the meaningfulness of the magnitude of tenapanor's serum phosphate lowering effect and whether it provides benefits that outweigh potential risks. In trials, statistical tests are used to determine the difference between treatments -- in other words, to detect a signal over noise -- and are an important fundamental part of trial design.

For the evaluation of clinically meaningfulness, clinicians looked at the mean effects observed in control trials, but also looked at the proportion of patients achieving a meaningful response from treatment, because as with all drugs, a proportion of patients will benefit from treatment and some will not. As stated in the FDA briefing book, focusing on the mean effect ignores the fact that some patients may have a larger and clinically relevant response to treatment.

This slide shows a waterfall distribution of the serum phosphate change from the baseline for all tenapanor-treated patients in Study 301 during the 26-week enrichment period. Each bar represents an individual's patient's last measured serum phosphate. Fifty-three percent of patients on tenapanor achieved a reduction of at least 1.2 milligrams per deciliter, and 46 percent achieved a reduction of at least 1.5.

Importantly, the response to tenapanor varies across patients. This confirms the different biological responses achieved with tenapanor and demonstrates that a meaningful proportion of patients have large reductions in their serum phosphate. We also see a consistent pattern across monotherapy and combination therapy studies. Fifty-three percent of tenapanor-treated patients achieved a 1.2 reduction or greater in Study 301, 46 percent in Study 201, and 41 percent in the resistant population of Study 202.

Now let me turn to a comparison of tenapanor versus sevelamer in Study 301. During our NDA

review, the agency requested a comparison of serum phosphate reduction during the 26-week randomized treatment period between tenapanor and sevelamer. In Study 301, patients were randomized 3 to 1 to tenapanor or sevelamer, and while there were no prespecified efficacy analyses, serum phosphate measurements were done in an identical fashion for patients across both treatment groups during this 26-week period.

Serum phosphate change is plotted here for the tenapanor and sevelamer over the first 26 weeks of the study. We see an early and sustained decrease in both the tenapanor- and sevelamer-treated groups. On average, the tenapanor arm showed a smaller reduction in serum phosphate than the sevelamer arm.

I understand the variability and the biologic response to tenapanor as observed in the waterfall plot. We asked ourselves whether the difference in the effect observed for tenapanor versus sevelamer was due to a smaller magnitude of serum phosphate reduction for tenapanor or was it

due to a smaller proportion of patients showing the response to tenapanor; therefore, we looked at the prespecified definition of response using the agency's guidance to use multiple time points for each treatment group. The definition of early response in this analysis was having at least a 1.2-milligram per deciliter serum phosphate reduction on at least 2 of 3 measurements at weeks 1, 2, and 4.

The magnitude of the tenapanor response over time tracked closely to that of sevelamer; therefore, the separation seen in the full population was confirmed to be due to the greater proportion of patients responding to sevelamer and not a major difference in the magnitude of the serum phosphate lowering effect. Also keep in mind that the reductions in serum phosphate seen with tenapanor were achieved with one small pill taken twice a day versus a median of 9 tablets a day with sevelamer.

Here is a more detailed look at the serum phosphate reductions seen in Study 301 by various

measures. In the subset of patients that are likely to tolerate tenapanor and remain on therapy, there's a slightly lower but clinically meaningful response rate at the end of the 26-week randomized treatment period compared to sevelamer-treated patients of equal treatment duration. In addition, in the bottom graph, those remaining on treatment for a year have similar response rates. Achievement of the standard practice target at serum phosphate less than 5.5 milligrams per deciliter is similar for tenapanor and sevelamer.

I would like to address the agency's concern that patients will remain on treatment without benefits. We analyzed patients in our studies who showed an early response to therapy to determine if they continued to respond, and equally important, to confirm that those who do not respond early could be identified and discontinued from treatment.

We took into consideration the FDA's feedback if any such analysis needs to account for intrasubject variability by being based on multiple

measurements of serum phosphate over time, thereby reducing the effects of intrasubject phosphate variability in classifying patients as responsive or non-responsive. FDA's analysis as presented in their briefing document does not use multiple time points but is based on only a single measure of serum phosphate at an early time point and a single measure at a later time point, enhancing the influence of phosphate variability in misclassifying patients early.

In our analysis, patients have been divided into those with an early response and those without an early response during the 26-week treatment period of Study 301. The definition of response was having at least 2 of 3 serum phosphate measurements decrease by at least 1.2 milligrams per deciliter from baseline; therefore, and early response is shown as a median of the serum phosphate values from weeks 1, 2, and 4 on the X-axis, and late response was determined by the median of values for weeks 17, 22, and 26 on the Y-axis.

Each symbol represents an ITT patient that received tenapanor during the 26-week treatment period. Those in blue met the criteria for an early response and those in orange did not. Of those with an early response, 79 percent were also identified as having a late response. These patients appear in the lower left-hand quadrant of the scatter plot. Likewise, 66 percent of those determined not to respond early also did not respond later in the treatment period. These patients appear in the upper right-hand quadrant of the scatter plot.

These data support that patients who respond to tenapanor can be identified early and tend to remain responsive. Equally important, patients who do not respond can also be identified early in treatment. Similar analyses of other time points in Study 201 confirm the consistency of this approach, and when applying the multiple time points analysis of early versus late response to the sevelamer data from the randomized treatment of Study 301, we see a very similar response pattern.

To sum up efficacy, while our clinical studies were not specifically designed to measure effect size, a review of the data suggests that the mean serum phosphate reduction is approximately 1.4 milligrams per deciliter. These data include the placebo corrected serum phosphate difference of 1.4 in the phase 2 dose-finding study. The mean serum phosphate reduction in Study 201 at the end of the 8-week treatment period was 1.1 milligrams per deciliter. Following 301 at week 26, it was 1.4 versus 1.8 milligrams per deciliter for sevelamer.

The difference in the rise in serum phosphate between placebo and patients remaining on tenapanor during the randomized withdrawal period of Studies 201 and 301 were 0.8 and 1.4 milligrams per deciliter, respectively. In patients who responded to treatment in both Studies 201 and 301, the mean serum phosphate reduction using the predefined primary analysis definition of responder was 2.6 milligrams per deciliter for the 8- and 26-week randomized treatment period responders,

respectively.

Study 202 was performed in a resistant population and demonstrated a serum phosphate reduction of 0.7 milligrams per deciliter for tenapanor plus binder compared to placebo plus binder was observed at week 4. This suggests that in the real world where patients are continually monitored, patients likely to be treated and remain on tenapanor will have a clinically meaningful serum phosphate reduction.

It is important to note that the serum phosphate lowering effect of tenapanor varies across patients; however, as demonstrated by the waterfall plots, a meaningful proportion of patients have a large reduction in their serum phosphate, and patients who have a biologic response to tenapanor have a serum phosphate reduction similar to patients who respond to sevelamer with a much lower pill burden in our studies, 2 pills per day for tenapanor versus a median of 9 tablets per day for sevelamer.

Equally important, when reduction in serum

phosphate occurs, it is observed early in treatment, and perhaps more importantly, patients who respond early usually continue to respond to tenapanor treatment. Likewise, we have demonstrated that patients who do not benefit can be identified early and switch to other treatments. These data, coupled with standard practice, will allow a nephrologist to identify patients who respond to tenapanor therapy and avoid prolonged use and those who do not. Therefore, we believe that tenapanor can be an important additional therapeutic option that fits into the current treatment paradigm for managing patients with hyperphosphatemia requiring maintenance dialysis, an area where there is a substantial need for new therapies.

Now I will turn the presentation over to Dr. Williams for review of safety.

Applicant Presentation - Laura Williams

DR. WILLIAMS: Thank you, Dr. Spiegel.

Across the entire clinical development program, tenapanor demonstrated an acceptable

safety and tolerability profile. The FDA's briefing document noted that except for diarrhea and related tolerability issues, their safety analysis did not raise significant concerns.

The clinical development program provides a robust assessment of safety in more than 1200 patients from the CKD on dialysis safety analysis set, with more than 930 tenapanor-treated patients representing more than 140 patient-years of tenapanor exposure.

Study 301 provides the most extensive treatment exposure with safety data for up to 52 weeks, and it evaluated tenapanor in the setting of an active control, sevelamer, the most commonly prescribed phosphate binder. Therefore, I'll review data primarily from this study. Additional safety data across the full clinical development program are provided in the briefing document.

Importantly, approximately 65 percent of patients in the sevelamer arm were sevelamer experienced having been treated with sevelamer just prior to enrollment in this study. By default,

most patients who had tolerability issues to sevelamer would have discontinued therapy prior to the study, and as such, the adverse event and study discontinuation rates were expected to be lower in the sevelamer arm in this study versus the naive patient population presented in sevelamer's package insert.

Here's the overall safety data from Study 301 across all treatment periods, with tenapanor in blue, sevelamer in gold, and placebo in gray. The 26-week randomized treatment period is on the left, followed by the 12-week randomized withdrawal period and the 14-week safety extension. Overall, a higher proportion of tenapanor patients reported an adverse event and discontinuation due to an AE compared with the sevelamer enriched population.

Here's a more granular view of AE intensity separating moderate and severe events to provide additional clarity and context on the table 13 noted in FDA's briefing document. There are lower rates of AEs with severe intensity, and those rates

are similar to sevelamer in each treatment period. Despite being an enriched population, the proportion of patients experiencing a serious adverse event, or SAE, was higher in the sevelamer arm throughout each phase of the study, as were AEs leading to hospitalization.

There were 18 deaths in this study, and rates were similar across treatment groups. No deaths were considered related to study drug by investigators. Diarrhea was the most common adverse event in the tenapanor group, with most events occurring during the 26-week randomized treatment period.

For reference, MedDRA classifies any report of bothersome loose stools, loose bowels, or mushy stools as diarrhea events, whether or not there was a reported increase in stool frequency. Diarrhea rates across treatment groups were much lower during the randomized withdrawal period with a slight uptick when tenapanor was reintroduced to some patients during the 14-week safety extension period. Most diarrhea events were mild or moderate

in intensity. In general, the frequency of other AEs was low with higher rates in the sevelamer arm.

During the randomized treatment period, AEs that led to discontinuation were more common than the tenapanor group at 24 percent compared to 1 percent in the sevelamer group, with 16 percent discontinuing due to diarrhea. When present, most patients reported only having a single diarrhea event with most events occurring early in treatment and resolving within a median of 14 days.

This table highlights the impact an enriched population can have on GI-related adverse events, particularly for phosphate binders. You've seen the data from Study 301 as it relates to diarrhea rates for tenapanor versus tenapanor, as shown here. Rates for other non-diarrhea GI events in this study were actually less than 5 percent for either treatment arm.

To provide additional context, we looked at the phase 3 study used to support sevelamer's approval that had a similar treatment duration as Study 301. The safety profile in this sevelamer

naive population, as reported in the package inserts, is more consistent with that seen across most treatment-naive phosphate binder studies. The overall AE rate is higher here than in Study 301, as is the diarrhea rate at 19 percent, and notably, there are much higher rates of other non-diarrhea, GI-related AEs. Finally, there was a similar rate of discontinuations due to any GI event at 16 percent.

We explored potentially more worrisome downstream consequences of diarrhea with a post hoc analysis evaluating the temporal association between diarrhea and adverse events of special interest, which consisted of AEs mapped to the preferred terms represented in this table. Data show that most patients with diarrhea events had no temporally associated adverse event of special interest in either treatment arm, and among the 3 percent of tenapanor-treated patients with diarrhea who had a temporally associated adverse event of special interest, the rates were approximately 1 percent or less and similar to

sevelamer.

Although not shown here but included in the briefing document, we also reviewed serum electrolytes and other laboratory values, and blood pressure measurements, and found no clinically meaningful changes in these values, in general, and more specifically among patients with reported events of severe diarrhea.

In general, similar safety tolerability profiles were seen in both Studies 201 and 202, which are also presented in the briefing document. Thus, in summary, these data demonstrate that tenapanor has an acceptable safety and tolerability profile. Diarrhea was the most commonly reported adverse event as anticipated based on tenapanor's mechanism of action, and it was appropriately managed. Most cases occurred early, were mild to moderate in intensity, were not treatment limiting, and tended to resolve within a median of 14 days.

Importantly, events of severe diarrhea were infrequent and potentially more worrisome, downstream consequences of diarrhea like

dehydration, hypotension, syncope, falls, and hospitalizations were uncommon. In the long-term Study 301 with an active safety control, the safety profile was comparable to or better than sevelamer. These safety data, coupled with the efficacy results shared by Dr. Spiegel, provide a positive overall benefit-risk assessment for tenapanor.

Thank you. Dr. Sprague will now conclude the presentation.

Applicant Presentation - Stuart Sprague

DR. SPRAGUE: Thank you, Dr. Williams.

I'm Stuart Sprague, chief emeritus of Nephrology and Hypertension at NorthShore University Health System and professor of medicine at the University of Chicago. I'd like to provide my clinical perspective on the tenapanor data.

For decades, pharmacological treatment of hyperphosphatemia has been limited to the use of one class of therapy, phosphate binders. Despite our best efforts, most patients do not consistently achieve target serum phosphate concentrations Even when patients are doing everything we

ask -- restricting their diets, taking many large pills with meals, and always having a supply of binders on hand -- they find the treatment of hyperphosphatemia to be extremely frustrating and challenging. On multiple occasions, I've had patients tell me that it's not worth taking their binders since they still have high serum phosphate concentrations no matter what they do.

As my nephrology colleagues know, our control of phosphate is distressingly poor. Phosphate binders often lead to worsening constipation and GI distress and are not effective at consistently controlling serum phosphate for the majority of our patients.

We need to be able to offer something else to meet the needs of each patient. Tenapanor effectively lowers serum phosphate when used alone or in combination with phosphate binders. The dosing regimen is simplified with fewer smaller pills taken twice a day, providing a much needed treatment option to improve the management of hyperphosphatemia.

A sizable proportion of patients on tenapanor have serum phosphate reductions that are clinically meaningful. As standard practice, we monitor serum phosphate at least monthly so I can identify treatment response early to maintain therapy in patients who respond and use alternative treatments in those who do not.

Today, the FDA is asking you to consider the magnitude of tenapanor's treatment effect and whether that effect is clinically meaningful. I believe that the best estimate of tenapanor's treatment effect is approximately 1.4 milligrams per deciliter, as seen in Study 301, the largest most robust study testing the 30-milligram dose and previously presented with a 30-milligram dose in the placebo-controlled phase 2 study.

Here you see treatment estimates for randomized withdrawal studies cited in the prescribing information of currently marketed phosphate binders, with a yellow band highlighting the 1.5 to 2.2 serum phosphate reduction that FDA considers as clinically meaningful. The tenapanor

treatment effect aligns with the benchmark set by the approved phosphate binders, but 1.4 is not the minimum threshold for clinical meaningfulness. Results are meaningful even at the lower range of the treatment effect seen.

In Study 201, the point estimate was minus 0.8, which is still a meaningful reduction in serum phosphate. If I have a patient with a serum phosphorus of 6.3, and I could get them to the target of 5.5 with tenapanor, that is clinically meaningful.

I treat patients with these phosphate binders and I'm familiar with their safety and tolerability profiles. This table shows registration trial data of treatment-naive patients for these various phosphate binders. As you can see, the proportion of patients with GI adverse events and the discontinuation rates due to adverse events are in line with those seen with tenapanor. I am used to managing GI adverse effects with phosphate binders, and will be able to manage them when I use tenapanor.

Tenapanor could help many of my patients both as monotherapy or in combination with phosphate binders. There are a number of considerations when making treatment decisions around managing hyperphosphatemia, including the severity of the hyperphosphatemia, the current treatment regimen, tolerability, history of GI issues, and dosing preferences.

Unfortunately, 40 percent of my patients in any given month remain uncontrolled. I care for a 47-year-old patient receiving hemodialysis with uncontrolled hyperphosphatemia. Despite trying multiple binders alone and in combination, he enrolled in a tenapanor clinical trial, was switched to tenapanor monotherapy, and his serum phosphate was consistently in control for the first time since starting dialysis. At trial completion, he asked if there is any way to continue on the medication. Unfortunately, he had to return to binders, and now again has poor controlled hyperphosphatemia.

Often I worry about compliance to taking a

large number of phosphate binder pills. For example, I have a 58-year-old patient on multiple binders who follows his diet closely, yet only has intermittent serum phosphate control. He sometimes misses his lunchtime dose while working, a problem that could be alleviated with tenapanor. I also have treatment-naive patients for which I would consider a tenapanor regime.

The point is different patients have different needs, and having a new option with a different mechanism of action would help me successfully individualize treatment and help more patients achieve target.

Overall, tenapanor provides clinically meaningful serum phosphate reductions with a positive benefit-risk assessment in both monotherapy and combination therapy. The development of tenapanor represents an important advance for patients and our field, where current therapies are not able to consistently achieve our targets.

Tenapanor has the potential to change a

hyperphosphatemia treatment paradigm, and I sincerely hope that it becomes available for us to use. Thank you. I'll now turn the presentation back to the sponsor to take your questions.

Clarifying Questions

DR. LEWIS: We will now take questions for Ardelyx. Please use the raise-hand icon to indicate that you have a question, and remember to lower your hand by clicking the raise-hand icon after you have asked your questions. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can.

If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and the end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

I will take the liberty of beginning. I have two questions for the sponsor. One question

is, both in your labeled use of this drug -- and I understand the protocol -- the recommendation was to give the medication with breakfast and dinner; however, my understanding of how this medication works would indicate that it would be effective if not given simultaneously with food. Could you comment on that?

My second question -- do you want me to ask them one at a time, or does it matter?

DR. WILLIAMS: No, you can --

(Crosstalk.)

DR. LEWIS: Okay.

My second question is that I'm thinking about this concept of non-responders. Is there any reason to believe that there are people for whom tenapanor would not inhibit their NH3 [ph] inhibitor cellular phosphate movement, or is it related to compliance and the amount of phosphate foods they're eating, et cetera? Do you have compliance data?

Thank you. Those are my two questions.

DR. WILLIAMS: Thank you. I'll ask

Dr. Spiegel to address both questions; the first one with respect to dosing around breakfast and dinner, and the second one as it relates to non-responders and whether or not that is a compliance issue versus otherwise.

Dr. Spiegel?

DR. SPIEGEL: Thank you. David Spiegel.

In some of the earlier studies, different dosing regimens were tested, and there was once-a-day tested versus twice-a-day testing, looking at stool sodium and urinary sodium in healthy volunteers. And what it showed was that the BID dosing was more effective in increasing stool sodium, so that was the reason that it was taken forward into the development program.

DR. LEWIS: Excuse me, though. I'm trying to understand why it's recommended to be given with breakfast and dinner as opposed to --

DR. SPIEGEL: Yes.

DR. LEWIS: -- just any old time during the day.

DR. SPIEGEL: Correct; sorry about that.

So it was also studied away from meals versus right before meals, so the recommendation is right before breakfast and right before dinner. When it was studied away from meals, again, similar findings to the once-a-day dosing was seen, that it was less effective in increasing stool sodium and decreasing urinary sodium. So it was felt to be best to be taken right before breakfast and right before dinner.

As far as your second question in terms of non-responders, as far as we know, everyone has the NHE3 receptor, other than the knockout mice, which have been studied. So as far as we know, everyone that was studied has a response as far as increasing stool sodium and decreasing urinary sodium.

The secondary signals from inhibiting this antiporter to the paracellular tight junctional changes that occur are not completely understood. But as far as we know, everyone does show change in there tight junction confirmations and decrease in paracellular phosphate absorption, but there

certainly could be some variability across different populations in terms of that response. And that may explain why some patients have a large response to tenapanor, and some patients appear to have a much smaller response.

DR. LEWIS: Do you have compliance data?

DR. WILLIAMS: Yes, we do. Compliance was actually one of the criteria that -- I'm sorry. This is Dr. Williams again. Compliance was one of the criteria for which patients could remain in the study. Our compliance was approximately 82 percent for the tenapanor arm in the randomized treatment period and about 80 percent for the sevelamer arm.

DR. LEWIS: That is all for my questions.

Dr. Bairey Merz?

DR. BAIREY MERZ: Thank you, Dr. Lewis. My question is for Dr. Williams or her designee.

Did you have quality-of-life and/or satisfaction measures, 2 versus 9 pills, and then increased diarrhea versus not in the all-comers versus your withdrawal population or your tolerating population? Quality-of-life and

treatment satisfaction would be important, given these pros and cons.

DR. WILLIAMS: Great. I'm going to ask Dr. Spiegel to review with you some of the patient-reported outcomes data that we captured in our open-label study as it relates to treatment satisfaction, which you just noted, and also would like to have him discuss some additional data that we collected in Study 201 as it relates to diarrhea in this patient population.

Dr. Spiegel?

DR. SPIEGEL: Thanks. David Spiegel.

We conducted a study called 402, and that study, it was an open-label study, but it took patients who were on phosphate binders, and there were two cohorts which are relevant to your question.

Cohort 1 had their binders discontinued and were started on tenapanor, and then the binders could be added back, if needed, to get control. Cohort --

DR. WILLIAMS: I'm sorry. Can we have

permission to show the slide so that you can --

DR. LEWIS: Yes, of course. Yes, please show the slide.

DR. WILLIAMS: Thank you.

DR. SPIEGEL: I'm sorry. And cohort 2 had their phosphate binders decreased by 50 percent and were started, and had tenapanor added to that regimen.

Then there was a questionnaire that was given at baseline in the end of the the 10-week part A of that study, and the questionnaire was around their phosphate binder management, whether it was improved, whether it was worsened, and why they felt it was either worsened or improved, and these are the results that are shown here.

About 84 percent of patients felt, overall, that their phosphate management regimen was improved, and when we drilled down to understand why that was the case, about two-thirds of the patients felt it was actually due to the pills they were taking. They had a lower pill burden, the pills were smaller, and they had to take them less

frequently. And interestingly, a third of the patients felt that their phosphate binder management was improved because they had an improvement in their bowel movement frequency. So presumably these are patients who were constipated at baseline, which is common in dialysis patients, and tenapanor provided some relief for those patients.

I would also say that in this study, the combination therapy, in addition to improving the quality of life in these patients, also further decreased their serum phosphate by 1 milligram per deciliter, and in cohort 1, the pill count went from 8.8 a day down to 5.5 a day, which was the switch, and in cohort 2 at the end, it went from 9.3 down to 8. So there was a reduction in pill burden, an improvement in quality of life, and an increase in patient satisfaction.

Regarding --

DR. BAIREY MERZ: Can --

DR. SPIEGEL: -- I'm sorry?

DR. BAIREY MERZ: Can I just ask about this

slide? These were all-comers or these were the tolerators?

DR. SPIEGEL: These were all-comers in Study 402 --

DR. BAIREY MERZ: Thank you.

DR. SPIEGEL: -- that completed the periods and had the questionnaire done twice; yes.

DR. LEWIS: Thank you.

Dr. Emerson?

DR. SPIEGEL: I'm sorry. Did you want me to talk about the stool?

DR. WILLIAMS: Yes. Dr. Lewis, there was another --

(Crosstalk.)

DR. LEWIS: I'm sorry --

DR. WILLIAMS: Thank you.

DR. SPIEGEL: Yes. I think there was another part of the question related to the stool frequency, and let me put that up.

In Study 201, patients did a daily stool diary, both in terms of the quantity and the quality of their stool. The quality is shown on

this right, which is this standard Bristol stool chart, and what you see on the left-hand side is the stool consistency, and what you see is -- and these are the three different doses that were used in Study 201. But what you see is there is a slight increase in this score, which means a slight loosening of the stool, but it stays within what's considered the normal range for bowel movements, and you can see it kind of stays level essentially over the course of the treatment.

When we think of diarrhea, we all think of number 7, which is these watery stools, and that was not what we saw in the study. It was a softening of the stool and an increase in still frequency a little bit, all within the normal range.

DR. BAIREY MERZ: Thank you. That's all for me.

DR. LEWIS: Thank you, Dr. Merz.

Dr. Emerson?

DR. EMERSON: Yes. This is Scott Emerson. I have a few questions related to your EAC [ph]

analyses compared to the non-responders.

The first is, in your briefing book, you gave us disposition for the randomized withdrawal phase, but you did not break down that disposition by responders versus non-responders. Of particular interest to me is you had 7 patients who discontinued due to hyperphosphatemia. On the tenapanor arm you had zero on placebo. Were they responders or non-responders?

DR. WILLIAMS: Dr. Spiegel?

DR. SPIEGEL: If they discontinued, they were non-responders. In terms of the demographics for the specific breakdown of non-responders versus responders, we'd have to try to get that to you later. I don't think we have that particular breakdown.

DR. EMERSON: Again, I'm asking about figure 28 in your briefing book. So this is during the randomized withdrawal phase -- just so that you do break this down correctly -- you gave this based on all randomized patients, but your EAC would only be among the responders. So what I am looking for

is, of those 7 patients who were listed as hyperphosphatemia -- it's during the randomized withdrawal phase -- how many of those were responders during the randomized treatment phase? Okay, and I appreciate that later.

Along those same lines, then, for both the data that you present in CO-39 and CO-40, I'm interested in a dose response by the definition of response; since we didn't have it totally prespecified, that your intent would be that the indication would say that if you didn't respond by -- and I'm making this up -- week 4, that they should not continue.

Then this safety question that the FDA alluded to -- are you having patients persisting on a treatment that's doing no good -- I would like to see some idea of dose response with particular concern about the fact that the direction, the point estimate, was wrong among the non-responders using the prespecified criteria.

So do you have anything on that?

DR. WILLIAMS: If you might, can you please

repeat the question? I just want to make sure that our response is appropriate.

DR. EMERSON: Okay. One thing that I would be interested in, since we have CO-39 up, just to clarify this, you give me this for the responders, but I'm also interested in seeing what the data would be for the non-responders. But if we might see CO-40, maybe this would be the better starting place.

CO-40, you give me these estimates based on only the definition based on 1.2. And I'll just note, the non-responder subset's in the wrong direction. We have those 7 patients that have ultimately discontinued for hyperphosphatemia if they stayed on tenapanor. I was wondering if you could break down this non-responder subset more and by a few other criteria so that we can see if there is a huge safety issue, depending upon how badly your non-response was.

DR. WILLIAMS: Okay. Dr. Spiegel?

DR. SPIEGEL: Well, I can certainly answer your question about the seven during the randomized

withdrawal period who had hyperphosphatemia. To get into the randomized withdrawal period in this efficacy analysis set, you had to, by definition, be a responder at the end of the enrichment period. So the answer to that question is yes; those 7 patients did have at least a 1.2-milligram per deciliter reduction at the end of the randomized treatment period.

Honestly, I --

DR. EMERSON: Well, just to clarify, table 11 gives the denominator of 128, which is the inclusion, both your primary analysis group and the non-responders. So you saying that they all responded, that's very interesting, and I'd really like to know that, but I just want you to make certain that that's correct.

DR. WILLIAMS: Yes. We actually have a slide that I think would answer that question. We're having some technical difficulties in terms of pulling it up, so I'd like to bring that back to you after the break, if that's ok.

DR. EMERSON: Okay. That'd be fine. And

again, that they sort of could contribute to my worries on this non-responder subset where your direction went wrong, and whether there was any sort of a dose response on that.

Along these same lines, then, in your briefing book, table 11, you perform analyses based on what the final dose of tenapanor was at the end of the randomized treatment period, which patients, as I understand it, would have continued on whatever dose they had titrated down to; but your table 11 is an inappropriate comparison because you're pooling the placebo groups for each of those.

Do you have a properly stratified analysis wherein the strata defined by the final tenapanor dose, that we compare the two treatment arms with that?

DR. WILLIAMS: So again, you are asking if we have the efficacy results stratified out by the dose that patients were on during the randomized withdrawal period?

DR. SPIEGEL: That's right. Well actually,

since they would have been on either placebo or they would have been on the tenapanor dose that they finished the 26-week period with. That's correct? Am I correct in stating that?

DR. WILLIAMS: Yes, you're correct, and we --

DR. EMERSON: Okay. So I'd like to see, again, if you have a slide for table 11, and I can point exactly to the numbers that are wrong. You combine all of those different strata in your placebo group to compare them, and I want to see, again, whether there is this idea -- it's a little bit going to Dr. Lewis' question of what's the story about patients in their response and what's the story also in terms of their adverse event profile that would make them titrate down?

DR. WILLIAMS: Alright. I'm going to ask Dr. Spiegel to address part of that question.

DR. SPIEGEL: David Spiegel. I hope this answers at least some of your question.

Obviously, the difference between those randomized to placebo versus those staying on

tenapanor in the randomized withdrawal period was 1.37 in the total efficacy analysis population. If you look at those who just stayed on the 30-milligram dose and were not titrated down, that difference was 1.69, whereas those that went down to 20, it was 0.96, and those that went down to 10, it was right about [inaudible].

So down-titrated, they maybe did lose a little bit of efficacy. Again, I hope I have sort of addressed --

DR. EMERSON: No. I need to see what the placebo patients in those same strata were.

DR. SPIEGEL: Oh, so in terms of what the rise in the placebo was?

DR. EMERSON: That's right, because you've lumped all the placebo patients together, and it's not at all a foregone conclusion that the same patients would behaved that way, so you're --

DR. SPIEGEL: I think I understand now.

So here is this, I guess, 1, 2, 3 -- the fourth column over shows the placebo, and in each of those substrata, 30, 20, and 10, the placebo

group went up about 1.81.

DR. EMERSON: Except -- no, that's not correct. That's not correct. Your sample size gives 68, which is roughly the total number of placebo patients across those three strata. You have three strata according to the final dose at the end of the randomized treatment period. The sample sizes should be roughly comparable for placebo. I'm interested in what the estimates would have been.

DR. WILLIAMS: Yes. I'm afraid we'll have to try and get that information back to you after the break. The data that Dr. Spiegel is sharing here is consistent with what we shared in our study report, but we can try and see if we can tease out that information during the break.

DR. EMERSON: So whether or not it's what you shared in your thing, it's an incorrect analysis; an incorrect analysis. So it's important -- and again, just recognizing that a lot of the safety of this is the amorphous safety of what is the safety of marketing a drug and

convincing people to take it when they're not truly getting a benefit. Having better point estimates on this will go a long way towards that.

I'll let that do me for now, and I'll come back later with the other questions. Thank you.

DR. LEWIS: Thank you.

Mr. Conway?

MR. CONWAY: Thank you, Dr. Lewis. I guess my question is to David Spiegel, but I'll defer to folks to prioritize, or to Dr. Chertow.

Obviously, I'm a patient, and it's an honor to serve on this committee, and I'd like to anchor this into some more real world. As a patient I've taken at least 165,000 pills, so I understand some of these issues at a personal level and also for a patient population level, in practical terms.

But I wanted to ask about the slide that had been put up, and I believe it's slide number 56 by you folks, the comparative slide. Maybe it's -- sorry. It's 2 hands that has the 2 pills in one hand and I think 9 pills in the other hand, and this might be wrong. It might be number 65.

But here's what my question is.

In the presentations, your presentation and FDA's presentation, that talk about clinical effectiveness -- that's the slide; thank you very much. So clinical effectiveness, and I've heard two members of your team talk about clinical effectiveness, and you've actually alluded to and talked about how practitioners see clinical effectiveness and patients.

So I just wanted to ask you this question, which is Dr. Fried asked about QoL data, and in your words, or one of your team member's words, can you just break it down for those who are listening today, what patients would say clinical effectiveness is, based on these studies and based on information you heard from them?

DR. WILLIAMS: Dr. Sprague?

DR. SPRAGUE: Thank you. Stuart Sprague.

Yes, and since you are a dialysis patient, you probably know, on a regular basis, the staff, the dietitian, and frequently the physician or the nurse practitioner, will go over your labs every

month, and we want you to have a certain phosphate level. And many of you are taking, as we mentioned before, 10-12 pills just to control phosphate.

Most patients, in my view, feel that when they have their phosphate level below 5.5, which is the target we've been using on a regular basis, they find that clinically effective. And I do believe -- and you might be able to address this as well -- that if you can get that with 2 or 6 pills a day, as opposed to 10 or 12, you would find that a much more easy and practical approach in order to control your serum phosphate and would consider that clinically effective.

Is that how you wanted the question I understood.

MR. CONWAY: Yes, it is.

Dr. Lewis, I have one quick follow-up, which is this. On the quality-of-life data that you folks did -- I think you had presented it on slide 28 -- how was that used by FDA, from your perspective.

DR. WILLIAMS: I'm sorry. Is that a

question to the sponsor or is that a question --

MR. CONWAY: It's a question to the sponsor. No, it's a question to the sponsor.

DR. WILLIAMS: In terms of how --

DR. LEWIS: I think he's asking if the FDA took into consideration your optimized trial, where the quality-of-life data was.

MR. CONWAY: That's correct. Thanks, Dr. Lewis.

DR. WILLIAMS: Yes. And if you're asking this to sponsor, that information certainly is included in our dossier, and I'm sure the agency has considered the data.

MR. CONWAY: Okay. Thank you.

That's all, Dr. Lewis.

DR. LEWIS: Thank you, Mr. Conway.

Dr. Soergel?

DR. SOERGEL: Thanks, Dr. Lewis.

Along the same theme as Mr. Conway was touching on, FDA and the sponsor I think both agreed that decreasing pill burden could be an important treatment goal. So I'm curious. If you

look at -- and then Dr. Sprague introduced an interesting clinical scenario where you have somebody with a more modestly elevated serum phosphate and trying to get them to their treatment goal of 5.5 or below with fewer pills could be an advantage to the patient.

So I'm curious. If you look at CO-44, where you show a proportion of individuals who achieved less and 5.5, do you have that by baseline serum phosphate? Could you show that individuals with more modestly elevated serum phosphates, a higher proportion of those individuals actually achieved that less than 5.5? Thank you.

DR. WILLIAMS: Dr. Spiegel?

DR. SPIEGEL: We're working to see if we have that data by baseline serum phosphate. But again, to get into Study 202, all the patients had to be poorly controlled, both at screening and study entry. So they all had serum phosphates above 5.5 at baseline, and many of them significantly higher than that, but I don't know if you have a specific breakout by how high they were.

But I think your concern is, were patients going from 5.6 to 5.4? So no; these patients had significant reductions in their serum phosphate in Study 202.

DR. LEWIS: Dr. Soergel, does that answer your question?

DR. SOERGEL: Well, partially. I'm interested if you have baseline serum phosphate by category; for example 5.5 to 6, and you can show that tenapanor -- even in the randomized treatment period or in the randomized withdrawal period, that more patients can achieve their treatment goals and sustain it.

Again, I was curious from Dr. Sprague's sort of vignette of a patient who had a modestly elevated serum phosphate. Can you get a patient to their treatment goal with a much lower pill burden than you can with the current phosphate binders that are available?

DR. WILLIAMS: Dr. Spiegel?

DR. SPIEGEL: Yes. We're trying to pull up the data for 202. But I can tell you for

Study 301, which was a larger study, which didn't have as strict entry criteria, that about 49 percent of the patients had a serum phosphate greater than or equal to 7.5, and that study entry criteria was obviously not as high as Study 202. So while I don't have the data at hand, I suspect a significant proportion of patients in Study 202 also had serum phosphates greater than or equal to 7.5 at study entry. And as I say, we can try to get you that data specifically after the break.

DR. SOERGEL: Yes. I mean, I'm actually asking the other question, which is, the people with lower serum phosphates, can you treat them with tenapanor with fewer pills and actually get them to their treatment goal much more effectively than you could with multiple pills with a binder?

So it's a slightly different question. I'm trying to see if there's a less aggressive approach that you could take with respect to the number of pills you'd administer, and get patients to their treatment goals more effectively.

DR. WILLIAMS: Yes. I'm going to ask

Dr. Chertow to try and address your question.

DR. CHERTOW: Glenn Chertow, Stanford University. Thank you for your question.

I think it speaks to the flexibility that we need as providers. There's more than one way to skin a cat as it were, and right now we have four categories of binders, as you've heard, but all of the options we have for treating hyperphosphatemia are binder options. And whether a patient has mild elevations of serum phosphate and might benefit by having fewer pills, and doesn't have an enormous burden of hyperphosphatemia, or patients who have a greater burden of hyperphosphatemia who might need combination therapy, having a new therapeutic approach with a different mechanism of action, and a complementary mechanism of action, gives us more flexibility as clinicians.

DR. SOERGEL: Okay. Thank you.

DR. SPRAGUE: Well --

DR. LEWIS: Thank you.

Dr. O'Connor? I'm sorry.

DR. SPRAGUE: It was Stuart Sprague. I just

wanted to make another comment.

Again, for those of us who care for these patients, and at least the patient on the panel, if someone's taking 9 pills a day with each meal and have to carry them around, and they can be controlled with 2 pills a day, albeit maybe taking it before breakfast and dinner, I think they would be much happier and pleased with that type of regimen, and I do believe the studies show that there are patients that transition that way. So I do believe that's a very important thing for patients' quality of life and their overall adherence, not just with phosphate binders, but with other medications, when they could cut their pill burden down.

DR. LEWIS: Dr. O'Connor?

DR. O'CONNOR: Hi. Dr. O'Connor here.

Two quick questions. One, I assume we're at the top of the dose-response curve because of the side effects of diarrhea, so if you could just articulate how the rate of diarrhea increases, or decreases, by dose, just in some general terms.

Then I have a question specifically on CO-49, which is the study comparing the drugs here. What was the difference in the pills administered to the patients here? Because it looks like the patients on the sevelamer got an adequate response and change in phosphorus, and I'm just curious how many pills it took, and it appears like they may have been adherent to what that pill management strategy was.

DR. WILLIAMS: Yes. I'm going to address your second question first, since that slide is up, CO-49. You're correct. In terms of the difference in pill burden, for tenapanor, the result that you see here is based on taking two small pills a day, so one small pill twice a day. Then for sevelamer, the median dose increased from initially 6 pills, or a median dose of 6 pills per day, to 9 pills per day at the end of the study. So that's the response to your second question.

For your first question, just in terms of dose response as it relates to the adverse events profile, I'm showing you here data from the 4-week

phase 2b study because there's a placebo arm there, so you can sort of see those. Certainly, there is a dose response in terms of AEs, particularly when you get to the 30-milligram BID dose compared to the lower doses of 1 and 3 milligrams BID. So in this study, again, we studied doses from 1 to 30 milligrams BID and 3 and 30 milligrams QD. And you are correct in terms of the dose responsiveness as it relates to safety, and most of that --

DR. O'CONNOR: Thank you.

DR. WILLIAMS: Yes. Okay.

DR. LEWIS: Thank you.

Dr. Fried?

And would those of you who don't have another question lower your hands, please?

DR. FRIED: Hi. My question is actually a follow-up question to that.

Given that the side effects of diarrhea are dose response, often with drugs that have known GI side effects you start lower than titrate, but I noticed your study starts higher and drops. But in study, I believe it's 32, you still have, in your

2b study, a fairly significant drop in phosphorus. So I was wondering about the dosing regimens, from a tolerability point of view, why start high and go down rather than start low and go up as tolerated?

DR. WILLIAMS: A good question. Again, the results that I showed you from the phase 2b study give us a placebo-adjusted dose response, with the greatest reduction occurring at 30-milligram BID dose. So what we were trying to do, obviously, is balance the tolerability that we saw with diarrhea and the efficacy that we got with the higher dose.

So certainly, starting low and titrating up is one way to do it. Starting at the most efficacious dose and titrating down, if patients had tolerability issues, is another way, and that was the reason we chose it, again, because we were targeting efficacy in a setting where we could truly balance the tolerability that we saw with diarrhea.

DR. FRIED: So just one follow-up question. Is the side effect of diarrhea something that wanes over time, or if you have diarrhea, it continues?

DR. WILLIAMS: Yes. It generally wanes over time. As we noted before, the median duration of diarrhea was about 14 days, and most patients actually had a single episode. Eighty percent of patients actually had a single episode. So it happens early, it's generally mild to moderate in intensity, and resolves relatively quickly.

DR. LEWIS: Thank you.

Dr. Nachman?

DR. NACHMAN: Yes. Thank you. Patrick Nachman. Several of us have asked similar questions in different ways. If we look at the EAS of the randomized withdrawal protocol, or phase, the placebo-corrected effect of tenapanor seems to be somewhere between minus 0.7 and minus 1.4, based on Studies 201, 301, and 202, and much has been made or said about the pill burden.

If you take a patient who has a baseline phosphorus of about 6.5, and you decrease their phosphorus, placebo-corrected, by about 1, then you will achieve your target with the 2 tablets of tenapanor. What would be the pill burden on

sevelamer for that patient?

The converse story is if you start with somebody with severe hyperphosphatemia, let's say about 8, it seems to me that it's very unlikely that they would achieve target with just the 2 tablets of tenapanor, so when we're comparing pill burden, I think we need to compare it based on the baseline hyperphosphatemia.

In the optimized study that is described on page 90 of Ardelyx's brief, if I read this paragraph correctly, the difference in pill burden between the phosphate binder and tenapanor was somewhere between 2 and 3 tablets total daily. It's not 2 versus 10 or 2 versus 9. Can you comment on this?

The final summary of my long question is the following. When we're going to be asked to discuss whether we're supporting monotherapy versus not, I would want to know what is the profile of the patients in whom you think that tenapanor as monotherapy will achieve goal as monotherapy, not in addition to nine other tablets of sevelamer, for

example. Thank you.

DR. WILLIAMS: Yes. Oh, I'm sorry.

I understand your question, and I'm going to ask Dr. Spiegel to address that, as we did look at patients separated out by their baseline serum phosphorus levels, those that were less than 7 and a half and similar to the one that you just described with serum phosphate levels of 8. So we separated them out, and we'd like to share that data.

Dr. Spiegel?

DR. SPIEGEL: David Spiegel. This slide shows those patients who had serum phosphorus at study baseline and greater than 7 and a half for tenapanor versus sevelamer. The top group of bars is for the 26-week completers and the bottom is for the 52-week completers, and it's broken out by achievement of different serum phosphate reductions or the targeting goal of less than 5.5.

What you can see is obviously in the completer populations, the results are pretty similar between tenapanor and sevelamer. Now, the

tenapanor dose we know is one tablet twice a day. I don't know that for each of these bars we know the sevelamer dose, but I can guarantee you, it's significantly higher; yes, 6 to 7 tablets per day, at least, for those groups.

DR. LEWIS: Thank you.

Dr. Butler?

DR. BUTLER: Thank you, Dr. Lewis. This is Javed Butler. My question is for Dr. Chertow, and this is a disease state question.

Did I get this right, that patients with high levels are associated with adverse clinical outcomes, and that there are no randomized-controlled trials that today guide us on how much the levels should be lowered in terms of a well-conducted outcomes of study? And if this understanding is correct, despite the limitations of observational data and biases, are there any real-world evidence data that the thresholds that we're talking about here -- 1.5, or 1.2, or less than 5.5 -- when they're achieved, they're associated with improved outcomes for these

patients? Thank you.

DR. WILLIAMS: Dr. Chertow?

DR. CHERTOW: Glenn Chertow, Stanford University.

Thank you, Dr. Butler. You are absolutely correct with your first statement. And with respect to your second question and comment, there are a number of observational data linking higher levels, higher serum concentrations, of phosphate with adverse clinical outcomes. I showed one during my presentation.

This is data from one of the two large dialysis organizations showing adjusted risks of death. Very similar data were published a year or two later from the second of two large dialysis organizations by a separate group, and these data have been consistently demonstrated from the Dialysis Outcomes and Practice Patterns study and in studies not only in the United States but overseas.

There are also a number of other studies which have linked hyperphosphatemia with other

cardiovascular complications, including cardiovascular calcification, cardiovascular events, and fractures. We are disappointed that there aren't the same levels of randomized clinical trials that we've become accustomed to seeing in cardiovascular medicine, but the observational data are consistent, and repeatable, and have been present for years.

DR. BUTLER: If I may follow up.

Thank you very much for that, but my question was, are there any observational data from large dialysis databases, that if you take a person whose level is 9 and lower it by 1.5, or whose level is 6.5 and lower it to less than 5 .5, that those patients that achieved those thresholds end up doing better than those patients who don't achieve those thresholds, realizing that there are a lot of confounders who might and might not confound. But still, just to get a sense, are there any observational data that lowering levels to these thresholds improve outcomes?

DR. CHERTOW: So I think your observation

and your statement is absolutely right. There are data, as there are for other targets that we use in dialysis practice, including metrics with which the nephrologists on the panel will no doubt be familiar, like Kt/V, a metric of dialysis efficiency. It's been described as a dose targeting bias. They're very difficult -- I'd argue impossible -- to disentangle some of the confounding from being able to achieve targets and the benefit of achieving targets. We've seen that to a large degree in the evaluation of anemia in this population, where patients who achieve higher hemoglobin concentrations do better, although we don't have strong evidence that increasing hemoglobin concentrations improves outcomes. So we don't have the data, but the observational data are compelling, biologically plausible, and consistent.

DR. BUTLER: Thank you very much.

DR. LEWIS: Thank you.

Dr. de Boer? Unmute.

DR. DE BOER: Yes. Thank you, Dr. Lewis.

Ian de Boer, University of Washington. I

appreciated the question about quality of life I think from Dr. Fried earlier, and I was wondering whether we could revisit the data that were shown in response. I'd like a little more context on what study this came from, what was the time frame evaluation, was there a comparator group, et cetera.

DR. WILLIAMS: Yes. You are referring to the data that we showed from Study 402, which was the questionnaire as it relates to patient-reported outcomes on treatment satisfaction?

DR. DE BOER: Yes, please.

DR. WILLIAMS: Alright. I'm pulling it up, and -- I'm sorry. That's a different one. Just give me one minute. Here we go.

Now, can you again repeat your question as it relates to this?

DR. DE BOER: Sure. This is Study 402. That was the first part of my question. Can you remind me the design of 402 and what was the time frame when these questions were asked, and was there a comparator group for the questions and

responses?

DR. WILLIAMS: Yes. I'll take this one down, and we'll pull up the study design, and I'll have -- actually, let me just ask Dr. Spiegel to walk you through the design for Study 402.

DR. SPIEGEL: David Spiegel. This was an open-label study, so patients entered who were on phosphate binders who had baseline serum phosphorus at 5.5 to 10 on a stable dose of phosphate binders. And then they were randomized to one of two different cohorts that were relative to the questionnaire, either cohort 1, where they had a straight switch, they came off of their binders, and they went on tenapanor 30 milligrams BID, or cohort 2, where they had the binder dose decreased by at least 50 percent, and then had tenapanor added to that regimen, and then it could be some adjustments to binders after the first couple of weeks.

The questionnaire was done in this part A, which was a 10-week study, so it was done at the baseline while they were on their binders, and then

at the end of the 10-week period of time. So there was no control arm per se. The patients served as their own control from baseline to the end of part A of that study. Hopefully that answered your question.

DR. DE BOER: It does. It's on a 10-week before or after comparison of switching from phosphate binders to tenapanor. Do I have that correct?

DR. SPIEGEL: Right, either switching or having a dose reduction, and that be added into their -- correct.

DR. DE BOER: Thank you.

DR. LEWIS: Thank you.

Dr. Emerson, I apologize. I'm going to try to work your question in later, but I think we all need at least a five-minute break.

So we will take a quick five-minute break. Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during the break. We will reconvene at 11:45 AM Eastern Time.

(Whereupon, at 11:40 a.m., a recess was taken.)

DR. LEWIS: We will now proceed with the FDA presentation, starting with Dr. Aliza Thompson.

Dr. Thompson?

FDA Presentation - Aliza Thompson

DR. THOMPSON: Hello. My name is Aliza Thompson, and I, along with my colleagues Ling-Wan Chen and Selena DeConti, will be giving FDA's presentation on tenapanor's efficacy and safety.

Over the next 45 minutes or so, we will touch upon serum phosphorus as a surrogate for clinical outcomes in patients with chronic kidney disease on dialysis, including the regulatory framework in which we have thought about serum phosphorus as a surrogate. We will also discuss tenapanor's efficacy and safety.

As I noted in my opening comment, FDA accepts effects on serum phosphorus as a valid surrogate endpoint and basis for approval of products intended to treat hyperphosphatemia in patients with chronic kidney disease on dialysis,

and as agreed with the FDA, the development program for tenapanor was designed to demonstrate efficacy in lowering serum phosphorus in patients with chronic kidney disease on dialysis.

To date, four major classes of agents have been approved in the United States to control serum phosphorus levels in adults with chronic kidney disease on dialysis: calcium-based binders; sevelamer-based products; lanthanum carbonate, and iron-based binding agents. These agents were approved based on effects on serum phosphorus. In studies that established the efficacy and safety of these agents, the therapies lowered serum phosphorus by approximately 1.5 to 2.2 milligrams per deciliter.

So why does FDA accept serum phosphorus as a surrogate endpoint? As previously noted, in epidemiologic studies, elevated serum phosphorus levels have been associated with an increased risk of secondary hyperparathyroidism, vascular, valvular, and other soft-tissue calcification and cardiovascular disease in patients with chronic

kidney disease. And as you saw earlier today, in patients on dialysis, higher serum phosphorus levels have also been associated with increased mortality.

Such epidemiologic data, as well as biologic plausibility, suggests that treating hyperphosphatemia will improve patient outcomes. However, as you've already heard, data from randomized-controlled trials, demonstrating that treatments that lower serum phosphorus improves patient outcomes, are currently lacking.

Given that we have accepted serum phosphorus as a surrogate endpoint and basis for drug approval, how should we think about the size of the treatment's effect on serum phosphorus? Is any magnitude of an effect sufficient? What constitutes a clinically meaningful treatment effect? This is a question we have struggled with, and one that we are asking you, the committee, to address.

In some diseases, we have data from interventional trials that can be used to

understand the quantitative relationship between treatment-induced changes in the surrogate endpoint and changes in clinical outcomes. In this disease state, we do not. To date, the Division of Cardiology and Nephrology has not stipulated that applicants demonstrate a treatment effect larger than some threshold; however, we have indicated that, one, the magnitude of the treatment effect should be clinically relevant and, two, if the size of the effect on serum phosphorus is significantly smaller than the size of the effect of currently approved phosphate binders, then applicants should address the clinical relevance of the effect size.

What about comparative effectiveness? What role does that play in our decision about whether a product should be approved for the control of serum phosphorus in patients with chronic kidney disease on dialysis?

I want to emphasize that there is no comparative effectiveness requirement for drug approval, however, in considering what might constitute a clinically relevant treatment effect

on serum phosphorus, we have considered the precedent set by previously approved treatments, as well as the existing data, both the strengths and limitations of those data, supporting the use of serum phosphorus as a surrogate endpoint. The division also believes that being much less effective than existing therapy means that a drug could delay or possibly prevent patients from reaching their target serum phosphorus levels.

Benefit-risk assessment is an integral part of FDA's review of marketing applications for new drugs. As part of this assessment, we consider both the evidence and also the uncertainty. Based on our review of the data included in the applicant's marketing application, the division concluded that tenapanor is effective in reducing serum phosphorus when used as monotherapy or in combination with existing agents in patients with chronic kidney disease on dialysis.

However, we also noted sources of uncertainty as it relates to tenapanor's benefits. These include, one, whether the magnitude of

tenapanor's effect on serum phosphorus is clinically meaningful when administered as monotherapy and in combination with existing agents; and two, whether it is possible to use a patient's early response to treatment to identify patients who are responders; in other words, assess for response in a patient at some early time point and discontinue treatment in patients who do not appear to have an adequate response.

With that as background, I will turn the presentation over to my colleague, Dr. Ling-Wan Chen.

FDA Presentation - Ling-Wan Chen

DR. CHEN: Good morning, committee members and guests. I am Dr. Ling-Wan Chen, the statistical reviewer in the Division of Biometrics II at the FDA. I will present the efficacy reviewed in three studies in tenapanor.

There were two trials to support use as monotherapy, Studies TEN-02-201 and TEN-02-301. In this presentation, I will simply refer to them as Study 201 and Study 301. Study 201 included an

8-week initial treatment period followed by a 4-week, placebo-controlled randomized withdrawal period. Patients in Study 201 would have 8 weeks of tenapanor treatment during the so-called randomized treatment period, where patients received different doses of tenapanor. Those who completed the 8 weeks of tenapanor treatment would enter the randomized withdrawal period and be randomized to either stay on the tenapanor treatment or placebo.

Study 301 was a phase 3 study that included a 26-week, open-label treatment period, with a 12-week, critical control, and randomized withdrawal period. Patients in Study 301 would have 26 weeks of tenapanor treatment first. Those who completed 26 weeks of tenapanor treatment would enter the randomized withdrawal period and be randomized to either tenapanor arm or placebo arm. Note that the trial also included an active control sevelamer arm for the purpose of safety comparison.

The primary analysis focused on the randomized withdrawal period marked in red, where

the primary endpoint for both studies was the change in serum phosphorus from the end of the randomized treatment period to the last visit with a serum phosphorus assessment during the randomized withdrawal period.

Study TEN-02-202 was a 4-week randomized, double-blind, placebo-controlled trial to support use in combination with existing phosphate binder treatment. In this presentation, I will refer to this study as Study 202. The primary endpoint was the change in serum phosphorus from baseline to week 4.

Here are the key inclusion criteria for Studies 301 and 202. In both studies, the patient should take at least 3 doses of phosphate binder per day, and the prescribed dose remains the same during last 3 or 4 weeks prior to screening. For Study 301, patient's serum phosphate levels should be between 4 and 8 milligrams per deciliter in screening. Analyzed serum phosphorus levels should be between 6 and 10 with an increase of at least 1.5 in serum phosphorus after washout for the

enrollment. For Study 202, participants' serum phosphorus levels should be within 5.5 to 10 at screening and also at the end of the run-in period.

For the administration of tenapanor, participants randomized to tenapanor would be initiated 30 milligrams taken twice daily just prior to breakfast and dinner. In the study, tenapanor was supplied as 10-milligram tablets, and the dose could be down titrated or up titrated to a maximum of 30 milligrams twice a day. Therefore, participants would take 1 to 3 tablets twice a day to achieve the total daily doses of tenapanor.

On dialysis days, patients on hemodialysis were instructed not to take study drug at the meal prior to dialysis, and instead to take it before another meal. If patients skipped a meal, they should take study drug with another meal during the day or at around the time that the meal would have been consumed.

I will now describe the key data sets used in three studies. For Studies 201 and 301, the key data sets defined by the applicant in the protocol

and SAP [indiscernible] were in the intent to treat, ITT, population, and the efficacy analysis set.

The ITT population defined by the sponsor includes the patients who met the study entry inclusion and exclusion criteria; completed the randomized treatment period and entered the randomized withdrawal period, and received at least one dose of study drug during the randomized withdrawal period; and had at least one post-treatment serum phosphorus measurement during the randomized withdrawal period. Although this is not how an ITT population is typically defined, in this presentation, we will follow the sponsor's naming convention and refer to this population as the ITT population.

The efficacy analysis set was a subset of the ITT population. Specifically, the efficacy analysis set only includes patients, while the ITT population achieved a reduction greater or equal to 1.2 in serum phosphorus levels at the end of the randomized treatment period. This efficacy

analysis set is the sponsor's predefined primary analysis set, it [indiscernible], a subset of which a good response during the initial treatment period would likely show treatment effect in the randomized withdrawal period.

For Study 202, the key data sets defined by the applicant for the primary efficacy analysis was the full analysis set, which included subjects who had at least one post-baseline serum phosphate measurement during the study.

Next, I'll explain the subject disposition. For Studies 201 and 301, the blue bar represents the number of subjects initially randomized to the tenapanor treatment in the study. The red bar represents the number of subjects in the ITT population in the randomized withdrawal period, and the purple bar indicates the efficacy analysis set, which includes only subjects in the ITT population who had a baseline reduction of 1.2 in serum phosphorus during the randomized treatment period.

The number on the top of the bar shows the number of subjects in each category. For

Studies 201 and 301, the efficacy analysis set only includes about half of subjects who are in the ITT population of the randomized withdrawal period. Of those subjects who are initially on tenapanor at the start of the trial, 30 percent of them were included in the efficacy analysis set for Study 201 and 31 percent were included in the efficacy analysis set for Study 301.

For Study 202, the green bar represents the number of subjects randomized to the study, and the full analysis set was shown in orange. Only one patient who was randomized to the study was excluded in the full analysis set.

Here I will present the three primary efficacy results for three studies, and the one highlighted in purple on the prespecified primary analysis for Studies 201 and 301. In Study 201, the mean treatment difference between tenapanor and the placebo was negative 0.8 in the efficacy analysis set and negative 0.7 based on the ITT population. The efficacy analysis set in Study 201 did not show a fatal treatment effect than the ITT

population.

For Study 301, the least square mean difference between the tenapanor and the placebo arm was negative 1.4 in the efficacy analysis set, which was the largest mean treatment effect observed among three trials. If the ITT population was used, the treatment effect was only negative 0.7 and more modest in reduction. The sensitivity analyses using a mixed model [indiscernible] a major mixed model [indiscernible] primary approach. For Study 202, which was intended to support use in combination with existing phosphate binder treatment, the treatment effect was negative 0.7.

In conclusion, although the estimate of the average treatment effect in the two studies was similar in the ITT population, negative 0.7, the average treatment effect differs in the efficacy analysis set, negative 0.8 in Study 201 and negative 1.4 in Study 301.

In addition, the efficacy analysis set only included about 31 to 37 percent of the subjects who initially started with tenapanor. Therefore, the

analysis of the ITT population perhaps provides the best estimate of the average treatment effect in the subset of patients who are likely to tolerate tenapanor and remain on this therapy. Tenapanor's average treatment effect on serum phosphorus, when used in patients who tolerate and remain on the therapy, is about negative 0.7.

Today, four major classes of agents have been approved for the proposed indication in the United States. The product [indiscernible] approved for the control of serum phosphorus lowered the serum phosphorus levels by 1.5 to 2.2. Therefore, the magnitude of the mean tenapanor effect appears to be less than that observed with approved agents.

During the review process, one question was raised. Focusing on the main treatment effect ignores the fact that some patients may have a larger clinical relevant response to treatment. We explored whether it might be possible to use a patients' early response to treatment to identify patients who are responders.

Ideally, the strategy used to identify patients with a meaningful response to tenapanor would identify these patients early in the course of treatment so that patients with a poor response can switch to a more effective therapy. To assess whether it might be possible to identify patients who are responders, based on the patients and their response to tenapanor, we explored this issue from several perspectives.

The first one is whether the strategy defined in Studies 201 and 301 can identify patients with a meaningful response to tenapanor. We also conducted several exploratory analyses to assess whether patients who responded to tenapanor well in the early weeks would also likely respond well in the later weeks.

As presented previously, the predefined strategy used in Studies 301 and 201 focused on subjects who achieved a reduction at least greater or equal to 1.2 in serum phosphorus levels in the randomized treatment period, prior to the randomized withdrawal period.

Please note that there was a 26-week randomized treatment period in Study 301, which was more longer than the 8-week randomized treatment period in Study 201. This was expected to identify patients with a meaningful response to tenapanor in the primary analysis; however, the strategy seems effective in Study 301 but not so in Study 201.

The treatment effect in this subset of population was negative 0.8 and negative 1.4 for Studies 201 and 301, respectively. Therefore restricting the primary analysis set [indiscernible] to subjects who had at least a reduction of 1.2 during the treatment period did not appear to reliably identify patients who would have a larger treatment response with tenapanor.

In principle, it may be possible to individualize treatment based on the patient's early response to treatment. Here we conduct the post hoc analysis on the 26-week randomized treatment period data in Study 301. In this exploratory analysis, we focused on subjects who achieved serum phosphorus reduction in at least 1.2

in the early weeks such as week 1 or week 2.

The table here shows about 45 percent of subjects reached a serum phosphorus greater or equal to 1.2 at the early weeks and also maintained a serum phosphorus reduction level at week 26, and less than 30 percent of these subjects reached a serum phosphorus level less than 5.5 in week 26. Please note that the data, based on a 26-week treatment period, did not have a placebo control arm.

The figure here displays the distribution of serum phosphorus levels at week 26 for the subjects who had a good serum phosphorus reduction greater than or equal to 1.2 in the early weeks. The left figure is for subjects who had a response in week 1 or week 2. The right figure is for subjects who had a response in week 2 or week 4.

In [indiscernible] guidelines, one suggested treatment goal for the dialysis patients was that the serum level of phosphates should be lowered to 5.1. The figure of distributions of serum phosphorus levels at week 26 is wide, and a

considerable proportion of subjects had a serum phosphorus level above 5.5 at week 26. This expects that [indiscernible] the subjects had a good phosphorus reduction in the early weeks.

Here are the distributions of serum phosphorus levels at week 26 for the subjects who reached a serum phosphorus level less than 5.5 in the early weeks. The plot shows similar wide distributions of serum phosphorus in these subjects at week 26 even though they had a relative low serum phosphorus level in the early weeks.

We also conducted an exploratory analysis of the randomized placebo-controlled period of Study 201 to assess whether patients with a serum phosphorus level less than 5.5 at an early week could consistently maintain serum phosphorus below these levels in later weeks.

Here we focused on patients with a serum phosphorus level less than 5.5 at week 1 of the randomized placebo-controlled period. The left figure is for the tenapanor group and the right figure is for the placebo group. The top of the

blue bar represents the number of subjects who reached a serum phosphorus below 5.5 in each week. For example, at week 1, 56 subjects in the tenapanor group had a serum phosphorus level below 5.5. The top of the pink bar represents the number of subjects who had a serum phosphorus level less than 5.5 at week 1 and also at a particular follow-up week. For example, among these 56 tenapanor subjects who had a serum phosphorus level below 5.5 at week 1, 26 of them also had a serum phosphorus below this level at week 4.

The triangles with dashed lines indicate the number of subjects who had a serum phosphorus level less than 5.5 consistently in all the prior weeks. For instance, at week 1, of the 56 tenapanor subjects who had a serum phosphorus less than 5.5, 33 of them were able to maintain their serum phosphorus below this level by week 2, and 27 of them were able to maintain their serum phosphorus level throughout week 3. By week 4, 17 of these subjects could maintain their serum phosphorus level in all 4 weeks.

As shown in the left figure, 30 percent of the tenapanor responders at week 1 maintained their serum phosphorus level below 5.5 throughout the 4 weeks. Similarly, it was about 23 percent for the placebo group on the left figure. In essence, there is a fair amount of variability in serum phosphorus measurements, and the statisticians may not be able to easily discern.

In conclusion, these exploratory results suggest that it may be possible to individualize therapy based on a patient's early response to tenapanor, but further data are needed to support the efficacy of a specific strategy. If such a strategy were to be implemented, it would need to take into consideration the variability in serum phosphorus measurements.

Now I will hand over to Dr. Selena DeConti, who will discuss the clinical safety overview.

FDA Presentation - Selena DeConti

DR. DeCONTI: Good morning. I'm Selena DeConti, and I'll present a brief overview of the safety analysis for this risk that we've

identified with the use of tenapanor.

Tenapanor is designed to act locally in the GI tract and is minimally absorbed. It's already approved in the U.S. at a dose of 50 milligrams twice daily in adults with irritable bowel syndrome with constipation, and this product has a labeled warning for severe diarrhea.

Overall, our safety analysis did not identify significant safety concerns for the chronic kidney disease patient population, and this was other than the expected adverse reaction of diarrhea, which is our safety topic of today.

The safety analysis for diarrhea focused on the initial treatment periods of the studies, and this was because of the high incidence of early withdrawal primarily for the diarrhea, which limited the interpretability of the safety data collected later in the trials. Also important to note about the initial treatment periods, there were no blinded initial treatment periods, comparing tenapanor monotherapy to placebo.

For diarrhea to be reported as an adverse

event, the patient had to consider it bothersome, and diarrhea was then classified by investigators as mild, moderate, or severe, based on criteria. Our analysis focused on those patients classified with moderate to severe diarrhea.

As a reminder, for moderate cases, the patient experienced discomfort enough to cause interference with usual activity and/or required specific treatment. Now, for severe cases, the patient was incapacitated with the inability to work or do usual activity and/or the diarrhea required significant treatment measures. These definitions are also included on the next slide.

This slide show the studies included in our analysis for diarrhea and the key details for severity and tolerability. The rates were reported in the initial treatment periods of Studies 301 and 201, and in all 4 weeks of Study 202. Tenapanor is presented here in blue and the comparator is presented in gray.

As you can see, all studies confirm that tenapanor can cause significant rates of diarrhea,

whether with monotherapy in Study 301 or in combination with existing phosphate binders in 202. I'll focus on the findings in 301, which represented the majority of the study population and had the longest initial treatment period, and you can find further analysis of these diarrhea events in the FDA briefing document.

In Study 301, diarrhea was reported in 54 percent of tenapanor-treated patients compared to 8 percent of the sevelamer-treated patients. For severity, moderate or severe diarrhea, presented on the second row, was reported in 39 percent of the tenapanor-treated patients in Study 301 versus 3 percent of the sevelamer arm.

As an assessment of tenapanor's tolerability, we analyzed rates of dose decreases and discontinuation. As shown on the third row, dose reductions were reported in 32 percent of the tenapanor-treated patients in Study 301 versus none in the sevelamer arm, then as shown on the last row, tenapanor was discontinued in 16 percent of patients in Study 301 versus 1 percent in the

sevelamer arm. When you add the dose reductions in 32 percent and the discontinuation in 16 percent, you add these two together, this equals 48 percent; so almost half of the tenapanor arm required modification of treatment for tolerability.

This slide provides some additional details on the diarrhea. Most moderate to severe cases were reported within the first week, with the majority within the first day or two. In the moderate to severe cases, the diarrhea continued for a mean duration of 43 days once it started, with over 30 percent of patients experiencing moderate to severe diarrhea for more than 30 days. Diarrhea was recurrent, meaning two or more episodes were reported for a patient in 14 percent of tenapanor cases versus 2 percent of the sevelamer cases in Study 301.

There were serious cases that included intractable diarrhea and dehydration, which resulted in hospitalizations and study discontinuation. The majority of the cases resolved after dose modification or discontinuation

of tenapanor. We analyzed various subgroups to determine whether certain baseline characteristics could help identify patients at risk for diarrhea. We could not identify predictive factors for severity such as age or weight.

In conclusion, tenapanor causes moderate to severe diarrhea in this patient population. In addition, diarrhea is associated with significant dose modification and discontinuation of tenapanor monotherapy.

Uncertainties include whether the safety profile observed in the studies underestimates this magnitude and severity of the clinical effects of diarrhea or are we looking at electrolyte abnormalities; dehydration; hypotension; dizziness; potentially falls in the real-world setting; and whether the impact of diarrhea on tolerability will limit adherence to long-term treatment. Thus, the safety of tenapanor must be weighed against the clinical benefit.

Thank you for your attention, and that's the conclusion of the FDA presentation.

Clarifying Questions

DR. LEWIS: Thank you.

Dr. de Boer, Dr. Butler, and Dr. Emerson, your hands were up from the previous session. If you could put them down and then put them up again for this session.

We will now take clarifying questions for the FDA. Please use the raise-hand icon to indicate that you have a question, and remember to lower your hand by clicking the raise-hand icon again after you have asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can.

If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you, and the end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

I, Dr. Julia Lewis, will begin with one

question.

I think I have not seen, in either the briefing documents, the way my patients might think of this, and I wonder if the FDA looked at this. So if you think that 8 ferric citrate tablets lowered the phosphorus by an average of minus 2.2, that means 2 ferric citrate tablets would lower it by a minus 0.55, and the 2 tenapanor tablets do that even in the ITT population better than that, and they're much smaller. So if I were to ask my patients, would you want to take two small pills and substitute that for 3 or 4 of those big horse pills we're giving you, I'm pretty sure they'd like that.

Did you guys analyze the efficacy per pill for all the available drugs, based on minus 1.5 or minus 1.8, or whatever it was?

DR. THOMPSON: This is Aliza Thompson for FDA. I think in order to answer a question like that, you'd need a different trial design. You'd actually need to take patients and randomize them to a set dose of one therapy, versus a set dose of

another therapy, versus a set dose of the same therapy with somewhat more pills. So I don't think we can actually get at that issue from the trial that was conducted.

Does that answer your question?

DR. LEWIS: Well, it argues that my question isn't relevant. But, yes, I was just wondering if you had a table that did the math that I did, because I think it's pretty safe to say that if it took 8 ferric citrate to do a minus 2.5, less ferric citrate would have done less, or sevelamer, or any of them. So I'm not as worried about doing the math, but if you haven't looked at it that way, that's fine.

DR. THOMPSON: Dr. Lewis, maybe just also a quick clarification as well. The study that was 301, all the patients are on sevelamer. And in terms of the instructions that were given for how sevelamer would be given, just bear in mind that the only entry criteria for the study was that you had to be on at least, I guess, 3 pills a day of a medication, and they were just told to sort of

follow the package insert.

So again, I think, at least based on 301, we'd be limited in our ability to do that, as well, if that helps.

DR. LEWIS: But they were 9 to 2, right? Yes, it helps some, but they were 9 to 2. But in any case, thank you.

Dr. Fried?

(No response.)

DR. LEWIS: Dr. Fried, you're muted.

DR. FRIED: Sorry. I had to unmute myself. This is Linda Fried from Pittsburgh, and thank you.

My question is for Dr. Chen. You're indicating that the study design affects an estimate of the effect size. In understanding the 1.5 to 2.2 with the other phosphorus binder studies, were those also intent to treat? If we look at the intent-to-treat analysis that you conducted, in the 1.5 to 2.2, are we comparing intent to treat to intent to treat? Thank you.

DR. THOMPSON: Thank you. This is the Aliza Thompson, and I'm actually going to take that

question.

In terms of that reference, 1.5 to 2.2, and how did we derive that, in essence, if you look across the trials that were done to support approval of the phosphate binders, a number of different designs were used: dose ranging designs; crossover designs; some of them used randomized withdrawal designs; and some included also randomized withdrawal with a responder population. But if you look at the entire data package from those trials, they give you an estimate, or we believe they give you an estimate, of about 1.5 to 2.2.

Our sense of the treatment effect size with this program is that if you look across the trials, that, on average, what you would expect here in patients who tolerate the therapy is the treatment effect of 0.7 milligrams per deciliter. All of the trials that were done across all these programs, all of them were somewhat different, so I think it is hard at least to take one trial and compare it directly just to another trial.

Does that answer your question?

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

DR. LEWIS: Dr. Emerson?

DR. EMERSON: Yes. Thank you. This is Scott Emerson.

Back to the efficacy and what would be a meaningful difference, I'd be interested in the FDA's opinion of the observational data that was presented by Dr. Chertow about the observational data and the effects. I'm going to presume those measurements that were there were what the measurements tended to be on some level of phosphate binders, but maybe not optimal levels.

But as I look at that and do my quick back-of-the-envelope calculation, I'm getting about a 20 percent increase in mortality as associated with a 1-milligram difference in the serum phosphate, which would then, if I took the 0.7 or 0.8, translate to roughly a 15 percent increase per difference if we believed that the treatment would achieve that same difference.

How would you view that in terms of clinical

importance?

DR. THOMPSON: Hi. This is Aliza Thompson, and thanks for that question. I think that when we look at observational data, it's challenging because it's difficult to differentiate causation from just association that could be due to confounding factors, so I think it's very challenging.

On the one hand, I think it's probably reasonable to believe that large treatment effects on serum phosphorus, in a population with very high levels, such as the dialysis population, conclude that those will lead to improved outcomes, but I do worry about using those data and not discounting them for the fact that there is likely confounding in the relationship.

I do worry as well that when you get down to smaller treatment effect sizes, especially in the setting of very complex diseases and complex pathways, that the relationship may not hold as well in terms of the ability of treatment effects on the surrogate to translate into treatment

effects on an outcome.

Does that answer your question?

DR. EMERSON: First, I'll say, number one, I'm the first not to believe observational data. Unfortunately, I think, as you predicated all of this, we're in that world; so we're in the world of saying that the FDA is accepting this as a surrogate, based on plausibility, and I don't have an argument against that. I think just the whole calcium deposition and phosphate levels would make a big argument for that. But the idea that when we're in that level, I was actually quite impressed with the data that was presented by Dr. Chertow of a consistent effect of roughly a relative risk of 1.2 for each 1-milligram difference, starting out at the 5.5, say, level, on up into the 9 or 10.

So yes, discounting it, I would do that. There's also the frailty of the patients and things like that. But again, just as we're looking at that, is there a really, really good reason for you to say that the low range isn't as believable as in the upper range, given that data?

DR. THOMPSON: And are you making a comment or asking --

DR. EMERSON: Again, I'm trying to understand where we're drawing the line. Safety is a separate thing. I'm just looking at the efficacy and the magnitude of the effect right now.

DR. THOMPSON: Yes, and I think in many ways that's why we're here today for the discussion with the advisory committee meeting, because of the limitations of the data. I don't know, beyond the concerns that I've conveyed, about the observational data in terms of interpreting smaller sizes of treatment effects, but also note -- and I believe Dr. Mendley could speak to this -- that there is an ongoing trial attempting to generate additional data that will inform understanding of the benefits of phosphate lowering.

DR. EMERSON: Okay. On the other side, the safety question, where we're worried about the diarrhea, the sponsor made the claim that by selecting for patients who are already on phosphate binders, and then removing those phosphate binders,

and then reapplying them in the randomization, or for half of the population and so on, that we should expect that we are selecting for a tolerance among the phosphate binders.

This was certainly an issue that we considered very much in the missing data in the clinical trials oversight committee that worried a lot about this, and the sponsor did not present it in terms of the graded severity of the diarrhea, but they did present on terms of the label for the sevelamer.

Do you have a comment on that, whether you believe that the mechanism of action for causing diarrhea on sevelamer and the tenapanor would be similar enough that this doesn't hold, or whether you really believe this could be quite different mechanisms of action for the safety endpoint?

DR. THOMPSON: Thank you for that question.

Selena, do you want to offer a response? And if you need further clarification on the questions, please ask it.

DR. DeCONTI: Yes. I guess I would go ahead

and repeat that question. What's your specific question? This is Selena DeConti.

DR. EMERSON: Well, across these studies, we have very different patient populations in terms of what their prior treatment was and the selection pressure there might be, and the sponsor tried to invoke that this was a major issue in the much higher diarrhea seen on the tenapanor relative to the sevelamer in 301 during the randomized treatment period, and, a priori, I believe in such selection pressure unless the mechanism of action for the adverse effect might be very different.

So what is your feeling as we try to judge that concept and the patients, if you will, self-selecting by stopping the treatment if they run into very much diarrhea? Are we really seeing it greatly increased in the same patients or is this an aspect of what the selection pressure might be?

DR. DeCONTI: This is Selena DeConti. I believe that we're really seeing a significant increase in the diarrhea. I note that almost half

the patient population was sevelamer naïve, so, yes, some have pre-phosphate binder use prior to studies, but that doesn't account for all of the tolerability difference, in my opinion.

DR. EMERSON: Okay. Thank you

DR. DeCONTI: Does that answer your question?

DR. EMERSON: Yes.

DR. THOMPSON: This is Dr. Thompson; just a follow-up comment. I don't think there's any reason to think that the mechanism of action for a phosphate binder causing diarrhea is the same as for this product. The mechanism of action of this product is responsible, in part -- that both contribute to the phosphate lowering is also playing a role, my understanding, is in the diarrhea.

So if your question was related to the mechanisms of action being different between sevelamer and this product for the diarrhea, I don't think that's the case.

DR. EMERSON: Thank you.

DR. LEWIS: Dr. O'Connor?

DR. O'CONNOR: Yes. Chris O'Connor. Question for Dr. Chen and Dr. Thompson.

On slide 16, the EAS data sets for the primary efficacy endpoints -- and obviously it looks like there's uncoupling between 201 and 301, and I don't know if you want to bring that slide up. I wonder if you have an explanation for that uncoupling between the ITT and EAS. Should we weight 301 greater because of the greater sample size, and was the EAS the primary efficacy endpoint proposed at the beginning of trial, or were these moved up during the trial to be the primary endpoints? Thank you.

DR. THOMPSON: This is Dr. Thompson. I think you had two questions, if I understood correctly. I think the second question was whether the EAS was not the initial analysis population; is that correct?

DR. O'CONNOR: Yes, that's one of the questions.

DR. THOMPSON: And then the other question

was pertaining to understanding the inconsistent results as it relates to the effect of the EAS, using the EAS versus the ITT strategy?

DR. O'CONNOR: It uncoupled coupled between 201 and 301, [indiscernible -- audio breaks].

DR. THOMPSON: Thank you for clarifying.

DR. O'CONNOR: And the point, should we as committee members weight 301 greater because of the greater sample size?

DR. THOMPSON: Right.

Ling-Wan, do you want to address those questions? Maybe start with whether the EAS was the initial analysis population?

DR. CHEN: This is Ling-Wan Chen, the statistical reviewer. In the study design, we agree that the EAS will be in the primary defined analysis set.

The second question is about if we should weight more on Study 301 into the sample size. I think because the two studies are using the randomized withdrawal period and using the standard strategy in two studies, we should weight equally

to see consistent results based on the predefined strategy.

Does that answer your question?

DR. O'CONNOR: Yes. Thank you.

(NO response.)

DR. O'CONNOR: No further questions, Dr. Lewis.

(Pause.)

DR. DE BOER: Dr. Lewis, we can't hear you. It's Ian de Boer here. I'm happy to take the next question if you're --

DR. LEWIS: Oh, sorry. That's my fault.

Dr. Mendley is actually the next one.

Thank you, Dr. Mendley.

Thanks, Dr. de Boer.

DR. MENDLEY: Susan Mendley from NIDDK. I was interested in taking a look at slide 26 and 27 again because it was an unusual presentation of the data.

So you're showing us a histogram of the distribution of serum phosphorus at different weeks among the responder set, and your presentation

suggests that you thought that tenapanor would have changed the population distribution of phosphorus, and I'm a a little confused. Is that a reasonable expectation of the trial, that the distribution of phosphorus would have changed between -- and the same on slide 27.

DR. THOMPSON: This is Aliza Thompson. Thank you for that question.

Ling-Wan, can you clarify what the slide is actually showing?

DR CHEN: Hi. This is Ling-Wan Chen, the statistical reviewer for this application. Slide 26 is showing the actual serum phosphorus labeled at week 26. The goal here is we want to see the distribution of the serum phosphorus level at week 26 among those early responders. From these two graphs, we observe that even though the early responders had a good reduction in the early weeks, they could not reach a good serum phosphorus level at the end of the randomized treatment period.

DR. MENDLEY: They look like

[indiscernible].

DR. CHEN: In this graph, we only observe the data, so it will be slightly biased. The missing data was not included in these two figures.

DR. THOMPSON: This is Aliza Thompson. Maybe just to add a comment -- and Ling-Wan, you can perhaps correct me if I'm wrong as well -- I think one of the questions that comes up is if you just say, okay, I'm going to look at subjects with a serum phosphorus reduction greater than 1.2 at week 1 or 2, and whether they hit or kept their serum phosphorus below 5.5 at the later time point, you can always raise the issue, well, even if you didn't have a lot of people below the threshold, they could have been really near the threshold.

So I think part of what is being shown here is just how wide the distribution is, meaning that this was not about patients just missing the 5.5. You could have patients who actually had serum phosphorus levels of 7, and some actually quite low.

I'm going to stop because I think Jialu may

also have a comment.

DR. ZHANG: Yes. This is Jialu Zhang, the lead statistician. Like Dr. Thompson mentioned, this is to show the variability of the measurements. I also wanted to point out that this is based on a single visit at week 26. What sponsor had shown was their late responder based on 3 visits, but in order to define the late responder, it's only the patient who achieved the certain goal in 2 of 3 weeks, which we call the late responder. So both the sponsor's analysis and our analysis showed the variability of this serum phosphorus level measurement.

DR. MENDLEY: Thank you. So we're seeing a wide range of phosphorus values; am I correct?

DR. THOMPSON: Yes, you're seeing a wide range at week 26 in patients who achieved the desired reduction at week 1 or 2 that's on the left, and then the same analysis is repeated using the reduction in serum phosphorus at week 2 or 4.

DR. MENDLEY: Thank you. That's clear now.

DR. LEWIS: Thank you.

Mr. Conway?

MR. CONWAY: Thanks, Dr. Lewis, and I guess this to Dr. Thompson.

At the start of the day, FDA's initial comments talked about, medically, the desire to show or that we were examining magnitude of effect, and you also referenced the ideal, which is one of the ideals, but by name, an ideal of less pill burden. So here's my question.

How is FDA using, in this division, quality-of-life data as presented in the analysis on efficacy and magnitude of effect? Because I'm a little bit confused about this. It seems to me there's a lot of data that's being presented, but the pivot points that were laid out at the start, it's not wrapping back to what the practical impact is on patients or how that patient's experience is informing what's being recommended by FDA or in the FDA analysis here. Thanks.

DR. THOMPSON: Yes. This is Dr. Thompson. Thanks for that question. I very much agree that patient experience data is very important, and

maybe we could circle back to the applicant. I don't believe the data that they described from Study 402 were actually included in the marketing application that was initially submitted to the agency, so if they could clarify, I just want to say that, generally speaking, these types of studies can be really challenging to design, and I think we would need our internal experts to perform a comprehensive review of the study to really comment further.

I do know that they did collect some data from the Kidney Dialysis Quality of Life Survey and the Dialysis Symptom Index Survey in Study 301, and I don't believe it showed any different or meaningful treatment effect, but maybe the sponsor could clarify.

DR. WILLIAMS: Yes, certainly. You are correct. In my response earlier, I noted that the 402 data was the NDA, and that is incorrect. It's actually published data that is available based on -- and it's exactly what we shared this morning.

As it relates to the quality-of-life data in

Study 301, I think it's important to note that while the manifestations of persistent hyperphosphatemia that Dr. Chertow alluded to are definitely true, hyperphosphatemia itself, it's asymptomatic. It doesn't have any symptoms whereby you ask a questionnaire from a quality-of-life standpoint that shows benefit. So the patient satisfaction data that we collected in Study 402, for that reason, we thought that was really, really important. And again, that data is published and it aligns exactly with what we shared this morning.

MR. O'CONNOR: Great. Thank you, Dr. Lewis. That's it for me.

DR. LEWIS: Thank you.

Dr. de Boer?

DR. DE BOER: Thanks, Dr. Lewis. I had lowered my hand. My question has been, in part, addressed by --

DR. LEWIS: Could you say your name just for the record, even though I said it?

DR. DE BOER: Ian de Boer, University of Washington. I'll withdraw my question for now. It

was largely covered by Mr. Conway. Thank you.

DR. LEWIS: Okay.

Dr. Soergel?

DR. SOERGEL: Thanks, Dr. Lewis. David Soergel, industry rep. I have two questions; either this slide, slide 26, or slide 25, on the responder analysis.

I think the earlier comment was made that there's a difference in the analysis that the FDA has done and the sponsor's done. On the sponsor's slide with the scattergram -- I think it's on slide 53 of the sponsor presentation -- they show about a 79 percent concordance between early responders and late responders, which would seem to be a pretty robust level of predictiveness.

So the first question is to the agency about how they view the sponsor's data, considering that concept of being able to predict responsiveness later, recognizing that multiple measurements will allow for a reduction in variability in the measure.

The second question is for Dr. DeConti. On

slide 33, you made the comment that if you add the number of individuals who required dose reduction and had discontinuation, you get about half the patients. But I believe in the study design itself, titration was part of the study design, so there's a recognition that one might need to titrate this medicine to the appropriate level of efficacy and tolerability. So I wonder if making that addition in that context that you provided is appropriate, and maybe ask for some more clarification on how you view that. Thank you.

DR. THOMPSON: Thank you. If I understand, the first question was about the 79 percent concordance reported by the sponsor in their post hoc analysis.

Ling-Wan, do you want to address our impression of that analysis?

DR. CHEN: Sure. This is Ling-Wan Chen, the statistical reviewer for this application. First, I would like to explain the differences between our analysis and the sponsor's analysis, and I will explain this in two parts.

The first, the sponsor and the FDA used different definitions of the response in the early weeks and the later weeks. For example, we define the later response as the patients who had a reduction greater or equal to 1.2 at week 26, but the sponsor defines the later response as the patient who had at least 2 serum phosphorus reductions greater than or equal to 1.2, 8 weeks, 17, 22, and 26 measurements.

Second, when you calculate the late response rate among the early response patients, the applicant only focused on those patients who had observed the value in later weeks. In their case, there were 50 patients who were early response but did not have observation in later weeks, or that they saw [indiscernible] the denominator of their response rate is all patients who had observations in the later weeks. The fair prediction rate was 79 percent.

In all cases, we compute the late response rate among all the early responders. In this case, the missing rate at week 26 among all the early

responders in tenapanor was about 33 to 35 percent, while 79 percent early response was considered late response according to sponsor's definition. One only needs two out of the three visits to maintain serum phosphorus levels to be late responders, so conditionally, the sponsor's calculation and our calculation are not much different.

I believe that the question here is whether the physician feels comfortable to prescribe the drug to patients, based on the sponsor's definition and the results, which require a long treatment period and observations while considering the variability of serum phosphorus measurements. This is my answer for the first question.

DR. THOMPSON: Thank you. And I do want to stress that the applicant's analysis, essentially that denominator that was noted doesn't consider the patients who did not follow up measurements, who may not have them because of inadequate efficacy or perhaps tolerability issues that led them to discontinue the therapy.

Do you have a follow-up question related to

that or should we move to your other question?

DR. SOERGEL: No, no. Thank you for that response. I think it would be helpful to know, I guess, of the difference in the denominators, how many patients were withdrawn because of efficacy, because for those individuals who were withdrawn for tolerability reasons, obviously you would consider those later measurements differently, I would think. So either FDA or sponsor, it'd be helpful if the majority of the patients are missing data because of withdrawal for poor efficacy. I think it's a different situation than if you're having patients withdrawn for tolerability.

DR. THOMPSON: That's a fair point. I don't believe we've done that analysis.

Ling-Wan?

DR. CHEN: Yes. I think we did not have this analysis.

DR. LEWIS: So then moving on --

DR. SOERGEL: And --

DR. LEWIS: -- go ahead.

DR. SOERGEL: No. I was just going to ask,

maybe if we have time -- I don't know, Dr. Lewis, if we have time. But maybe if the sponsor has those data, that would be helpful.

DR. LEWIS: Sure. I doubt they have it right away, but maybe they do.

If you have it right away, that would be great, and you have the slide ready; otherwise, we'll find time.

DR. WILLIAMS: Yes, not even a slide. I think from an efficacy standpoint, very few patients discontinue because of efficacy; actually, only seven. So most of the discontinuations that happened were related to diarrhea.

DR. LEWIS: Thank you.

Dr. Soergel, does that --

DR. THOMPSON: Actually -- this is Dr. Thompson -- we may just -- and I may need just a clarification there. Are we talking about Study 301?

DR. SOERGEL: I was talking about Study 301, yes.

DR. THOMPSON: Yes. I think maybe we can

circle back after the meeting just in terms of the number of people who discontinued during the randomized treatment period for efficacy reasons. And maybe I'm confused, but do you want to take a second look at that?

Dr. Lewis, I just wanted to make a quick question for you. I think we wanted to have an opportunity as well to just clarify some of the statements that were made during the applicant's presentation. I don't know when would be -- and I don't know if "clarify" is the correct term, but just to show some analyses that perhaps speak to some of the analyses the sponsor presented.

Will be there an opportunity, or could there be an opportunity to do so?

DR. LEWIS: You know, let me hold on the question. I'm going to get Commander Bonner's input into that. I think kind of a rebuttal is not a typical thing asked, if the committee members don't ask you specific questions that would allow you to do that. But let me see what Dr. Bonner says the rules are.

Dr. Butler? I mean, Commander Bonner.

DR. BUTLER: Thank you, Dr. Lewis. Javed Butler. My question is to either the FDA or the sponsor.

I'm really struggling to understand the value add for this new therapy in terms of the pill burden on which there has been a lot of discussion that has occurred today. Why I understand the importance of pill burden, we are discussing an idealized scenario that you require 9 pills with one strategy and 2 pills with the other strategy.

However, the reality is that you have non-responders who will require more different pills; you have responders who do not have sustained response, and over time may require more therapy; then you have responders, but they are already borderline, so they went from 6 to 5.4, in which case the standard therapy will not be 9 pills; and then finally you have those patients who discontinue because of tolerability.

With all the data that we have, do we actually have the number of patients and their

distribution across the ranges of baseline levels in terms of efficacy and safety? What exactly is the pill burden value from the data that we have?

DR. THOMPSON: This is Dr. Thompson. I do want to point out, as well, that in the trials, actually, I think as was noted, patients were -- for example, if you were taking a total 60 milligrams per day of tenapanor, you actually took 6 pills. So I think it's a little challenging there, but I do want to emphasize that I think a key issue here, even before one talks about pill burden, is efficacy. And in terms of the average size of the treatment effect, based on the data that we're seeing in these trials, we think the average size of that treatment effect is 0.7 milligrams per deciliter, relative to what we saw in the other development programs.

DR. BUTLER: But we don't --

DR. LEWIS: But in fairness, the pill burden could be two, not six. They did the 10-milligram pill, and they have a 30-milligram pill, and that's what they're asking. The 10-milligram pill was so

they could titrate, right?

DR. THOMPSON: The pill burden, or rather how the trial was done, presumably was to allow for titration, but the sponsor should answer that.

DR. LEWIS: But if they have a 30-milligram pill, nobody would keep anyone on three 10's, I would imagine.

Anyhow, Dr. Butler, did that get at your question?

DR. BUTLER: Sort of indirectly, but I still don't know what actually happened to the patient in the data that we actually have in terms of the pill burden across the spectrum of baseline levels, but perhaps those data are not there. Thank you very much.

DR. LEWIS: Dr. Nachman?

DR. NACHMAN: Yes. Thank you, Dr. Lewis. Patrick Nachman.

In 2016, there was a network-based meta-analysis of all the trials that have looked at phosphate binders of any kind, and I'm looking at the paper here. There were a total of

77 randomized-controlled trials, including something like a total of 12,000 patients or so. In none of the categories of phosphate binder, there was an association between treatments and decreased mortality.

There has been a lot of discussion today that we don't know how to measure efficacy. We don't know if a small decrease or a larger decrease in phosphorus level is associated with benefit. We acknowledge the fact that we believe there is an association based on the reverse, that if phosphorus is high, therefore outcomes are worse, but we don't know that bringing it down is beneficial.

Dr. Thompson, at the beginning of your presentation this morning, you instructed us not to think about this as a re-evaluation of surrogate endpoint, but I'm having a very hard time defining what is benefit here. I mean, to make my case at the extreme, taking fewer non-effective M&Ms is not a benefit if it's just M&Ms. So we do need to have a better understanding of what is benefit. How

would you suggest we separate the two issues, or how are you separating the two issues in your evaluation? Thank you.

DR. THOMPSON: This is Dr. Thompson. I think that's a very challenging question; in fact, in part why we're here today. The only thing that I can offer is that -- I can't remember if it was about 10 or 15 years ago -- we took a general matter to an advisory committee. At the time, we were trying to understand whether we should accept serum phosphorus as a surrogate endpoint in the pre-dialysis population; that was part of the focus.

The response we got back from the advisory committee, at least as it relates to the data supporting the use of serum phosphorus as a surrogate endpoint, was focused on the biologic plausibility, as well as a sense that within a larger strategy of controlling the abnormalities associated that we see in these patients, and other therapies as well that we give to treat secondary hyperparathyroidism, that this as part of a larger

strategy was leading and would result in improved outcomes, particularly as it relates to bone health.

So unfortunately, the data are what they are, but I do think it makes it very challenging when you start talking about treatment effect sizes that are much smaller than existing therapies, to really understand the benefits and weigh them against the risks of a product. I think that doesn't answer your question, but that's the best I can do.

DR. LEWIS: Dr. Nachman, do you have any follow-up questions or is that ok?

DR. THOMPSON: No. Thank you. Thank you very much. That answers my question. I just want to state that I'm not paid by M&Ms. I didn't need to advertise for them.

(Laugher.)

DR. LEWIS: Okay. I really like them, so I was happy that you even mentioned them.

Ms. Alikhaani?

MS. ALIKHAANI: [Inaudible]. Yes --

DR. LEWIS: Ms. Alikhaani, I'm having trouble -- there you go.

MS. ALIKHAANI: Yes. I am very concerned about older patients who already have a lot of different medical problems and are typically in a very fragile condition. I'm concerned because in the 301 study, over half of the patients in the tenapanor group had adverse events of diarrhea compared to the 2 percent of patients in the sevelamer group.

Because diarrhea has a serious potential outcome relating to dehydration and also the cardiovascular issues -- ischemia, hypotension, and also falls -- I think that in a real-world setting that there are a lot of potential problems with older people that can have deadly outcomes, and I'm concerned about that. Also, in the FDA presentations, it was pointed out that it was unclear whether healthcare providers would be able to identify in clinical practice whether a patient is benefiting from tenapanor, given the variability with the serum phosphorus levels.

So I'm wondering what could be done, or what would be recommended as a way to mitigate this issue with the healthcare providers being able to identify in their offices whether a patient is really benefiting, because if you can't tell if the patient is doing any better, I don't know what the point is. It can't just be about how many pills you take, but there are other outcomes associated with the risk factors that are also very serious and I think have to be looked at very closely.

DR. LEWIS: Thank you, Ms. Alikhaani. I don't think this is the question. This is maybe a comment that we can bring back up in our discussion time.

MS. ALIKHAANI: Well, I thought --

DR. LEWIS: Oh, go ahead. I thought there was a question there, but maybe I'm --

DR. LEWIS: Yes --

(Crosstalk.)

DR. LEWIS: -- go ahead. I might have missed it.

MS. ALIKHAANI: Yes, There is a question.

What could be done to help mitigate the fact that those uncertainties -- there's lack of clarity on whether healthcare providers will be able to identify in clinical practice whether a patient is benefiting from tenapanor because of the variabilities in the serum phosphorus levels. What could be done to help mitigate that?

DR. THOMPSON: This is Dr. Thompson. I think the idea here is, given the data that we've seen thus far, we want the sponsor to do a prospective study that actually tests a strategy for giving this, and show that you can effectively identify patients early on who are having the optimal response. That was our proposal at the time. We did not approve the application because we didn't think the available data were sufficient to ensure that clinicians could easily discern which patients were actually receiving the benefit.

Does that answer your question?

MS. ALIKHAANI: Yes, and I think that what you're recommending is very reasonable. I think we need to have that additional information because

the providers have to be able to clearly ascertain whether the drug is helping the patient or not, to decide whether or not to continue and take further risks possibly. I think that especially family members and caregivers of the patient, outside of the doctor's office, would also want to see something like this. I don't know if there was an advisory committee helping to lead the trial that consisted of these family members and caregivers, particularly when it comes to these older patients who are at higher risk, I think, of potential really bad outcomes, especially regarding cardiovascular disease related to dehydration.

So I think that what you're recommending is a really good idea, and it seems reasonable to me.

DR. LEWIS: Okay. I'm going to cut lunch a bit, but we've only got a few minutes.

Dr. de Boer?

DR. DE BOER: Thank you. Ian de Boer, University of Washington, and this is following up on the questions from Drs. Butler, and Nachman, and this most recent one, too, a question for

Dr. Thompson. I do appreciate and recognize how difficult this question about what the clinically relevant change in serum phosphate is, and soliciting the panel's input there.

We really are in a catch-22, in which we have no high-quality data on clinically relevant outcomes, either available or [indiscernible] to address that issue. And we all are recognizing the observational data here and in other intermediates we've seen in the past, like hemoglobin, and Kt/V, which Dr. Chertow referred to.

I guess my question is -- and maybe it's out of scope here, but why are clinical outcomes not being asked, either before or after approval of a drug for phosphate lowering?

DR. THOMPSON: Sir, this is Dr. Thompson. I think in the dialysis setting, at least historically, I think one would respond -- and then I very much credit the NIH for doing the study that they're doing -- that doing such a trial historically would not have been considered ethical, potentially, but could be wrong. So I

think that that is one piece of it.

I think another piece of it is when we talked about approving these agents for use in the pre-dialysis population, which although some patients have very, very high levels, you're also talking about a much broader population with lower levels, we did take the position that if a pharmaceutical company wanted to get an indication for treating hyperphosphatemia in patients who weren't on dialysis, they would need to establish a benefit beyond serum phosphorus lowering.

I don't know if that answers your question.

DR. LEWIS: Okay -- I'm sorry.

Dr. de Boer, does it answer your question?

DR. DE BOER: It's a tough question, but it does in part. Thank you.

DR. LEWIS: Unfortunately, I apologize to the people who still have questions; we're just going to try to figure out how to fit them in later. But we need to stop for our lunch break, and also maybe to load slides the OPH.

So we will now break for lunch. We will

reconvene at 2:00 p.m. Eastern time. Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during the lunch break. Additionally, you should plan to rejoin at around 1:45 p.m. to ensure that you are connected before we reconvene at 2. Thank you.

(Whereupon, at 1:15 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(2:00 p.m.)

Open Public Hearing

DR. LEWIS: We now begin the open public hearing session.

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it's important to understand the context of an individual's presentation.

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

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

The FDA and this committee place great importance in 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 for 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 only speak when recognized by the chairperson. Thank you for your cooperation.

Speaker number 1, your audio is connected now. Will speaker number 1 begin and introduce

yourself? Please state your name and any organization you are representing for the record.

DR. NIGWEKAR: Hi. My name is Dr. Sagar Nigwekar. I'm a nephrologist at the Mass General Hospital and an assistant professor of medicine at the Harvard Medical School, and also a co-director of the Kidney Research Center at the Mass General Hospital. I do not have any financial interests. I specialize in the management of patients with a rare disease known as calciphylaxis, as well as other conditions of calcification, including vascular calcification and mineral bone disease among patients with kidney disease.

Hyperphosphatemia, as I understand, is a frustrating complication with significant unmet need in the field of nephrology. To begin with, there are robust epidemiological and experimental data that support the role of excess inorganic phosphate as a toxin to cardiovascular and other organ systems.

In my group's previous work related to the rare disease of calciphylaxis, which predominantly

afflicts patients with end-stage kidney disease, we have noted that persistent hyperphosphatemia has a significant risk factor. Patients with calciphylaxis have a high burden of morbidity, primarily related to non-healing and painful skin lesions, and sadly suffer from high mortality, as high as 50 percent to 80 percent at one-year follow-up.

At present, there is no effective or approved treatment for calciphylaxis, so focus is on addressing and mitigating the influence of risk factors such as hyperphosphatemia. The challenge is that the currently available pharmacotherapeutic approaches for hyperphosphatemia are either not well tolerated or have limitations for their efficacy. Some of the agents also impair the absorption of micronutrients and vitamins that are important to our dialysis patients, such as vitamin K. In fact, our group's work has shown that vitamin K deficiency is a major risk factor for calciphylaxis.

So here we are in clinical medicine, trying

to treat hyperphosphatemia with an agent such as sevelamer, which is one of the phosphate binders that may inadvertently introduce vitamin K deficiency. Furthermore, patients with calciphylaxis frequently have nausea related to pain and are not typically eating their meals at regular times. This last point makes it challenging for them to take phosphate binders, as they are tied to the timing of meal intake.

Wouldn't it be great to expand our portfolio of phosphate lowering agents and have an effective agent that has a mechanism of action distinct from phosphate binding, and also has an acceptable tolerability --

DR. LEWIS: Thank you.

Thank you, Dr. Nigwekar. I'm sorry. We stick to the three minutes to be fair.

DR. NIGWEKAR: Thank you.

DR. LEWIS: Thank you.

Speaker number 2, your audio is connected now. Will speaker number 2 begin and introduce yourself? Please state your name and any

organization you are representing for the record.

DR. TIETJEN: Good afternoon. I am Dr. David Tietjen, a nephrologist in private practice in Huntsville, Alabama. I have no financial disclosures. I have been taking care of chronic dialysis patients for over 35 years, which incidentally is nearly three-quarters of the time for which maintenance hemodialysis has been in widespread use in the U.S.

You have undoubtedly seen the evidence that overall mortality of dialysis patients is very high, and that it has not improved to any great extent over the decades. You have also seen that uncontrolled hyperphosphatemia is strongly associated with higher mortality. Efforts to address this aspect of the bone mineral imbalance so prevalent in ESRD have met with limited success. While there are quite a few approved agents for management of elevated serum phosphorus, all have a common mode of action, namely phosphate binding, and all require extreme dedication from the patient insofar as administration with every meal, and even

snacks, is a concern for there to be any chance of actually lowering phosphorus levels.

Given the track record of all the phosphate binders developed and used during my career, it is plain to me that a drug with an alternate novel mode of action is much to be desired. Such an agent exists, the subject of this hearing today. Tenapanor is proven to be safe; indeed, it is already FDA approved for another indication; and it is effective at decreasing serum phosphorus levels, alone or in combination with binders.

Its administration is only required twice daily and not tied to food intake. Furthermore, patients I have observed utilizing this drug during clinical trials find it easy to take and highly tolerable. Therefore, I submit this thought for your consideration.

As long as thoroughly vetted clinical guidelines and, very likely, future value-based care benchmarks all include a target phosphorus level, one that current drugs quite often fail to achieve, then regulatory agencies must do their

part to provide clinicians such as myself the tools with which to treat our patients to those goals. Tenapanor is, in my opinion, an agent which would be of tremendous help for such an effort in the future.

In conclusion, I ask this committee to unanimously recommend approval of tenapanor for treatment of hyperphosphatemia in ESRD patients on dialysis. Thank you.

DR. LEWIS: Thank you.

Speaker number 3, your audio is connected now. Will speaker number 3 begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. WISH: Good afternoon. My name is Dr. Jay Wish, and I've been an academic clinical nephrologist for over 40 years. I have no financial relationship with the applicant.

Controlling serum phosphorus with phosphate binders in dialysis patients is one of the biggest challenges that we as nephrologists face. What currently available phosphate binders have in

common is GI side effects that limit adherence and high pill burden or the need to chew and swallow large pills that are distasteful. As a result, adherence with phosphate binders is suboptimal, with only 56 percent of dialysis patients in the United States having serum phosphorus less than the recommended upper limit of 5.5 in any given month.

When I went to school, 56 percent wasn't asked [indiscernible]. This is not for lack of trying. Nephrologists have frequent conversations with patients regarding the importance of taking their phosphate binders as prescribed to promote bone and cardiovascular health. We ask patients about barriers to adherence, including side effects and pill burden, and we try to match each patient with a phosphate binder that best aligns with them.

When ferris citrate was first approved as a phosphate binder, I discussed with many of my patients, who were complaining of constipation and bloating from sevelamer, whether they'd be willing to trade those symptoms for diarrhea that was associated with a newer agent. Most of those

patients eagerly accepted the offer, and very few have asked to switch back. There is no one-size-fits-all approach to lowering serum phosphorus levels. It has been said that the best phosphate binder is the one the patient will take, which underscores the adherence barriers associated with these agents.

Tenapanor's unique mechanism of action lowers serum phosphorus without the risk of metal absorption or the constipation and bloating that occur when sevelamer expands by absorbing water. Perhaps more significantly, unlike phosphate binders that must be taken with every meal and require the patient to have the binder pills on hand wherever that meal might occur, tenapanor is taken twice daily in the morning and evening, working around the clock to inhibit GI phosphate absorption. This is a much more patient-friendly approach to phosphate reduction, and patients should have the option to determine if this therapy is more suited to their lifestyle.

Our patients need choices of safe and

effective agents they can use to treat their disorders. As nephrologists, we provide advice and information about the risks and benefits of each agent, allowing for informed decision making and patient ownership of their care. We give context to the decision-making process by individualizing the advice to patient's unique clinical, economic, and lifestyle situation.

In the dialysis setting, we see our patients many times per month so drug side effects can be properly evaluated and addressed. My patients trust me to individualize treatment for multiple complications of their kidney disease, including hypertension, anemia, and hyperparathyroidism, discussing the advantages and disadvantages of various therapies, some of which are effectively combined in a step-wise fashion due to differing mechanisms of action.

Now we also have the opportunity in the treatment of hyperphosphatemia to employ a different mechanism of action and combination therapy. I strongly believe that this is an

opportunity that should not be squandered. Thank you.

DR. LEWIS: Thank you.

Speaker number 4, your audio is connected now. Will speaker number 4 begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. MOE: My name is Dr. Sharon Moe, a nephrologist and researcher in Indiana. I am the chief of the Division of Nephrology and Hypertension, the associate dean for Clinical and Translational Science, and the medical director of the Office of Clinical Research at the IU School of Medicine. I have chaired the international and U.S. clinical practice guidelines to help phosphate control.

I have conducted research on the adverse effects of phosphate on blood vessels and cardiac function for 30 years. I use this work to explain to patients the importance of lowering their phosphate. I tell them that I take rat blood vessels, put them in a dish, and add phosphate, and

the blood vessels turn into bone. The lower the phosphate, the less calcification. This is critical, as patients who lower their phosphorus will have less arterial and heart calcification, and that kills our patients with kidney disease.

What I also know due to my experience in patient care, research, guideline committee work, and emails from clinicians is that managing hyperphosphatemia is frustrating for patients and their care team. Why? Because phosphate binders are large pills that must be taken with meals, ruining what joy there might be in eating.

When I give talks about phosphate lowering agents, I can compare and contrast all of the available agents based on their trials, but I always end with the slide that says, "The best phosphate binder is the one that patients will take." That is why we need multiple choices, including tenapanor, that is a small pill that does not need to be taken with meals. Having multiple choices ensures finding one that works for that patient, their diet, their lifestyle, and their

GI tract. This is the only way to improve adherence.

Nephrologists like myself mix and match phosphate binders to achieve the best drop in phosphate with the least side effects for that patient. This is not dissimilar to chemotherapy and management of hypertension or rheumatoid arthritis. You start with one of the multiple medications approved, and then change based on efficacy and side effects for that patient. Sometimes you start specific medications because of the so-called side effects.

Approving tenapanor will give us, and more importantly the patients, a chance to have drugs that work for them. To effectively do so will require many different phosphate lowering agents with different mechanisms of actions. Treatments only work if the patients take them. Please approve tenapanor to give us an entirely new mechanism of action to add to our arsenal of therapies. I don't want my patients' blood vessels to turn to bone. Thank you.

DR. LEWIS: Thank you.

Speaker number 5, your audio is connected now. Will speaker number 5 begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. SILVA: Good afternoon. I am Dr. Arnold Silva, a nephrologist and director of clinical research at Boise Kidney and Hypertension Institute in Boise, Idaho, in conjunction with Frenova Renal Research. I have served as a clinical investigator on studies evaluating the safety and efficacy of the phosphate blocker, tenapanor, to treat hyperphosphatemia in patients with end-stage kidney disease receiving dialysis. I am not financially compensated for my time today.

Hyperphosphatemia significantly impacts the clinical outcomes of patients with end-stage kidney disease. In 26 observational studies conducted over the last two decades, serum phosphate levels greater than 5 are associated with an increase in mortality and hospitalization for cardiovascular events and can also affect the patient's

eligibility for a kidney transplant.

Maintaining phosphate in the target range is, however, associated with a reduction in cardiovascular morbidity and mortality. These observations have resulted in the recommendation by the Kidney Disease Improving Global Outcomes, KDIGO, that serum phosphate be lowered to the normal range of 2.5 to 4.5. Nevertheless, despite the importance of maintaining phosphate in the normal range, a serious unmet treatment need remains.

Traditionally, hyperphosphatemia has been managed with dietary phosphate restriction and phosphate binders, however, 77 percent of dialysis patients are unable to consistently achieve a target phosphate level irrespective of the type of phosphate binder used. I believe tenapanor can significantly help more patients achieve target phosphate levels.

Phosphate absorption by the gut occurs by both paracellular and transcellular pathways. Tenapanor is not a phosphate binder, but rather a

phosphate blocker that works via novel mechanisms to block the primary paracellular pathway of phosphate absorption. Studies with tenapanor used alone or in combination with a phosphate binder have shown that 47 percent of patients achieve a phosphate level less than 4.5, which translates to a 63 percent improvement versus the standard-of-care outcomes reported in the June 2020 Dialysis Outcomes and Practice Patterns Study. Tenapanor also markedly reduces the pill burden for dialysis patients. Studies have shown that lowering the number of pills taken by patients significantly improves compliance with medical treatment regardless of the disease state.

In summary, I enthusiastically recommend the approval of tenapanor, a much needed additional tool to better manage hyperphosphatemia, and would like to thank the committee for the opportunity to speak today. Your consideration is most appreciated.

DR. LEWIS: Thank you.

Speaker number 6, your audio is connected

now. Will speaker number 6 begin and introduce yourself? Please state your name and any organization you are representing for the record.

MR. FORFANG: Yes. My name is Derek Forfang from San Pablo, California. I'm a third-generation diabetic with kidney failure, and I have no financial disclosures for speaking today. I'm representing myself.

When my kidneys failed in 1998, it was the most difficult time in my life. I felt the disease was a disease of losses. I lost my well-being, my livelihood, and my freedom to eat well. I had mastered a diabetic diet, but this was a whole other thing when it came to eating a low phosphorus diet. My dieticians gave me a few pages of high phosphorus foods to avoid, and I stopped eating those.

But that wasn't that simple. My phosphorus was still high. I started taking binders and quickly got up to 6 binders with each meal and 2 binders with each snack. Carrying binders around every day was burdensome. I had Ziplocs of binders

that I would put in my pockets when I would go to a friend or family member's house. When they would prepare foods, either I didn't know what was in the food or I knew it was something I shouldn't eat, but I would still eat a portion to be polite; and because I needed to keep my glucose at a manageable level, I had to eat. I felt guilty that I was eating something I shouldn't, especially if I forgot to bring my binders, which happened on occasion.

The joy of eating for me was mostly gone. Even with all of that, I have suffered consequences of high phosphorus. I have calcium deposits in my heart, left lung, the lining in my stomach, as well as severe vascular complications and amputations.

We need new tools to fight phosphorus. Binders cause me bloating, loss of appetite, severe constipation, and they were difficult for me to swallow. They'd pop back up in my mouth. I have to swallow them several times. My children, who now are grown, remember the huge white pills sitting by my dinner plate. Tenapanor could have

possibly helped me by lowering my phosphorus, maybe taking no binders or few binders, and help me alleviate the constipation I have suffered for two decades, many times now not having a bowel movement for over two weeks. An older patient counseled me that I should consider my bowel weight and how many days that I haven't had a bowel movement when talking with my nurse about setting my dry weight. It's a huge issue for me and many other patients, and we take stool softeners daily.

We have multiple tools to fight high blood pressure. I probably have taken more than a dozen different medications over the years in different combinations, finding what works best for me, and the blood pressure has been under fair control. But we only have one tool to fight phosphorus, and it's not great to say the least.

Please approve tenapanor. We are fighting for our lives and we need your help. When we talk in percentages today, we're talking about hundreds of thousands of patients, the individual care in our lives, so I want you --

DR. LEWIS: Thank you.

MR. FORFANG: -- to please consider that.

DR. LEWIS: Thank you, speaker number 6.

MR. FORFANG: Thank you so much.

DR. LEWIS: Thank you.

Speaker number 7, your audio is connected now. Will speaker number 7 begin and introduce yourself? Please state your name and any organization you are representing for the record.

MS. HARTWELL: Hello. My name is Lori Hartwell, and I'm the founder and president of Renal Support Network. RSN empowers people who have kidney disease to become proactive in their care, and most importantly, have hope. I founded RSN back in 1993 after having four kidney transplants and spending over a decade on dialysis. Phosphorus has always been a struggle to manage, as it's in most foods and drinks as a preservative. If not managed, it can have a long-lasting impact on our health. I do not have any financial disclosures.

I am pleased that innovative therapies are

being developed that have the potential to lower phosphorus with less treatment burden for people that have advanced kidney disease because they are desperately needed. We currently have only one class of therapy available for hyperphosphatemia, phosphate binders, which often places a significant treatment pill burden on people who have kidney failure. Large pills can be difficult to swallow. It is often necessary to take a handful of pills with every meal and snack, while at the same time monitoring and limiting fluid intake.

Tenapanor has the potential to significantly reduce the current pill burden that could lead to better quality of life, better patient compliance, and most importantly, better outcomes. Phosphorus levels and their impact on bone and mineral management are critical to people who have kidney disease. We suffer and become debilitated if phosphorus is not managed appropriately.

As the FDA acknowledges that tenapanor trial results indicate safety and efficacy, why not allow doctors and patients to have the choice? Quality

of life and patient compliance is important. Currently, in any given month, 42 percent of patients are unable to achieve their target phosphorus levels, and over a 6-month period, 77 percent of patients are unable to maintain target phosphorus levels.

For patients dealing with hyperphosphatemia, we need treatment options. Drug treatments don't work for all patients in the same way. Phosphorus management is one of the most difficult -- and I just want to repeat, difficult -- elements we must manage, and we need all the tools available to do so. Some of my peers have had calciphylaxis, and it's the most painful thing anybody would ever have to endure, and we want to avoid that.

Please approve tenapanor, as it could provide the innovative treatment my kidney kin need to thrive. Allow doctors and patients to have treatment options that can be clinically meaningful to their well-being so we can live the life we were meant to live. Thank you for listening to the patient's perspective.

DR. LEWIS: Thank you.

Speaker number 8, your audio is connected now. Will speaker number 8 begin and introduce yourself? Please state your name and any organization you are representing for the record.

MR. BARRIOS: Good afternoon. My name is Alex Barrios, and I'm here as a patient representative for the National Kidney Foundation. I have no conflicts to report.

Thanks so much for the opportunity to provide my perspective. I'm currently an in-center hemodialysis patient, and I feel strongly about the need to advocate for ways to improve the management of high phosphorus. I find there's a major lack of understanding between the patients and their care team as it relates to the struggle with taking phosphate binders, communicating what's important to us, and the need for clear and concise directions around medication management for lowering phosphorus.

A few weeks ago, the National Kidney Foundation did a survey among 475 dialysis patients

to better understand experiences with managing their phosphorus levels. The survey found that more than 80 percent of respondents struggle to manage their serum phosphorus levels, and 92 percent are interested in a new treatment to help manage their phosphorus. These and the other survey results point to the difficulty people living with kidney failure, being treated with dialysis, have coping with a low phosphorus diet and their current medication schedules.

As a patient advocate, I know the importance of providing educational resources to patients and their caregivers in small bite-sized pieces of information. Patients are overwhelmed with so much information about the medicines we take, often without even understanding exactly how the medication should be taken in the first place. This has been my personal experience with phosphate binders.

Medication management should be discussed at all points during the patient journey, especially for those with elevated phosphorus and incredibly

high pill burdens. I agree with my fellow patient surveys that there should be additional treatment options to help meet the needs of all patients, and particularly those with dangerously high phosphorus. This will allow for patients and doctors together to make decisions around the best possible treatment for the individual.

Lastly, as a person of color, health equity and health literacy must urgently be brought to the forefront in all aspects of kidney care in order to address the mistrust of doctors and healthcare systems in all communities. Thank you to the FDA for allowing me to speak on behalf of all my fellow patients. We greatly appreciate your commitment and efforts to improve outcomes for the kidney community.

DR. LEWIS: Thank you.

Speaker number 9, your audio is connected now. Will speaker number 9 begin and introduce yourself? Please state your name and any organization you are representing for the record.

MS. BURTON: Good afternoon. My name is

LaVarne Burton, and I'm president and CEO of the American Kidney Fund. I do not have any personal financial relationship with the applicant.

The American Kidney Fund fights kidney disease on all fronts. As the nation's leading kidney nonprofit, AKF works on behalf of 37 million Americans living with kidney disease and millions more at risk, with an unmatched scope of programs that support people wherever they are in their fight against kidney disease, from prevention through post-transplant living.

On behalf of the American Kidney Fund and the patients we serve, I thank you for the opportunity to speak this afternoon. Historically, there has been a lack of innovation in nephrology. Many treatments have remained mostly unchanged for decades. Fortunately, in recent years, we've seen innovation in rare kidney disease, CKD progression, and the management of comorbidities. These have improved the quality and length of life for millions and represent a small but important growth in treatment innovation.

However, new treatments coming to market for people with kidney disease have been slow to come and insufficient. While we have been optimistic about the promise represented by recent investments in research and development, the actual impact has been disappointing. The FDA's rejections of drugs for kidney patients are keeping new and innovative therapies out of reach. As a result, America's has kidney problem will only get worse, particularly for people of color who are hardest hit by kidney failure.

Kidney disease is complex. Not every drug works for every person, and it is imperative that a variety of treatment options are available. The American Kidney Fund strongly supports the need to expand treatments for people on dialysis who must take phosphorus-binding drugs to control their serum phosphorus levels. While there are current drugs that address this need, patients need to be able to access a full range of treatments to make an informed choice about the medications that are best for them, such as those that will reduce the

pill burden by lowering the number of medications taken on a daily basis and ones that may open more diet choices.

According to the CDC, 360 people start dialysis every 24 hours in this country. These patients desperately need increased collaboration between the federal government and researchers to create clearer pathways to test and approve new drugs. Thanks again for allowing the American Kidney Fund to speak to you today. We appreciate the committee's careful attention to improving the lives of kidney patients through treatment innovations.

DR. LEWIS: Thank you.

Speaker number 10, your audio is connected now. Will speaker number 10 begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. PERGOLA: Good afternoon. I'm Dr. Pablo Pergola, a practicing nephrologist in San Antonio, Texas, with over 25 years of experience treating patients on dialysis and with hyperphosphatemia.

I'm not being compensated for my presentation today.

I have first-hand experience treating dozens of patients with tenapanor in multiple clinical trials. You're gathered today to evaluate expanding the indication of the approved drug tenapanor for the treatment of hyperphosphatemia that was already considered safe by the agency for use in patients with constipation.

For nearly 30 years, there has been no advancement in the treatment of hyperphosphatemia, except for the approval of non-calcium, non-resin phosphate binders. Nowhere in medicine, except for the dialysis procedure itself, have we seen less innovation. Despite phosphate binder use, 40 to 70 percent of patients cannot maintain serum phosphate levels consistently as a goal, despite using a liberal upper limit of 5.5 milligrams per deciliter, and a whole 90 percent of patients fail to maintain positive values consistently in the normal range, despite taking maximal doses of binders and receiving optimized dialysis therapy.

A significant number of patients cannot take binders at any dose or are unable to take them continuously due to side effects and thus remain undertreated patients. Patients taking phosphate binders routinely deal with significant side effects and have the additional burden of taking multiple large pills with every meal. In addition, because the amount of phosphorus is removed by dialysis, and binders are limited and fixed, patients must adhere to very strict diets that limit choices and affect protein intake, resulting in protein malnutrition.

Because of this mechanism of action, tenapanor has minimal or no systemic side effects, and the increase in bowel frequency, the most frequent side effect, is actually welcomed by many patients with chronic constipation, it is obvious to both patients and practitioners, and in my experience, self-limiting and easily manageable.

Given the challenges and limitations of available treatments for hyperphosphatemia, and the significant intra- and interpatient differences in

serum phosphate levels, the size of the phosphate lowering effect of a particular treatment should be based on individual patient needs and not by a statistical significance. Because of the unmet need, it is imperative to expand treatment options for our patients; in particular, therapies like tenapanor with a novel mechanism of action that is complementary to phosphate binders and dialysis.

In my opinion, the best way we serve our patients today is by supporting approval of tenapanor. Once available, patients and practitioners can then decide the most appropriate therapy for each patient, based on their individual needs. Thank you for your attention today.

DR. LEWIS: Thank you.

Speaker number 11, your audio is connected now. Will speaker number 11 begin and introduce yourself? Please state your name and any organization you are representing for the record.

MS. EVANS: Good afternoon. My name is Lisa Evans. I'm a 58-year-old, in-center hemodialysis patient living in Dalton, Georgia. I have no

financial disclosures.

I have polycystic kidney disease, an inherited condition that causes cysts to grow in the kidneys, and eventually led to end-stage renal disease with dialysis for me. My PKD was diagnosed during initial testing to be a donor for my mother in 2004.

Managing my phosphorus levels has always been difficult because of the number and size of the phosphate binders I need to take daily. Currently, I take four of these half-inch long pills with each meal. Can you imagine having to take 12 horse pills a day? And to make it worse, you need to take them with small sips of water because I'm restricted to 32 ounces of fluid a day. That's 4 glasses of any kind of fluid, no exceptions. It doesn't matter how thirsty I am or how hot it is, and it gets hot here in Georgia. Swallowing those big pills with only a small sip of water is almost impossible, and to make things worse, I need to take these big pills at different times during the meal for maximum effectiveness.

That's a challenge I face every day, 3 times a day.

My nephrologist understands the challenges of managing phosphorous and referred me to the tenapanor study. While in the trial, the tenapanor tablets worked much better for me than any binder I've taken. They brought my phosphorus level under control for the first time, and the tablets being so small was another huge benefit, as I could take them easily with my food restrictions. My life felt like my own again, as I didn't have to dread meal time and the burden it brings 3 times a day.

Since leaving the trial, my phosphorus level is creeping up again, and I'm not sure what will happen to me next, as the thought of having to take as many as 5 pills per mL is overwhelming. It's a horrible feeling to think about that on top of the dialysis I need to manage. But today you have the opportunity to help me, and so many others out there like me, by giving us another option to manage our phosphorus with our doctors. I ask you to think of us and the daily challenges we face managing our phosphorus as you consider your

decision today. Thank you for listening to my story.

DR. LEWIS: Thank you.

Speaker number 12, your audio is connected now. Will speaker number 12 begin and introduce yourself? Please state your name and any organization you are representing for the record.

MS. PACE: Good afternoon. My name is Lori Pace. I'm the senior director of nutrition services at Satellite Healthcare in San Jose, California, and I have no conflicts to report related to my statement today.

I've been a registered dietitian, taking care of people on dialysis for 25 years. In those 25 years, I've found phosphorus management to be the most challenging aspect of my work with this population. As a demand for convenience food increases, phosphate additives are increasingly abundant in our food supply, and conventional dialysis is inefficient at clearing phosphorus.

The overwhelming majority of people on dialysis are therefore dependent on phosphorus

binders to attempt to achieve control of serum phosphorus. In 18 years at the chairside with patients, day in and day out, in the real world, I've seen and heard my patients' ongoing struggles with binders, from side effects to challenges adhering to the complex dosing regimen, to negative impact on quality of life. Despite frequent counseling, I've had only a handful of patients in my career who understood and were able to consistently take their binders as prescribed and counseled.

Today, approximately half of the 8500 dialysis patients in my organization have a phosphorus level in the target range at any given time. With our current tools, we are not successfully helping patients to consistently achieve acceptable phosphorus levels. We need new tools to help improve patients' outcomes and quality of life. Tenapanor's unique mechanism of action and twice daily dosing hold a great deal of promise for arming patients with a tool that's both easier to use and clinically effective.

Given the significant data associating increased risk of mortality with increasing levels of serum phosphorus, any reduction in serum phosphorus is clinically meaningful for patients. One of the aspects I've found most rewarding about working in dialysis is the opportunity for frequent follow-up with patients. For dialysis interdisciplinary teams, there's a strong and effective care management function for both in-center and home dialysis patients. The IDT is usually the first to know when there's a change in a patient's condition such as side effects from medications or treatments. The IDT is able to assess and notify the treating nephrologist quickly, and the interventions are timely.

Nephrology dietitians are eager for better ways to help our patients with healthier more fulfilling lives. We currently spend countless hours with interventions and quality improvement projects related to phosphorus, with limited to no long-term effectiveness. Adding tenapanor to our toolbox for managing phosphorus would allow

dietitians to invest more time in the care and counseling of patients to improve other important outcomes in the population, such as prevention or treatment of malnutrition, management of diabetes or hyperlipidemia, and management and support of weight loss goals for transplant eligibility. Thank you for your consideration.

DR. LEWIS: Thank you.

Speaker number 13, your audio is connected now. Will speaker number 13 begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. GILLANI: My name is Mike Gillani, and I have no financial disclosure. I'm talking to you today about my condition. I have a chronic kidney disease. I'm sharing my story today because I want you guys to understand how difficult it is to maintain your phosphorus levels when you have a kidney disease. To keep my phosphorus level in control, I have to take eight large pills everyday with my meals, and even that did not help.

Once they put me on a trial drug called

tenapanor, my life was totally changed. For the very first time, my phosphorus level was under control and all the pimples on my body went away; otherwise, I always had to wear long-sleeve shirts and pants no matter how hot it is outside because I can't even touch my own skin, which was very, very painful. I thank you for your consideration. Thank you.

DR. LEWIS: Thank you.

Speaker number 15, your audio is connected now. Will speaker number 15 begin and introduce yourself? Please state your name and any organization you are representing for the record?

DR. CALLENDER: Hello. I am Dr. Ealena Callender, senior fellow at the National Center for Health Research. Our think tank conducts, analyzes, and scrutinizes research on a range of health issues. We do not accept funding from companies that make products that are the subject of our work, so we have no conflicts of interest.

Elevated phosphorus is a serious complication encountered by the majority of

patients with chronic kidney disease on dialysis. Tenapanor represents a novel approach to this major problem. Still, we are concerned about this product because the data do not show to be more effective than current options, and significant side effects may lead to poor patient compliance.

This new drug is intended for a patient population subject to significant inequities. In the United States, end-stage renal disease disproportionately affects black men and women. While black Americans represent 13 percent of the country's population, they comprise more than 30 percent of patients with end-stage renal disease in the United States. Blacks are also nearly four times more likely to progress from early kidney disease to end-stage renal disease than non-Hispanic whites. Also, hyperphosphatemia and its related adverse outcomes are more common in blacks than whites.

Furthermore, studies show that the prevalence of elevated serum phosphate significantly increases with decreasing income [ph]

outcome. At least 50 percent of dialysis patients fail to reach the ideal serum phosphate range despite having multiple approved options for management. Studies show the heavy pill burden and high prevalence of side effects contribute to poor adherence and decreased health-related quality of life. Patients need effective options that will make phosphorus control easier and more tolerable.

Today, the committee must decide whether the magnitude of tenapanor's treatment effect is clinically meaningful. Unfortunately, tenapanor's efficacy does not surpass that of currently approved medications. Data analysis shows that tenapanor causes a mean decrease of serum phosphorus, equivalent to about half that of approved treatment options. The effects are similar , whether the drug was used alone or in conjunction with other agents.

The committee also must consider the safety and tolerability of this new drug. Tenapanor's regimen of 2 to 3 pills taken twice a day contributes to improved tolerability. On the other

hand, diarrhea is a common side effect and led to discontinuation of the drug by 16 percent of trial participants. This data suggests adherence may be a problem in a real-world population.

Tenapanor satisfies the need for a simpler approach to treating hyperphosphatemia in chronic kidney disease patients on dialysis. While it may improve health-related quality of life by reducing the pill burden, it is not as effective as currently approved medications. It is unclear how approval of a drug with a limited treatment effect and high rate of side effects will benefit this group of patients facing a high mortality risk. Thank you for the opportunity to speak today, and I appreciate your time and consideration.

DR. LEWIS: Thank you.

Speaker number 16, your audio is connected now. Will speaker number 16 begin and introduce yourself? Please state your name and any organization you are representing for the record.

MR. SOLIS: Hi. My name is Alex Solis. I have no financial disclosures. I am 53 years old,

and I've lived in Nampa, Idaho for the past 20 years. I am a dad of three beautiful daughters, who are 18, 22, and 25. I used to work for the City of Meridian in Idaho until 2015 when I was diagnosed with end-stage renal disease. I was put on the transplant list in 2018, [inaudible - audio fades] -- to get a kidney due to, in part, of my problem managing my phosphorus level.

If you do not have to think about your phosphorus level, you might think that managing is just watching what you eat, but let me tell you, it is a real challenge to watch every single thing you eat, not just big meals, but everything, all day long. Every day is non-stop, and that takes 5 to 6 huge pills with every meal, every day, while not being able to drink that much water. All that is part of life when you are on dialysis doing your best, while you're and hoping your weight, your number, and the right kidney [indiscernible] will come along for you. It's a struggle I hope you never have to face.

When my doctor at my dialysis center told me

about the tenapanor trial, I was so happy to have another option. The pills were so much smaller and easier to take and may make such a difference in managing my phosphorus numbers. It helped me get to the next step, to my kidney transplant, that I received on August 2021. I'm so grateful to everyone and everything that supported me in getting my kidney and continue my work [inaudible].

The drug you're looking at today, as you think about your decision, I'd like you to remember that many people like me are out there who are doing their best to work with their doctors and manage their diets, and still struggle to manage their phosphorus. These are good people who are desperate to get a kidney transplant but can't because they can't manage their phosphorus levels. Despite doing all the right things, they deserve obtaining a -- like tenapanor. Thank you for all the hard work you guys are doing and/or --

DR. LEWIS: Thank you.

MR. SOLIS: Thank you.

DR. LEWIS: Thank you.

Speaker number 17, your audio is connected now. Will speaker number 17 begin and introduce yourself? Please state your name and any organization you are representing for the record.

MS. EDWARDS: Good afternoon, and thank you for the opportunity to share the patient perspective of the difficulties of managing phosphorus levels and how desperately we need a new way to treat phosphorus levels in dialysis patients.

My name is Dawn Edwards, and I have no financial disclosures. I'm a 32-year kidney patient from New York, New York. Of the 32 years I've been on this journey with kidney disease, 26 of them have been challenged with trying to manage my phosphorus levels. I only had a 6-year break with a transplant that failed and sent me back to dialysis.

Among the [inaudible - audio gaps] day-to-day challenges of being a dialysis patient, trying to manage acceptable phosphorus levels is one of the most challenging. I and many other dialysis

patients have endured years of lab reports with sad faces on them, followed by blame and shame from some dietitians for not making goal, only to try harder to take my binders with every meal and snack and to be vigilant about my diet, only to hear the same news the next month.

The fact is, [inaudible] -- to follow a low phosphorus diet, almost everything has phosphorous in it, and food labels don't show how much. It is even more daunting -- and patients that live in food deserts, with fast food on every corner and fresh fruits -- a car ride away.

I am fortunate as a home dialysis patient to work and to be able to order my groceries now, but at the pandemic, when everything shut down, we were unable to get food delivered to our neighborhood. The supermarket with the quality food was too far away, and I was left to look for groceries at the neighborhood Dollar Store. My 77-year-old mother and I ate grilled cheese and bacon sandwiches until [inaudible] -- as the provider, and of course my phosphorus levels were off the charts.

As a working woman, one of the things I enjoy is to go out and eat with my friends after work and on the weekends. I feel so embarrassed at the table, pulling out that huge bottle of pills that never fit into an evening bag, and wolfing down those six enormous pills during the meal, not even before or after the meal, so I could excuse myself.

Family and social gatherings always lead to a conversation about kidney disease, what I can and can't eat, and how do I swallow all those pills. Sometimes I get so embarrassed that I just skip taking them just to have a meal in peace. It is an interruption when I'm at work, and my --

DR. LEWIS: Thank you. I'm sorry.

Speaker 17, I'm sorry. Thank you very much. Your time is up.

Speaker number 18, your audio is connected now. Will speaker number 18 begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. MANLEY: Hi. My name is John Manley.

I'm a clinical nephrologist in Asheville, North Carolina, and I work with [indiscernible] Mountain Kidney Associates. I have no financial disclosures. I have personal experience with tenapanor as a principal investigator, and I study with peritoneal dialysis patients. During this study, I observed a marked improvement in serum phosphorus in several patients who, for quite some time prior to the study, had very poorly controlled phosphorus levels, and during the study, their phosphorus levels came into target range. I was very excited at the time of the study, but very disappointed when it was not FDA-approved

From a side effect perspective, it was very well tolerated. My patients were excited about using this phosphorus agent, and it was just very well tolerated. That's all I really have to say.

Clarifying Questions (continued)

DR. LEWIS: Thank you.

I want to apologize to anyone I had to cut off. To be fair, everybody gets the same three minutes, so I apologize.

The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. Prior to the committee turning its attention to the task at hand, I would like to take a moment to catch up a little bit. I would like to ask the sponsor if they have very specific, directed answers to Dr. Emerson's questions. If not, just say no.

Is a member of the sponsor going to speak?

DR. WILLIAMS: Yes. We actually have very direct responses to Dr. Emerson's questions, and Dr. Spiegel will address them now.

DR. SPIEGEL: Hi. David Spiegel.

I think the question related to what was the dose at the beginning of the random -- can you put the slide up, please?

So what was the dose of tenapanor at the beginning of the randomized withdrawal period, and what was the difference between the rise in the tenapanor and the placebo, the groups and rise to tenapanor/placebo, at those different dose levels, and that's what you see here.

The top couple of rows are the efficacy analysis set broken out by those starting the randomized withdrawal period at 30 milligrams, 20 milligrams, and 10 milligrams, and then you see the rise in the tenapanor, which is really very little, and then you see the rise in the placebo.

On the 30-milligram dose group, you can see the numbers. The tenapanor group went up very little, 0.11; the placebo group rose by 1.73 for a difference of 1.62 there. And I won't go over all the other numbers for you, but you can see here, there's a little bit of a dose-response curve. Those ending at 20, the mean difference was about 1.2, and those who ended up on 10, the mean difference was about 1 milligram per deciliter.

DR. EMERSON: The second question?

DR. SPIEGEL: In terms of the second question, I think you asked about the -- and I'm going to put the slide up here -- 7 patients who withdrew during the randomized withdrawal period, and whether they were responders or non-responders. And let me bring up this next slide for you here.

Three of them were actually in the responder population and four of them were in the non-responders. At baseline, study baseline, all of them had serum phosphorus that was about 7, and you can see at the time they withdrew, their mean and median phosphorus are listed on the last column there. So the median was about 6.5 in the responder group and about 8.9. So some of those withdrew because they hit a safety target, and some of those withdrew because of the hyperphosphatemia, and the investigator withdrew them from the study.

DR. EMERSON: Well, thank you.

DR. LEWIS: Dr. Emerson, do you have any follow-up questions?

DR. EMERSON: I don't. Thank you.

DR. LEWIS: Okay.

I think we'll take a few minutes. We had three open questions for the FDA.

Mr. Conway?

MR. CONWAY: Thanks, Dr. Lewis. Actually, I'll hold my question for later discussion. Thank you.

DR. LEWIS: Thank you.

Dr. Mendley?

DR. MENDLEY: Yes. Thank you.

Very briefly, assessing the responder set, the sponsor chose at 26 weeks to look at 2 out of 3 phosphorus lowering numbers, and you instead chose simply the last serum phosphorus measurement at week 26. That would be very typical for a cholesterol or blood pressure lowering effect, but why did you choose the 26 endpoint and not the multiple phos [ph] assessment that the sponsor chose, which could be considered more consistent with clinical practice?

DR. THOMPSON: This is Dr. Thompson, and maybe I'll start this off. I do want to note that in a setting of a formal dispute resolution, there are a range of analyses that are submitted to the agency that we review as part of a marketing application and certain analyses that FDA does. But what you're hearing today at the advisory committee meeting also may reflect, at least for the sponsor, additional analyses that were done

over time.

So if you just want to highlight that effect, Ling-Wan, do you want to clarify why the analyses we did focus on or we did these explorations as we did, or Jialu, do you want to add anything?

DR. CHEN: This is Ling-Wan Chen. I do not have any additional comment on this question.

DR. THOMPSON: Just to add --

DR. LEWIS: Dr. --

(Crosstalk.)

DR. LEWIS: Oh, sorry.

DR. THOMPSON: This is just to add. I think we highlighted in our letter, when we did not approve the application, that we thought a strategy would need to be based on multiple measurements, so our concern is just that the strategy has not been prospectively tested.

DR. ZHANG: This is Jialu Zhang. I maybe have a comment.

When we select the responder, we use either week 1 or week 2 or to week 4, so it's multiple

weeks trying to identify the responder. But looking at the late responder, we did only use the week 26, while the sponsor used the responder definition of 2 out of the 3.

So if that's acceptable criteria, that you got 67 percent of chance to maintain the phosphorus level as a responder, if that's acceptable, then the sponsor's analysis would be the one people should rely on; otherwise, if we're selecting the early responder, we did use multiple measurements.

DR. THOMPSON: However --

DR. MENDLEY: Yes, thank you.

DR. THOMPSON: Go ahead.

DR. MENDLEY: That's all I have.

DR. LEWIS: I'm sorry.

Dr. Emerson, was that you?

(Crosstalk.)

DR. MENDLEY: I understand the distinction that was made, so thank you very much --

DR. LEWIS: Oh, Dr. Mendley. I'm sorry.

DR. MENDLEY: -- the 26 weeks. This is Dr. Mendley, yes. Thank you.

DR. LEWIS: Yes. Sorry.

Okay. Dr. Emerson, you had an outstanding question for the FDA?

DR. EMERSON: I think I can hold off on that discussion. Thanks.

DR. LEWIS: Okay. Thank you.

We will now proceed with the charge to the committee from Dr. Aliza Thompson.

Charge to the Committee - Aliza Thompson

DR. THOMPSON: Thank you, Dr. Lewis.

As you've heard today, both during the meeting, as well as during our open session where we heard from a number of patients, there is a significant unmet need for well-tolerated treatments that can effectively control serum phosphorus, but ideally, such treatments would have a low pill burden.

I think it's fair to say that during today's meeting, you heard a lot about evidence as well as uncertainties. You heard about the evidence supporting serum phosphorus as a surrogate for clinical outcomes, as well as the limitations of

the data supporting its use. You also heard about the evidence, as well as the uncertainties as it relates to tenapanor's benefit. And finally, you heard about tenapanor's safety profile about its potential risks.

During today's meeting, you have asked all of us a lot of very challenging questions, and now it is our turn to have you answer some very challenging questions. We very much have learned a lot from the questions you've asked thus far, and very much look forward to hearing the discussion that follows. Thank you.

Questions to the Committee and Discussion

DR. LEWIS: The committee will now turn its attention to the task at hand, the careful consideration of the data before the committee, as well as the public comments. We will now proceed with the questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate, except at the specific request of the

panel.

After I read each question, we will pause for any questions or comments concerning its wording, then we will open the question to discussion. We will start with question 1.

Discuss the magnitude and clinical meaningfulness of tenapanor's treatment effect on serum phosphorus when administered as monotherapy.

Are there any issues or questions about the wording of the question?

(No response.)

DR. LEWIS: If there are no questions or comments concerning the wording of the question, we will now open the question to discussion.

Dr. Emerson?

DR. EMERSON: This question revolves around the results of Study 201 and 301, of which Study 301 is clearly the better study, both in terms of the length of exposure and the fact that it's more of a confirmatory study than was 201. I will remark that the design of Study 301 as the randomized withdrawal, complete with the

randomization of the subjects who did not make it into the EAS, I applaud. I think that's the correct thing to do, particularly given some of the questions that are arising here, and that is the safety question; do we know how to identify these patients?

The thing that strikes me the most here is, of course, the idea that the sevelamer group did better, so that is, to me, the major safety question that the FDA alluded to, is the idea that you might be diverting patients from a better therapy.

So in terms of efficacy, using either of the landmark analyses, if you will, either did we get an improvement of 1.2 on the delta or did we decrease it down to 5.5 looking at the randomized treatment phase. Then depending upon whether you want to look at attributable risk, well, roughly a 20 percent difference because sevelamer did better than that on the ITT analysis from the randomized treatment phase. If you wanted to put that into an odds ratio, it's around 2.4. I personally would

place more emphasis on the attributable risk.

So clearly, as a monotherapy, you aren't getting the response that I would certainly recommend to anybody, that they substitute the phosphate binding for that, and this doesn't, of course, answer the question of whether you can do it.

I will note the complicating factor of Study 301, which was, number one, that it said 65 percent of the patients had been exposed to sevelamer before, I don't know how current that was, how far in the past that was, which does affect the safety profile, that you've got a selection on that.

I'll also note that that clinical trial did allow titration of the binder's base to achieve the better serum phosphorus. It was allowed, but you started at the higher dose, and most of the adjustments were down due to toxicity, but as compared to just looking a little bit ahead, when we look at the combination therapy, that did the opposite; that would have the titration of the

experimental drug.

So I think the major issue here is that we could accept that the treatment doesn't work in everybody; that's ok. This randomized withdrawal study is what we recommended on the missing data thing to deal with cases where you were going to run into tolerability, and lack of response, and lack of compliance, generally, to be able to try to isolate the group of the people who will take this chronically.

But I understand the FDA's concern that it wasn't totally prespecified that we would regard that you would stop the treatment in the people who didn't meet the response. I mean, post hoc, yes, we can look at it and say, why bother continuing it, but it wasn't totally prespecified that that's the way it would be.

So I have some concerns that I think the FDA has on all of this. No question that the treatment works at some level; no question in my mind that, absence the safety sort of question, that if I take the observational data, which is all that we have

to go on, a difference of around 0.8 would correspond to roughly a 15 percent higher mortality and morbidity rate, according to the observational data we were shown.

So it's not up to the the 1.5 to 2.5 that we're seeing in other things, but as an incremental level, I think that could be of interest were there not for these other aspects not as effective as the phosphate binders.

DR. LEWIS: Thank you, Dr. Emerson.

Dr. Fried? And please say your name first, even though I said it.

DR. FRIED: Hi. Thank you. Linda Fried, Pittsburgh. I'm not sure about the dialysis, whether or not reduction in phosphorus will have the same magnitude of effect; however, we do try to get the phosphorus down.

I do think the phosphate binders are more effective than this drug. I see this drug, for those in monotherapy, would only be those who did not tolerate phosphate binders, which unfortunately is a fair number. I see probably, in truth, this

usefulness more as an add-on therapy, reflecting the difficulty in getting phosphorus down.

Clinical meaningfulness, yes, 0.8 to 1.4, I have a lot of patients whose phosphorus is in the 6's from trying to get down to less than 5.5, so I see its role, but as I said, not so much as monotherapy, except in those who don't tolerate it. Thank you.

DR. LEWIS: Dr. O'Connor?

DR. O'CONNOR: Yes, Chris O'Connor here. My concern is, is 0.7 enough when we're talking about a surrogate endpoint that has not been validated? In cardiology, we know that small changes in blood pressure and other parameters can't afford significant clinical benefit. That's what we don't know, and I'm cautious about using the observational data that Scott was keen to mention, the 15 percent.

I think what we're looking at is an effect size that's, at best, 40 percent less than current therapies. And I think if we start taking the bar down -- I think we have to have a high bar for

surrogate endpoints without clinical endpoints. If we start taking the bar down, this will be a continuous issue for the next time somebody comes in with a 0.6 with half the diarrhea; 0.5 with no diarrhea. So I really think we've got to talk about the clinical meaningfulness that we have today that we understand, and I'm concerned that 0.7 may not be there. Thank you.

DR. LEWIS: Dr. Mendley?

DR. MENDLEY: Susan Mendley, NIDDK. I'd like to make two points in regard to what Dr. Emerson pointed out.

Study 301 was not a comparison to sevelamer, so the fact -- sevelamer was a control, but it's true that the oral phosphate binders have shown a larger effect size, but we all agree that that by itself is a suboptimal course of therapy. Many patients don't tolerate it. You've heard from all of them how unpleasant it is.

We're not actually denying patients sevelamer; we're saying there's a meaningful subset of patients who simply don't tolerate oral

phosphate binders, and there is an effect for tenapanor, so as monotherapy in the right patient who tolerates the therapy, there's a measurable effect. I think that they have met their outcome. Thank you. That's all.

DR. LEWIS: Thank you.

Dr. de Boer?

DR. DE BOER: A few thoughts, most of which have already been mentioned. One is this question has to be related to the population, and it's a population of people who have confirmed response and tolerance of the drug, based on the design of the study, so there is a magnitude of serum phosphate reduction that's been shown. It's modified by the initial response, so this would have to be limited, of course, to people who have that sort of initial serum phosphate and drop.

I agree with Dr. Fried about this probably being the less common of the needs, and we heard very eloquently from patients, compelling stories about having too many drugs and not being able to control phosphate levels, so probably there is an

urgent need here. I think we probably all agree on that. The most urgent is in those people who have harder to control phosphates who are already on multiple drugs and need to get it lower, either adding or replacing drugs. And I think Dr. O'Connor's comments on the surrogate outcome limitations are important. Thank you.

DR. LEWIS: I think my hand might be next.

I agree that monotherapy is going to be for a subset of patients, but that's an important subset of patients who will then have an advantage of taking smaller pills, and I promise you that probably matters to almost all of our patients. And again, pill for pill, I think it is reasonably potent and competes well.

So I see a place for it. I think that one thing to keep in mind is that these patients spend 5 hours 3 times a day, 3 times a week minimum, with texts, nurses, they see dietitians and social workers repeatedly, and their physician or an NP 4 times a month. So any kind of diarrhea, any kind of side effect, any kind of anything will be noted

in the vast majority of patients quite quickly, and addressed. I think it's just a model of health care that's just so unique. Similarly, phosphorus is checked at least once a month, and when not at goal, often twice a month. So I do think that it has a niche in a subset of patients.

Dr. Merz?

DR. BAIREY MERZ: Thank you, Dr. Lewis. Noel Bairey Merz, Cedars-Sinai, Los Angeles.

I'm focused on this first question, which is basically benefit, and we don't know anything about significance for clinical events -- again, this has been said over and over again -- and I want to remind everyone that until we did hormone replacement therapy trials, we did not know risk-benefit for something that all women go through, which is menopause, and the results were surprising, and we heard from the FDA that a clinical trial for outcomes would be considered unethical.

So I think with that frame of mind, we have to look at there's already four on the market. As

you and many of the other nephrologists have discussed, there are concerns, and if we look at the concept of chronic disease management in so many of the things that we do, particularly, cardiovascular, as mentioned by Dr. O'Connor, usually lowers better, usually more choice is better, and shared decision making is what happens a lot when there's not such clear data. And as you point out, Dr. Lewis, these patients are well cared for. They're seeing specialists all the time.

So I think we can't really judge clinical efficacy, so we're going to need to fall back on historical chronic disease management principles for that, and I would favor this as an add-on therapy and as an alternative for folks that just cannot take existing therapy. Thank you.

DR. LEWIS: Mr. Conway?

MR. CONWAY: Thanks, Dr. Lewis. I just want to pull this back up to 100,000 feet, and what we're trying to do is we're trying to positively impact the patient population that is quite sick and quite ill, and I think we all understand that.

And hats off to the courage and determination of those who spoke during the public hearing, especially the patients, who could actually bring specificity and granularity to what it's practically like. It's not an easy life.

I respect Dr. Nachman about the difference between having two M&Ms and many M&Ms, that if they're not all that effective is huge if you're the one that has to eat the M&Ms because the person in the white jacket said eat the M&Ms. And in this case, I think it argues for the issue of patient care choice, shared decision making, as been mentioned, but also that trust between the nephrologist and the patient in respecting the patient's intelligence and ability to communicate with their health team about the experiences they have that's comfortable and things you don't like to talk about. Eh, after the first year of being a kidney patient, you kind of get that out of the way. Most people can kind of express that.

So in that case, I'd say that we ought to be focused on that subset of patients that don't do

well, and this is another tool in the toolbox for their doctors and for them, so I definitely support it. Thanks.

DR. LEWIS: Thank you, Mr. Conway.

Dr. Cook?

(No response.)

DR. LEWIS: Dr. Cook, you're muted on Adobe. Yes, there you go.

DR. COOK: Yes. Sorry. I didn't realize I was muted on the app.

I'm speaking solely as a statistician, and I'm going to trust that, for example, as a surrogate outcome, that this measure is acceptable. I am also skeptical of magnitude. Oh, I also can't address clinical meaningfulness, so I don't know the difference between a 0.8 and a 1.5, for example, so I trust that the clinicians have a handle on that.

But that said, observed effect size of the population averages, and populations are heterogeneous, and we've seen that you can cut the population in such a way that you can select people

who seem to be responders, and that's a population. You see a much larger nominal difference, on average, than you do among the people who are not responders.

That would suggest to me that there's probably even a further subpopulation -- which you could identify them -- to whom the effect size is even larger. And given that I don't see a compelling safety problem, I would argue, again, from my minimal clinical understanding, that approval of this would allow treating physicians the ability to put this in the arsenal and identify people for whom they seem to be responding. If their phos was decreased, it's probably the desired amount, then you can treat them with it, and if it doesn't, it doesn't. And I don't see any argument, or at least I haven't heard any argument, that would suggest that there is a downside to that approach. Thank you.

(Pause.)

DR. LEWIS: I'm muted.

Hey. Dr. Butler? Sorry about that.

DR. BUTLER: Thank you, Dr. Lewis. Javed Butler here. I just want to register a couple of things that are reasonably dissatisfying in this discussion.

One is, this issue of research in patients with phosphate issues being unethical seems like a difficult thing to accept. If your blood pressure is 200, or if your hemoglobin is 5, and you don't want to randomize, that makes sense. But I could say that it's unethical to not do a randomized trial if you're trying to lower blood pressure from 130 to 125, or you're trying to correct hemoglobin from 11.5 to 12.5. So I think that not having a randomized-controlled trial makes it really an impossible question to answer.

Then the second dissatisfying thing is that we're being asked to answer two questions. One is the clinical meaningfulness in terms of the outcomes. So granted that we're in a space without randomized-controlled data, but surely this is an incredibly high-risk population with an incredibly close follow-up and no lost to follow-up data on

these dialysis patients. Then you have data up to 52 weeks, so at least some secondary data and what happened to, actually, the patient, and that none of those secondary clinical data have been presented in this area of research seems highly unusual to me.

Then the second thing is there's a lot of patients' testimony, and everybody has talked about this huge issue of pill burden. And to have no data on, actually, what was the pill burden in the trial in those who had a sustained benefit, unsustained benefit, or side effect, and what actually was the distribution of pill burden not being presented as well also makes this thing a little bit more difficult. Thank you.

DR. LEWIS: Thank you, Dr. Butler.

Dr. Nachman?

DR. NACHMAN: Yes. Thank you, Dr. Lewis. Patrick Nachman. I really want to echo Dr. Butler's last comments. I was looking at Dr. Chertow's first randomized-controlled trial of sevelamer published in 2002, so 20 years ago, and we still don't know

whether lowering phosphorus is beneficial. So I completely echo Dr. Butler that the onus is on us to actually come to grips with this and not go on faith forward.

There's another aspect of the discussion that I'm a little uncomfortable with. We're asked about the meaningfulness as monotherapy, and a lot of the discussion is almost insinuating that we're going to take patients who are not tolerating a huge burden of pills go on the new medication and not have any side effects at all, and not have intolerance at all.

We're not comparing drugs with side effects with a drug without side effects. We're comparing two classes of drugs that have very similar side effects, and I haven't seen any data at all that if you take a patient who's not tolerant of one of the other five, four classes of medication, and they tried this one, they will magically get their phosphorus under control with 2 tablets only and no diarrhea.

I'm sure that there are patients that can

tolerate one medication and not the other, but I think we need to be careful about going on faith of what we're proposing here, especially as monotherapy because, again, the data does not suggest that there is a large patient population that will get their phosphorus under control with tenapanor monotherapy.

And if I may just add one wrench to this problem, there is a paper that just came out that looked at circadian differences in phosphorus, 8.5-[8].6 milligrams per deciliter change in phosphorus level is just dependent on what time of the day you measured it; just putting that out there.

DR. LEWIS: Okay

I have an actual quick comment, and I'm going to put Ms. Alikhaani on the spot and tell her that I want her to think if she could also add a comment to our discussion after Dr. Mendley.

I remember long ago, I was a fellow, when there was almost no phosphate binders, and then there was Amphojel a little bit. And I don't think

there's any question that there is a high phosphorus level that is bad for the skin, and bones, and muscles. So I agree that it's appalling that we don't know what the lower end of that is, and in fact there's good data that we might be restricting people's diets in ways that's harmful, based on just made up guidelines, as I say to my fellows. But I do think that it is going to be true that some phosphorus lowering is going to be necessary in some patients, and that having more things to try and do that with will be potentially a benefit.

Dr. Mendley?

DR. MENDLEY: Susan Mendley, NIDDK.

I want to reassure you, we don't have all the answers, but there is a prospective randomized trial of different phosphate targets among hemodialysis patients underway. We don't have any results, but that is in the works.

DR. LEWIS: I am so excited; I can't wait. I really love your trial.

DR. MENDLEY: Thank you.

But this is a trial of targets; it's not a treatment trial, but nonetheless, it answers Dr. Lewis' concerns, which I share, that we don't know what the right number to aim for is. Thank you.

DR. LEWIS: Ms. Alikhaani, did you have a comment on this question? And you don't have to, but I would like to include you.

(No response.)

DR. LEWIS: Okay. I'm going to assume not.

Now I'm going to summarize. I think that there were some unifying thoughts, which was that there is a need, and that there are important issues of patient choice, and that the environment in which the doctors and patients will be manipulating these drugs is a highly unusual safe medical environment.

Monotherapy is particularly problematic because of the effect size, and really how many people would be able to get to whatever we decide the goal is someday, validly. I guess we have a goal that's made up now, but it's not going to be a

huge number with the current effect, but it won't be zero, I think is what most of the people said; although I think many of the members were concerned about this shouldn't be a substitution trial and you wouldn't just take people off; and if switching them would be the right thing to do; and that the limitations of our available data about this as a surrogate is very hard for the committee as it was for the FDA, understandably.

We're skeptical of surrogates, we're skeptical of the magnitude, but again, there's probably a subset of people in whom this will be of potential benefit and well monitored for side effect. Dr. Emerson made a point that the 0.8, which is actually the ITT low end of it, at least is approximately a 15 percent higher mortality, and of course acknowledging that the fact that you have a higher mortality with a higher phosphorous doesn't mean what you used to lower it will improve that, but at least it suggests that there's a potential.

I will now move on to question 2. Discuss

the magnitude and clinical meaningfulness of tenapanor's treatment effect on serum phosphorus when administered in combination with phosphate binder treatment.

Are there any issues or questions about the wording of the question?

(No response.)

DR. LEWIS: If there are no questions or comments concerning the wording of the question, we will now open the question to discussion.

Dr. Nachman?

DR. NACHMAN: I'm sorry. I forgot to lower my hand. Patrick Nachman.

Okay. Dr. Emerson?

DR. EMERSON: This is Scott Emerson.

My major comment here is just the short time frame of the 202 study, a 4-week study, and the aspect that it basically was asking the question, if we took people on whatever phosphate binder they were, I'll remark, in diabetes, you would have said optimize that treatment before we use it as the control, but I didn't really see that

here.

But that having been said, the opposite's true here, showing if you could titrate tenapanor, that that would give you an additional 20 percent of people who were hitting the threshold of less than 5.5. I think this is the way it should be used. I think if this generalizes -- again, given the very short 4-week period -- it's an important tool to have.

DR. LEWIS: Okay. I'm going to give a pause here for any other members that have a comment.

Ms. Alikhaani?

MS. ALIKHAANI: Yes. This is Jacqueline Alikhaani. I'm sorry I didn't get to comment on the other question; I had some technical problems.

I'm very concerned about all of the uncertainty that surrounds the issue of serum phosphorus levels and agree with the conversations that have been going on from our experts on this panel about that. It was just heartbreaking, to me, hearing the testimony of the patients, and the providers, and caregivers that testified today. So

clearly, we need some alternative treatments for patients to choose from. We're not there yet.

This issue of pill burden is also very concerning. I can totally relate to that. My mother had kidney disease and kidney failure, so it's something that I'm very concerned about. I just think when we're having the lack of data that we need to make informed decisions the best way possible, it just highlights the issue about the need for clinical trials and data that are really very thorough and well designed so that we can get the sufficient evidence that really demonstrates the kind of qualitative and quantitative data that really can support the development of safe, effective, and alternative treatments for diverse patient populations.

So as it stands, I don't think we're there with this particular treatment. It just appears to me that there's not much difference between this new drug, tenapanor, versus the other treatment, which is sevelamer, in the 301 study. I think that we need more data to really get us to where we need

to be, and I'm very concerned that the patients are having to deal with taking all these huge pills, and so many of them every day. We've got to do something more about this. Thank you.

DR. LEWIS: Thank you.

Mr. Conway?

MR. CONWAY: Thanks, Dr. Lewis.

On this specific question, I do think it's another important tool in the toolbox. I do think we are there, based on the data that's been presented. I think the data on 402 is important to consider.

In terms of the onus, it's interesting because we heard some pretty amazing information about the lack of the science to show and to support status quo care. When it comes to choices, and innovations, and novel approaches, I do think the time is now because, clearly, you have a segment of the population that status quo does not work for, so I would trust that the nephrology community could use this as a tool and working with the patients, especially when it's administered in

combination. Thank you.

DR. LEWIS: Okay.

Ms. Alikhaani, do you have another question or comment?

MS. ALIKHAANI: No. Sorry. I'm just leaving.

DR. LEWIS: Okay.

Dr. Kasper or Dr. Soergel, do either of you have a comment?

DR. SOERGEL: Not at this time. Thank you, Dr. Lewis.

DR. LEWIS: Okay.

So then, I guess we move on to question number 3. Diarrhea was the --

CDR BONNER: Sorry --

DR. LEWIS: Oh, wait. I have to summarize. I'm going to to summarize. Yes. Thank you.

I think we said a lot of what we said in our answer to the first question that was applicable to the second question as well. Dr. Emerson made the point that 202 is a very short time frame, but that it did show that you can titrate tenapanor and

improve control, and he felt that was how it should be used.

Mr. Conway thought 402 was very important to consider the patient perspective on it, and as Ms. Alikhaani pointed out, the patient perspectives were pretty heartbreaking to listen to about the pill burden and having to take it with their meals, and all those things that were so hard for the many patients that have to do that; that we need alternatives and it's disappointing we don't have more data. Her concern, however, was that this treatment was not much different than sevelamer, so this wasn't the answer to those problems.

I will now go on to question number 3. Diarrhea was the most common adverse reaction in clinical trials of tenapanor in adults with CKD on dialysis. Discuss this risk from a safety and tolerability perspective.

Are there any issues or questions about the wording of the question?

(No response.)

DR. LEWIS: If there are no questions or

comments concerning the wording of the question, we will now open the question to discussion.

Well, I guess I'll begin since no one's commenting. I think constipation, particularly constipation related to some of the other binders but also related to many of the patients' primary disease, such as diabetes, is a more common problem. I see very, very, very many dialysis patients, and have for a long time, and many of them are on stool softeners or other kinds of drugs to unconstipate them.

I think there will be a subset of patients who will actually welcome a slightly looser stool. There will be other patients who, as was the case in these studies -- actually quite a few -- that found it intolerable, but they will sort themselves out. I think patients and doctors will walk with their feet, and I'm reassured by the fact that they are a carefully monitored population.

The only other comment I will make is that sometimes I think of diarrhea as sort of the giant nephron, and it does get rid of fluid. And in this

case, 3 grams of sodium, there's no hypothesis that that will benefit patients, but it would be an interesting one should this drug be looked at to see if it attracts dialytic weight gain or any of those things.

Dr. Merz?

DR. BAIREY MERZ: Thank you, Dr. Lewis. Noel Bairey Merz, Cedars-Sinai, Los Angeles.

I mirror your comments about them being carefully monitored, and there may be a subgroup that would benefit. Then I would just extend that to reflect that it is already approved for IBD constipation, so this is a known side effect as opposed to maybe a more serious risk. The FDA previously decided that this was safe enough to create a quality-of-life issue in IBD patients, and I would be satisfied with that as a safety -- I would be happy that it would be considered safe enough for this clinical problem. Thank you.

DR. LEWIS: Thank you.

Dr. Soergel?

DR. SOERGEL: Thanks, Dr. Lewis. David

Soergel, industry rep. I have two comments along this line.

I thought the presentation of how loose stools are characterized in the clinical trial was an important one because I think when we see the word "diarrhea," we oftentimes kind of devolve to thinking about very watery stools, et cetera, that can cause significant problems, and obviously there's a significant patient-centered tolerability issue, as you saw from the withdrawal rates in the trials.

However, I guess this comes to the second point, which is the concept of a responder analysis, which can be looked at in two different ways. Patients will declare themselves as responders in terms of their serum phosphate reduction, as we focused quite a bit on, but they also declare themselves as tolerability responders. And both of those measures, I think, are -- as you mentioned already, Dr. Lewis, in these patients who are highly monitored and followed -- something that could be managed with medicine. Thank you.

DR. LEWIS: Dr. Nachman?

DR. NACHMAN: Thank you, Dr. Lewis. I have a quick question for the sponsor.

I am assuming that because the drug is not absorbed and by its mechanism of diarrhea, that if a patient does get severe diarrhea, it would be short-lasting after drug cessation. Is that a correct statement?

DR. LEWIS: I --

DR. WILLIAMS: Yes, you're -- oh, I'm sorry.

DR. LEWIS: I'm sorry. I was just going to allow the monitor to answer that question -- the sponsor to answer that question, so go ahead.

DR. WILLIAMS: Yes, you're correct. Again, as we characterized in the presentation, the diarrhea, when it occurs, occurs relatively early. It's self-limiting, it resolves within 14 days, short on and off, and most patients, as we noted in the presentation, had a single episode.

DR. LEWIS: Could you identify who was speaking, please, for the record?

DR. WILLIAMS: I'm sorry. It's Dr. Williams

with Ardelyx.

DR. LEWIS: Thank you.

Dr. Nachman, did you have any other comments beyond the question?

DR. NACHMAN: I wish you hadn't said 14 days. That seems like a very long time to have diarrhea, but I'm assuming that's maybe not common, or that it would be shorter lived?

DR. LEWIS: You may answer the question, but identify yourself before you do.

DR. WILLIAMS: Thank you, Dr. Lewis. This is Dr. Williams. Again, that's a median of 14 days. I think what's important to note is that as soon as you stop the drug, or relatively soon after you stop the drug, the diarrhea goes away.

DR. LEWIS: Thank you.

Dr. O'Connor?

DR. O'CONNOR: Dr. O'Connor. Just addressing part of that, we saw from the FDA safety officer, on one of their slides that said a mean of 43 days. I'm not sure if that was maybe just moderate to severe diarrhea. But the comment I

wanted to make is that diarrhea can also result in downward adjustment of the drug. And one of the concerns we saw is that there was significant reduction in dose of the drug in some of the patients, and this would result in further attenuation of the effect size.

So I still have concerns that we're going to be making a decision, based on several hundred patients getting active therapy that have a significant amount of diarrhea that could further attenuate the effect size.

DR. LEWIS: Thank you.

Ms. Alikhaani?

MS. ALIKHAANI: This is Jacqueline Alikhaani. I am not comfortable with the diarrhea adverse CV outcomes, and also I'm concerned about how that can potentially contribute and lead to negative outcomes. I'm particularly concerned about older people and how they will do with this. I just hope there's a -- it would be great if we had a way to be able to provide this treatment to patients who benefit the most, and not give it to

those who demonstrate poor benefits. Thank you.

DR. LEWIS: Thank you.

Mr. Conway?

MR. CONWAY: Thanks, Dr. Lewis.

In regard to this discussion, I thought that the data that the sponsor provided, based on what I would call, I guess, the Bristol stool chart, was important in how you define diarrhea and loose stools, because in the broader context for this population, these issues of being constipated or having loose stools, it's endemic with the population and the types of things that you go through as the patient. Whether you're dealing with the antibiotics, whether you're dealing with gout, there are many different things that impact the population on this.

So it's not like we're looking at a one-off that's going to cause a condition. It is a highly monitored population. There are a lot of medical professionals that doctors talk to in the course of their treatment, and just interactions during the week, just to manage the disease. And because of

that, I don't think it's something that -- I think it's important, I think safety is a key issue, but I do think that this is something, in the realm of doctor and patient and doctor and medical team, they can arrive at the point that's best for the patient in terms of the outcome, based on the best advice of the doctor. Thank you.

DR. LEWIS: Thank you.

Dr. O'Connor, do you have another comment or is your hand up?

(No response.)

DR. LEWIS: Thank you.

Okay. I think I'll summarize.

I think that there certainly is a concern that it would be really ideal, one, to know what our goals should be and have more information, studies, but also to know who to give it to, who would most benefit, and not put people at risk who won't benefit. It is certainly a concern that was expressed, and it was a concern that diarrhea, particularly in the vulnerable, whether they be old or just frail, population could have serious

downstream consequences.

It was expressed by several of the speakers that they felt somewhat reassured by the Bristol stool chart, which revealed that some of the descriptions of the diarrhea really reflected slightly loose stools, or just soft stools, so it wasn't all massive watery diarrhea. There was some confusion about how long the diarrhea lasts. It is interesting that because of the relatively short half-life of the drug, you would not think it would last 14 or 43 days, in any case, but on the other hand, many of the situations seem self-limiting, and early and single episodes.

It was acknowledged by multiple people that this is a very highly monitored population and highly regulated, and that was reassuring. It was also reassuring that this drug has been approved and used successfully already for IBD with constipation.

So that's my summary. We will now move on to the next question, which is a voting question. Commander LaToya Bonner will provide the

instructions for the voting.

CDR BONNER: Thank you.

Questions 4 and 5 are voting questions. Voting members will use the Adobe Connect platform to submit their vote for this meeting. After the chairperson has read the voting question into the record and all questions and discussion regarding the wording of the vote question are complete, the chairperson will announce that voting will begin.

If you are a voting member, you will be moved to a breakout room. A new display will appear where you can submit your vote. There will be no discussion in the breakout room. You should select the radio button that is the round circular button in the window that corresponds with your vote, yes, no, or abstain. You should not leave the "no vote" choice elected. Please know that you do not need to submit or send your vote. Again, you need only to select the radio button that corresponds to your vote. You will have the opportunity to change your vote until the vote is announced as closed. Once all voting members have

selected their vote, I will announce that the vote is closed.

Next, the vote results will be displayed on the screen. I will read the vote results from the screen into the record. Afterwards, the chairperson will go down the roster and each voting member will state their name and their vote into the record. You can also state the reason why you voted, if you'd like, however you should also address any subparts of the voting questions, if any.

Are there any questions about the voting process before we begin?

(No response.)

DR. LEWIS: Okay. I will read question 4.

Do tenapanor's benefits outweigh its risk for the control of serum phosphorus in adults with CKD on dialysis when administered as monotherapy? A, provide your rationale; B, if you voted no, provide recommendations for additional data and/or analyses that may support a positive benefit-risk assessment for tenapanor as a monotherapy.

Are there any questions about the wording or issues about the wording of the question?

(No response.)

DR. LEWIS: If there are no questions or comments concerning the wording of the question, we will now begin the voting on question 4.

CDR BONNER: We will now move voting members to the voting breakout room to vote. There will be no discussion in the voting breakout room.

(Voting.)

CDR BONNER: This is LaToya Bonner. Again, I will read the vote results into the record: 9 yeses, 4 noes, zero abstain. The chairperson will go down the list, and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you'd like. However, you should also address any subparts, if there were any. Thanks.

DR. LEWIS: Thank you.

We will now go down the list and have everyone who voted state their name and vote into the record. You may also provide justification of

your vote if you wish to. We'll start with Dr. Bairey Merz.

DR. BAIREY MERZ: Noel Bairey Merz, Cedars-Sinai, Los Angeles. I voted yes, and my rationale is we heard about the gap of patients that are unable or unwilling to take the standard of care right now, so while I do support this as an add-on therapy, primarily I do think it should be made available for those patients that are otherwise being untreated. It is probably better than nothing. And I applaud the FDA in hearing that there will be a MACE [ph] trial. Thank you.

DR. LEWIS: Thank you.

Dr. O'Connor?

Dr. O'Connor. I voted no. My reason for voting no is really the difficult issue of a surrogate endpoint that hasn't been validated thoroughly with clinical outcomes, as we discussed. I think the degree of efficacy was modest, and I want to commend the sponsor for doing what they were instructed to do, and conducting, really, well-conducted clinical trials in this difficult

space. But I think going forward, a larger clinical trial with an active comparator, and getting a larger sample size rather than the several hundred that we saw in the efficacy analyses, that could have a meaningful clinical endpoint integrated into that trial, such as PROs and positive endpoints, would be a great service to the community. Thank you.

DR. LEWIS: Thank you.

Dr. Kasper?

DR. KASPER: Ed Kasper, Johns Hopkins. I voted yes. I think there is clearly a need for drugs such as this. I think tenapanor is effective, but not as effective as current therapy. I think the safety is acceptable because it's a highly monitored environment. I think there is clearly a role for this drug, and I, too, look forward to the results of the ongoing trial.

DR. LEWIS: Thank you.

Dr. de Boer?

DR. DE BOER: Ian de Boer. No. I believe there are insufficient data to support the clinical

benefits of this intervention. I certainly understand the need and the desire for new tools, but I think we need tools that work for outcomes that matter. I agree with Dr. O'Connor that we need more trials with clinical outcomes, and while the high-low trial is a promising step in that direction, we're likely to need additional ones, and I think those should be carefully considered in the future.

DR. LEWIS: Thank you.

Ms. Alikhaani?

MS. ALIKHAANI: Yes. This is Jacqueline Alikhaani. I voted no. I think we need more trial data to give us all the information that we need to make sure that the treatment is safe and effective as possible, and I particularly would like to see more certainty on this issue of variability in serum phosphorus levels. Thank you.

DR. LEWIS: Thank you.

Dr. Butler?

DR. BUTLER: Hi. Javed Butler. I voted yes, but it was a little bit of a reluctant yes. I

was not particularly concerned about the safety signal, which though not ideal, was acceptable. And in terms of the efficacy, I really have no new comments to add, other than the fact that I think this still probably deserves a higher bar of efficacy, but I did find that this particular application meets the precedence of what has been done previously in this area, and therefore I voted yes.

DR. LEWIS: Thank you.

Julia Lewis. I voted yes. Again, I think that this drug does offer smaller pills, which I think is likely to have less overall efficacy, but per pill, probably not, and I think our patients would always welcome another choice. I agree that it's a small subset that will respond to monotherapy, but let's make it available to them.

Dr. Fried?

DR. FRIED: Linda Fried. I voted yes. As was stated by others, I don't think there's a large role for monotherapy, but there is a population that doesn't tolerate many phosphate binders. I

think the diarrhea is manageable. In truth, I would probably start low and titrate up, rather than start high and titrate down, but I do think it provides an alternative until we have studies that show that we don't manage phosphorus. Currently, our quality goals are to get the phosphorus down, which with our current data we think helps our patients.

DR. LEWIS: Thank you.

Dr. Nachman?

DR. NACHMAN: Yes. Patrick Nachman. Thank you, Dr. Lewis. I voted no, and I want to start by saying that I'm very sensitive to the need and desire for more treatment options, and I'm very respectful of the patients' choice and treatment preferences, but I do think that demonstrating benefit is important.

Considering the small magnitude of the effect of tenapanor on serum phosphorus compared to placebo and apparent lesser magnitude of effect compared to currently proved agents, and considering that the very substantial proportion of

patients did not tolerate the medication, the patient populations likely to achieve control of hyperphosphatemia with this new agent as monotherapy seems to be quite small, and probably will have to have pretty mild hyperphosphatemia at baseline.

Conversely, if you start with very mild hyperphosphatemia, I don't know that we have any evidence that those patients will truly benefit from taking medications with side effects or a modest reduction in hyperphosphatemia. As a result, I'm not convinced that there is a sizeable patient population that will demonstrably benefit from tenapanor monotherapy.

Now, Dr. Lewis, you brought up patient populations that maybe the sponsor can evaluate more fully and demonstrate both efficacy, tolerability, and benefit. And the other patient population that I'm thinking of is patients on peritoneal dialysis, for example, who frequently have constipation along with hyperphosphatemia, and their constipation is a problem in doing peritoneal

dialysis. So I would encourage the sponsor to evaluate this fully in that patient population, for example. Thank you very much.

DR. LEWIS: Thank you, Dr. Nachman.

Mr. Conway?

MR. CONWAY: Thanks, Dr. Lewis.

Four good points; I think the sponsor met the trial outcomes, and I think it's an important innovation and a novel approach. I think there is an unmet need, and clearly that's been documented, I think, if you look at it in terms of patients who are not treated or patients who fall off of treatment because the current status quo is not tenable.

In regard to the status quo care, I was quite interested in the information from FDA about the lack of science on current standards, and I think it kind of makes the point about status quo care, which is you have therapies that are being recommended to patients that many patients find quite burdensome, and in that case, I think that the patient experience has disproportionate

importance in this decision and that those voices must be listened to.

On the final point of safety, I do believe it can be managed between patients and the nephrologists they choose to take care of them because those medical professionals and the wider kidney care teams are engaged in life-threatening, high-risk procedures every week with their patients, and their patients trust them. And for these side effects that were listed, I think it's within the realm of manageability. Thank you.

DR. LEWIS: Thank you.

Dr. Emerson?

DR. EMERSON: This is Scott Emerson. I voted yes. My concerns that I stated earlier are still standing, but I ultimately voted yes with the idea that I'm voting for the indication of lowering serum phosphorus rather than any particular clinical outcome. And I am putting in how I was looking at it, that the monotherapy should really only be used in people who really cannot take other means at first. But I recognize that there's no

control over such criteria because the patient and the doctor themselves are deciding whether they can't take it.

So I didn't see a reason to withhold something that clearly had efficacy, and it's just uncertain the amounts. But I felt that across the spectrum of all sorts of other AEs and what's known, that the labeling could be adequate to tell patients and doctors of the risks.

DR. LEWIS: Thank you.

Dr. Mendley?

DR. MENDLEY: Susan Mendley. I voted yes. I thought there was sufficient data provided to allow clinicians to individualize treatment with tenapanor for appropriate patients, to monitor for changes in serum phosphorus and stool consistency, and I trust the clinicians to do this right.

DR. LEWIS: Thank you.

Dr. Cook?

DR. COOK: Yes. Thomas Cook, and I voted yes because it seems that this drug clearly is having the intended effect, at least in a subset of

patients, and that there's no reason to withhold it from those patients, and its safety profile seems acceptable. Thank you.

DR. LEWIS: Okay. I will now attempt to summarize this. I broke it down into the yeses and the noes. I think those who voted yes all recognize the need, and for that matter, for the those who voted no.

There were comments about there are a subset of patients, probably small, who would benefit from monotherapy, either because they're unable or unwilling to take the available standard-of-care phosphate binders or that their phosphorous is not very high or above whatever goal we end up deciding is an evidence-based goal. After the high-low study, at least we'll have something.

Safety was generally considered acceptable, particularly in the fact that there's been a highly monitored group of patients who are seen by multiple members of the care team on a regular basis. The status quo care is burdensome, and we're not sure exactly that we're making people do

something they really are benefiting from, so their experience with that burdensomeness has a disproportionate importance.

For the noes, I think there was a sad truth that this is the circuit that has never been connected in a trial to a more clinically meaningful outcome, and that's really needed, and hopefully it's in the process of happening, so we need good trials. Larger clinical trials were asked for with active comparators as a suggestion. We need tools that work, and we have insufficient data from these trials that were presented today to convince the people who voted no that there was a clinical benefit, and demonstrating the benefit is important because of the potential side effects.

There was also, I think, a very excellent suggestion that the sponsor should consider particularly looking at some of the subpopulations such as PD patients who other PDs won't work if they're constipated, and they're usually very highly constipated. So that might be a targeted population that would particularly benefit.

We will now move on to question 5. It is also a voting question. I will read the question.

Do tenapanor's benefits outweigh its risk for the control of serum phosphorus in adults with CKD on dialysis when administered in combination with phosphate binder treatment? A, provide your rationale, which you will do in the part where we talk about why we voted; and B, if you voted no, provide recommendations for additional data and/or analyses that may support a positive benefit-risk assessment for tenapanor in combination with phosphate binder treatment.

Are there any issues or questions about the wording of the question?

(No response.)

DR. LEWIS: If there are no questions or comments concerning the wording of the question, we will now begin the voting on question 5.

Commander Bonner?

CDR BONNER: Thank you. Commander Bonner.

We will now move voting members to the voting breakout room to vote only. There will be

no discussion in the voting breakout room.

(Voting.)

CDR BONNER: The voting results are displayed. I will read the vote totals into the record: 10 yeses, 2 noes, 1 abstention.

The chairperson will go down the list, and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you'd like, however, you should also address any subparts of the voting question, if any.

I'll turn the floor back over to our chair. Thank you.

DR. LEWIS: Thank you.

We will go down the list and have everyone who voted state their name and vote into the record. You may also provide justification of your vote, if you wish.

We'll start with Dr. Bairey Merz.

DR. BAIREY MERZ: Noel Bairey Merz, Cedars-Sinai Medical Center, Los Angeles. I voted yes, and for all of the reasons previously stated.

Thank you.

DR. LEWIS: Dr. Christopher O'Connor?

DR. O'CONNOR: Christopher O'Connor. I voted no; again, millions of patients sadly with this condition; 200-plus patient trial; 116 on active therapy; modest efficacy on a surrogate endpoint. As a community, I think we must do better for our patients. Thank you.

DR. LEWIS: Thank you.

Dr. Kasper?

DR. KASPER: Ed Kasper. Johns Hopkins. I voted yes for all the reasons that I've already gone through, with the additional thought being that I really don't have any choice. With the surrogate endpoint without any hard outcomes, at this point, the whole point would be to drive phosphorus as low as you can get it, and I think this drug can help do that.

DR. LEWIS: Thank you.

Dr. de Boer?

DR. DE BOER: Ian de Boer. No. I firmly believe in individualizing care and empowering

shared decision making by providers and patients. But I do think that to be successful, this requires reliable information, and I think that our safety clinicians deserve better data to guide their decisions. Thank you.

DR. LEWIS: Thank you.

Ms. Alikhaani?

MS. ALIKHAANI: Yes. This is Jacqueline Alikhaani. I voted abstain because it's very difficult for me to compare benefits and risks without all of the data that was advocated earlier and throughout the meeting, data that's needed from additional clinical trials. I think that the patient voice is very important, and I'm a patient myself. I'm a healthcare consumer myself, but I think that when you have all of the data that you need, then you can really make a fully informed decision, and this is really important. Thank you.

DR. LEWIS: Thank you.

Dr. Butler?

DR. BUTLER: Dr. Lewis, thank you. This is Javed Butler. I voted yes. This was, again, a

reluctant yes for the very same reasons that I stated for question 4. Thank you very much.

DR. LEWIS: Julia Lewis. I voted yes for the same reasons.

Dr. Fried?

DR. FRIED: This is a Linda Fried. I voted yes for the same reasons. I actually think this is the population that are most likely to use medication, and think we can manage the side effects.

DR. LEWIS: Thank you.

Dr. Nachman?

DR. NACHMAN: Thank you, Dr. Lewis. Patrick Nachman. I voted yes for the converse reasons. I voted no previously for monotherapy. Essentially, I can summarize my thought to giving the benefit of the doubt. Recognizing all of the limitations of our data, if there is a patient population that is likely to benefit from substantial reduction in serum phosphorus, it would be those who have very severe hyperphosphatemia or complications thereof.

Dr. Moe has swayed my vote here. The idea

of patients with blood vessels turning into bone is resonating in my mind here, and those patients are not likely to get control with monotherapy; they are likely to require multiple agents. And if tenapanor can get them to the finish line, in addition to other agents, I think it's worth having that option on the table. Here again, I think that I would encourage the sponsor to give us data for these difficult hard outcomes about calcification [inaudible] or calciphylaxis. Thank you.

DR. LEWIS: Thank you.

Mr. Conway?

MR. CONWAY: Thank you. Paul Conway, voting yes, for reasons previously stated, and another very, very important reason.

I think that for the medical professionals that are trying to do the right thing, who are in the arena every day trying to help patients and those who go untreated, this gives them the option of taking status quo treatments that are out there, that are FDA approved, and adding to it another tool, and then working in combination with the

patient and the best therapeutics to try to arrive at the best solution for each patient. Thank you.

DR. LEWIS: Thank you.

Dr. Emerson?

DR. EMERSON: Yes. Scott Emerson. I voted yes for reasons that I basically outlined before. And despite the fact that in this exact area, it's sparse data over a small amount of time, but I think the other trial data contributed some information.

DR. LEWIS: Thank you.

Dr. Mendley?

DR. MENDLEY: Susan Mendley. I voted yes. As before, I think this is a safe and worthwhile tool to individualize therapy, and I voted to approve.

DR. LEWIS: Thank you.

Dr. Cook?

DR. COOK: Yes. I voted yes for the same reasons as previous. Thank you.

DR. LEWIS: Well, thank you all. That makes my summarizing job easier.

I think that, pretty much, if you were going to vote for monotherapy, add-on therapy is probably even more supported. It's more likely to be the population that it's going to be used and then benefit from, people with very severe hyperphosphatemia, and people that just need a little push to get past that finish line.

I think there was an expression of faith and trust in the medical environment and professionals to have another tool to use to individualize for specific patients. Study 202 was reassuring. On the other hand, adding yet another drug to exposing a very large population of patients for only a surrogate outcome, with only a small effect and potential side effects, was one of the no reasons. And even though individualizing care is important, doing that in the absence of reliable information is concerning and resulted in a no vote, and that better studies would be needed.

Before we adjourn, are there any last comments from the FDA?

DR. THOMPSON: Dr. Lewis, this is Aliza

Thompson. I just want to say thank you to all of the committee members. We greatly appreciate the discussion today and very much will take into consideration, obviously, what we heard from all of you today. Have a wonderful day.

Adjournment

DR. LEWIS: I want to thank all the members of the FDA for their thoughtful stewardship for the process and with a very difficult question that they went through. It was, I think, quite difficult. I want to thank the sponsor for persevering through that process and a clear presentation; the public for sharing their perspective and input; and especially the members of this committee for their dedication and hard work to benefit the public.

We will now adjourn the meeting. Thank you.

(Whereupon, at 4:24 p.m., the meeting was adjourned.)