FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

(CRDAC)

Virtual Meeting

Wednesday, December 8, 2021

9:44 a.m. to 5:13 p.m.

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

Moon Hee V. Choi, PharmD

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

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(Consumer Representative)

Volunteer and Advocate

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Los Angeles, California

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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

(9:44 a.m.)

Call to Order

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

My name is Julia Lewis, and I will be chairing this meeting. I will now call the December 8, 2021 Cardiovascular and Renal Drugs Advisory Committee meeting to order. Dr. Moon Hee Choi is the acting designated federal officer for this meeting and will begin with introductions.

Introduction of Committee

DR. CHOI: Good morning. My name is Moon Hee Choi, 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.

Ms. Alikhaani?

(No response.)

DR. CHOI: Ms. Alikhaani?

MS. ALIKHAANI: Yes. Good morning. I'm Jacqueline Alikhaani. I'm a Los Angeles-based heart survivor. I'm a heart patient and citizen scientist. I'm also a long time volunteer with the American Heart Association, and I also serve as an ambassador for PCORI, the Patient-Centered Outcomes Research Institute. It's great to be here.

DR. CHOI: Dr. Bairey Merz?

DR. BAIREY MERZ: Good morning. C. Noel Bairey Merz. I am a clinical investigative cardiologist at the Schmidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, with expertise in preventive cardiology, women's heart disease, and exercise. Thank you.

DR. CHOI: Dr. Butler?

DR. BUTLER: Good morning. I'm Javed Butler. I'm a cardiologist at the University of Mississippi in Jackson, Mississippi.

DR. CHOI: Dr. Cook?

DR. COOK: Thomas Cook, professor of

biostatistics at the University of Wisconsin-Madison. Thank you.

DR. CHOI: Dr. Kasper?

DR. KASPER: Good morning. I am Ed Kasper. I'm a clinical cardiologist at Johns Hopkins with an interest in advanced heart failure and heart transplantation.

DR. CHOI: Dr. Lewis?

DR. LEWIS: I'm Dr. Julia Lewis. I'm an adult nephrologist from Vanderbilt University Medical Center.

DR. CHOI: Dr. Moliterno?

DR. MOLITERNO: Hey. Good morning. This is David Moliterno. I'm professor of cardiology at the University of Kentucky.

DR. CHOI: Dr. O'Connor?

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

DR. CHOI: Dr. Rossert?

DR. ROSSERT: Good morning. I'm Jerome

Rossert. I'm a nephrologist working at AstraZeneca.

DR. CHOI: Mr. Conway?

MR. CONWAY: Paul Conway. I serve as chair of Policy and Global Affairs for the American Association of Kidney Patients. I've been a kidney patient for 40 years and a heart patient for 20 years. Thank you.

DR. CHOI: Dr. Gorman?

CAPT GORMAN: Hello. I'm Captain Greg Gorman. I'm a pediatric nephrologist with the Defense Health Agency and executive director of the Defense Health Board. Over.

DR. CHOI: Dr. Mendley?

DR. MENDLEY: Good morning. I'm Susan Mendley. I am a pediatric and adult nephrologist, and I'm a program officer at NIDDK. Thank you.

DR. CHOI: Dr. Nachman?

DR. NACHMAN: Yes. Good morning. Dr. Patrick Nachman. I'm an adult nephrologist at the University of Minnesota.

DR. CHOI: Dr. Palevsky?

DR. PALEVSKY: Hi. I'm Dr. Paul Palevsky. I'm a nephrologist at the University of Pittsburgh School of Medicine, chief of the kidney medicine section at the VA Pittsburgh Healthcare System, deputy national program director for the Veterans Health Administration Nephrology Program, and president of the National Kidney Foundation.

DR. CHOI: Dr. Joffe?

DR. JOFFE: I am Hylton Joffe. I'm the director of the Office of Cardiology, Hematology, Endocrinology, and Nephrology in FDA's Center for Drug Evaluation and Research.

DR. CHOI: Dr. Stockbridge?

DR. STOCKBRIDGE: Good morning. I'm Norman Stockbridge. I'm the director of the division of Cardiology and Nephrology at FDA.

DR. CHOI: 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 FDA.

DR. CHOI: Dr. Johannesen?

DR. JOHANNESEN: Good morning. I'm a

clinical analyst in the Office of Cardiology and Nephrology.

DR. CHOI: Dr. Zhou?

DR. ZHOU: Good morning. I'm Dali Zhou, the statistical reviewer in the Office of Biostatistics, CDER, FDA.

DR. CHOI: Okay. Thank you.

(Pause.)

DR. LEWIS: Dr. Moon Hee Choi will read the Conflict of Interest Statement for the meeting.

(No response.)

DR. LEWIS: Dr. Moon Hee Choi will read the Conflict of Interest Statement for the meeting.

DR. CHOI: Dr. Lewis, can you look at the chatbox, please?

DR. LEWIS: I am, and I am reading, and I'm not muted, so I'm not sure why you can't hear me.

MALE VOICE: I can hear you, Julia.

DR. LEWIS: Okay. Some people can hear me. Okay. I'm not muted.

Dr. Moon Hee Choi will read the Conflict of Interest Statement for the meeting. That is all it

says.

DR. CHOI: Dr. Lewis, number 3. I think you jumped to number 4.

DR. LEWIS: Okay. Let me go back. Sorry.

Okay. Sorry about that. My fault.

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 the 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 topic during breaks or lunch. Thank you.

Dr. Moon Hee Choi will now read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

DR. CHOI: The Food and Drug Administration is convening today's meeting of the Cardiovascular and Renal Drugs Advisory Committee under the authority of the Federal Advisory Committee Act 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 discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest 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 the new drug application, NDA, 215484, for the Nrf2 activator bardoxolone methyl capsules, submitted by Reata Pharmaceuticals, Incorporated. The proposed indication is to slow the progression of chronic kidney disease caused by Alport syndrome in patients 12 years of age and older. This is a particular matters meeting during which specific matters related to Reata Pharmaceuticals' 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. Jerome Rossert is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Rossert's role at this meeting is to represent industry in general and not any particular company. Dr. Rossert is employed by Astra Zeneca.

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 other participants to advise the committee of any financial relationships that they may have with the firm at

issue. Thank you.

DR. LEWIS: We will proceed with FDA introductory remarks from Dr. Aliza Thompson.

FDA Opening Remarks – Aliza Thompson

DR. THOMPSON: Thank you. Again, this is Aliza Thompson.

Good morning, everyone, and thanks in advance to our committee members for their participation in today's meeting. The purpose of today's meeting is to discuss the marketing application for bardoxolone methyl to slow the progression of kidney disease in patients 12 years of age and older with chronic kidney disease caused by Alport syndrome.

As you'll hear, Alport syndrome is a serious and rare genetic disease that can lead to progressive loss of kidney function and kidney failure, sensorineural deafness, and ocular abnormalities, which can lead to loss of vision in some patients. As you'll also hear, there are no approved pharmacological therapies for Alport syndrome, and there is urgent need for safe and

effective treatments.

(Audio feedback.)

DR. THOMPSON: I apologize. I'm hearing some backup or some additional noises. Thank you.

In support of the proposed indication, the applicant conducted a randomized, double-blind, placebo-controlled study in patients with Alport syndrome. The study met its prespecified primary and key secondary endpoint, which assessed on-treatment and off-treatment changes in kidney function, as measured by estimated glomerular filtration rate or eGFR. Nevertheless, we are bringing this application to an advisory committee because we believe the findings in the trial warrant public discussion.

I want to emphasize that the FDA review team recognizes that there is significant unmet need for treatments that can slow the loss of kidney function in patients with Alport syndrome and reduce the risk of progression to kidney failure. I also want to emphasize that the FDA review team recognizes that the law allows for regulatory

flexibility in determining what constitutes substantial evidence of effectiveness to the extent that such approaches are scientifically valid and do not compromise our regulatory standards of effectiveness.

However, for the reasons that will be discussed today, the FDA review team does not believe the submitted data demonstrate that bardoxolone is effective in slowing the loss of kidney function in patients with Alport syndrome and reducing the risk of progression of kidney failure.

As a backdrop to today's discussion, I would like to briefly discuss changes in eGFR as the surrogate endpoint in trials of chronic kidney diseases.

Kidney failure is associated with significant morbidity and mortality, however, it is also a late outcome of chronic kidney diseases. As such, we often use a surrogate endpoint, specifically changes in eGFR, to assess whether a drug is effective in reducing the risk of

progression to kidney failure and as a basis for full approval of drugs intended to treat chronic kidney diseases.

I know that our advisory committee members are very familiar with the term "surrogate endpoint," but for those of you in the audience who are not, surrogate endpoint is a clinical trial endpoint used as a substitute for a direct measure of how a patient feels, functions, or survives. The surrogate endpoint does not measure the clinical benefit of primary interest; rather it is expected to predict that clinical benefit.

Over the last decade, our understanding of changes in eGFR as a surrogate endpoint for progression to kidney failure in trials of chronic kidney diseases has grown dramatically as the result of important work that was done by the larger nephrology community. And while there is an abundance of evidence supporting the use of eGFR as a surrogate endpoint, there is a catch.

Drugs can have reversible pharmacodynamic effects on eGFR, and by that I mean, drugs can

cause reversible increases in eGFR or reversible decreases in eGFR. Importantly, these reversible pharmacodynamic effects can differ from a drug's long-term effects and progression to kidney failure. These reversible pharmacodynamic effects are often of unclear clinical significance. Moreover, they can complicate the ascertainment of a drug's effect on long-term disease progression.

In the case being discussed today, the reversible effect can increase in eGFR, which appears to take several months to manifest fully. In the case being discussed today, we also see worrisome effects on albuminuria and blood pressure.

So with that background in mind, I'd like to turn to the topics we would like the committee to address. The first topic we would like the committee to consider is whether CARDINAL phase 3 was adequately designed to assess for an effect in the progression of chronic kidney disease in patients with Alport syndrome.

The second topic is whether the available

data indicate that bardoxolone methyl slows the progression of chronic kidney disease and whether it is reasonable to conclude, based on the available data, that bardoxolone methyl will reduce the risk of progression to kidney failure when used chronically in patients with Alport syndrome.

The third topic is bardoxolone methyl's safety profile, and as part of the discussion of this topic, we ask that the committee include discussion of two questions. The first pertains to bardoxolone methyl's effect on albuminuria, blood pressure, and other parameters, and whether these effects raise concern about its long-term efficacy and/or safety in patients with Alport syndrome. The second pertains to the effect of bardoxolone methyl on body weight with a potential implication for pediatric patients.

Finally, we ask the committee to vote on whether the evidence demonstrates that bardoxolone methyl is effective in slowing the progression of chronic kidney disease in Alport syndrome and whether its benefits outweigh its risks. Although

we are interested in how you vote, I want to emphasize that we are particularly interested in the rationale behind your recommendation.

With that, I will turn the program back to Dr. Lewis, our committee chair. Thank you again for your time and for your help with this very important application.

DR. LEWIS: Thank you, Dr. Thompson.

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 upon 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 the Reata presentations.

Applicant Presentation – Melanie Chin

DR. CHIN: Good morning. I'm Dr. Melanie Chin, and on behalf of Reata Pharmaceuticals, I thank the advisory committee members and the FDA for the opportunity to present our data supporting the efficacy and safety of bardoxolone methyl for the treatment of Alport syndrome. Most importantly, we thank the patients suffering from this rare and serious disease who have participated in our clinical trial, especially during the pandemic.

Bardoxolone methyl received orphan drug

designation from the FDA, and the proposed indication states, "Bardoxolone methyl is an Nrf2 activator indicated for the treatment of chronic kidney disease caused by Alport syndrome in patients 12 years of age and older. Bardoxolone methyl has been shown to slow the progression of kidney disease in Alport syndrome."

It is an oral immediate-release capsule that comes in two strengths, 5 and 15 milligrams, and is intended for chronic daily administration. A dose titration schedule, which is based on a patient's pretreatment urinary albumin to creatinine ratio, or UACR, is used to determine the target goal dose of 20 or 30 milligrams.

Alport syndrome is a rare, serious, and rapidly progressive hereditary form of chronic kidney disease often diagnosed in childhood. There are no approved therapies. Mutations in the type IV collagen gene lead to structural defects in the glomerular basement membrane that cause inflammation, fibrosis, and loss of kidney function. Ultimately, patients progress to kidney

failure.

Bardoxolone methyl, which we will refer to as bardoxolone, targets chronic inflammation, which is known to drive CKD progression. Chronic inflammation impairs a single nephron GFR through its dynamic regulation and reduction of glomerular filtration surface area. In addition, it also induces profibrotic pathways that provoke irreversible kidney remodeling, resulting in nephron loss.

This plot shows the link between inflammation and CKD progression in Alport syndrome. The number of inflammatory cells is shown on the X-axis and serum creatinine levels on the Y-axis. These kidney biopsy data demonstrate that the degree of inflammation is significantly correlated with declining kidney function in Alport syndrome.

Bardoxolone's novel mechanism of action activates Nrf2, a transcription factor with anti-inflammatory and tissue-protective effects. By activating Nrf2, bardoxolone reduces oxidative

stress to restore redox balance, reduces mitochondrial dysfunction, and suppresses inflammation and fibrosis. Nrf2 has been shown to be suppressed in many forms of CKD and is linked to eGFR loss, and it has been validated as a therapeutic target in genome-wide studies of patients with nine different forms of CKD, including Alport syndrome.

Most existing therapies address CKD by reducing hydrostatic pressure within the kidney and do not directly target inflammation. We and our collaborators have characterized bardoxolone's novel mechanism in 20 different models of kidney disease.

Using in vivo imaging, we have shown that through activation of Nrf2, bardoxolone acutely restores the filtration surface area in the glomerulus, and as a result increases single-nephron GFR. Importantly, this is not associated with increases in glomerular permeability or pressure, which would be harmful.

Chronic treatment with bardoxolone slows

disease progression through its antifibrotic effects, which take longer to manifest.

(Pause.)

CAPT NGO: Panel members, this is Diem with FDA staff. Please hold the line. You are not disconnected. Please hold.

(Pause.)

DR. CHIN: We see suppression of inflammatory cytokines, as well as reductions in growth factors and extracellular matrix deposition, all of which prevent structural damage. We've demonstrated these effects in models of CKD, including hyperfiltration, protein overload, and diabetes. These multiple lines of evidence show that bardoxolone targets the underlying pathophysiology of CKD and provide its scientific support for its clinical development.

We began studying bardoxolone back in 2005 in oncology, and during these early studies, we noted effects on eGFR in patients with cancer, which led Reata to investigate bardoxolone in patients with CKD.

Between 2008 and 2012, we conducted multiple trials in patients with type 2 diabetes and CKD. In 2012, Reata stopped clinical development with bardoxolone in diabetic CKD after a safety finding in a large phase 3 trial. While our Japanese partners continued development in diabetic kidney disease, Reata decided to focus on developing therapies for rare diseases, and we began our development program in Alport syndrome in 2016.

As you will hear today, these early CKD trials informed our development program. Across all studies, we have noted the following observation. First, increases in measured GFR with bardoxolone, confirming that the change in estimated GFR represents a true change in kidney function; reductions in markers of vascular inflammation and injury; preservation of eGFR observed in studies that included six different forms of CKD; sustained preservation of eGFR in longer-term studies; and finally, off-treatment eGFR benefits after treatment withdrawal of drug.

Our entire CKD development program has

enrolled over 3,000 patients and exposed over 2500 subjects to bardoxolone, extensively characterizing its profile. As mentioned, our development has included challenges, as well as important learning. Study 903, otherwise known as BEACON, was the largest of these earlier studies and enrolled patients with type 2 diabetes and stage 4 CKD. Study 903 was terminated due to an increase in adjudicated heart failure events. After halting clinical development in diabetic CKD, we worked to understand this important safety finding.

The increased risk for these events was limited to the first four weeks after treatment initiation. A series of post hoc analyses indicated to us that bardoxolone was causing volume overload, which may have led to the heart failure. seen in Study 903.

We also saw imbalances in general fluid- and edema-related adverse events. Patients reported sudden increases in weight and blood pressure, but generally had preserved ejection fraction, and there was no signal for myocardial injury, and

troponins were unchanged.

Importantly, we were able to identify risk factors for these events, BNP greater than 200 picograms per mL and a prior history of heart failure. For patients without these risk factors, the risk for heart failure was 2 percent for bardoxolone and placebo. Our learnings from Study 903 allowed us to continue clinical development with bardoxolone.

In all studies conducted since 2012, shown here in yellow, we excluded patients with the risk factors identified in Study 903. These trials have exposed over 600 patients, and as we will discuss in the safety presentation, we have not observed the risk for heart failure in patients with Alport syndrome, other forms of chronic kidney disease, or pulmonary hypertension.

There were several factors that prompted us to initiate clinical development in Alport syndrome. From a scientific perspective, Nrf2 suppression and increased inflammation is linked to eGFR loss in disease progression in Alport

syndrome. Additionally, we were focused on developing therapies for rare diseases with significant unmet need, and the unmet need in Alport syndrome is clear.

These patients have one of the most rapid rates of progression and reach end-stage kidney disease at a relatively young age, and yet there are no approved therapies. The sustained preservation of eGFR with bardoxolone in an entire CKD trial could therefore be a meaningful benefit for this population. Importantly, these patients generally have few comorbidities that predispose them to the risk of heart failure previously seen in Study 903.

Here we show key baseline characteristics of the Study 903 population on the left and the randomized population from our pivotal Alport syndrome study, otherwise known as CARDINAL on the right. The studied Alport syndrome population was much younger than the 903 population, and few had a history of diabetes. And by design, few patients with Alport syndrome had any history of

cardiovascular disease, and patients had meaningfully lower baseline BNP levels than the patients in 903. This is consistent with the estimates for the overall Alport syndrome population, where less than 1 percent of patients had cardiac disease. And since Study 903 only enrolled stage 4 CKD patients, baseline eGFR was meaningfully lower.

Now, turning to our key development program milestone, in 2016 we had our pre-IND meeting where we agreed upon an adaptive phase 2/3 study design with the FDA. Because of bardoxolone's acute pharmacodynamic effects on kidney function, the FDA was clear that an off-treatment eGFR assessment was required to evaluate the drug's effect on the slowing of disease progression.

We incorporated the FDA's recommendations, including assessment of off-treatment endpoint at weeks 52 and 104. In the study-may-proceed letter received in December 2016, FDA reiterated that the key secondary off-treatment endpoint, following a 4-week withdrawal period, was essential for

approval. After that, as shown below in the timeline, we initiated the open-label, phase 2 trial in 2017, and FDA granted orphan drug designation later that year. Once the phase 2 trial met its primary endpoint, we initiated the phase 3 trial, and Study 1803 began in 2019 and is currently ongoing.

We had a series of FDA interactions and submissions after year 1 of Study 1603 phase 3 was completed, which culminated in a pre-NDA meeting in September 2020, and we submitted the NDA in February 2021, which brings us to this meeting today, where you are being asked to consider the benefit-risk of bardoxolone for the treatment of Alport syndrome.

Today, you will hear that Alport syndrome is a rare, serious, and rapidly progressive kidney disease with an urgent need for effective treatment. We will begin by talking about the trial design for Study 1603 phase 3, including data supporting the adequacy of the off-treatment duration to assess bardoxolone's effect on kidney

disease progression. We will then share the bardoxolone efficacy results.

Study 1603 phase 3 met its year 1 and year 2 primary and key secondary endpoints, and we will show these results are clinically meaningful, and consistent, and show bardoxolone slows the progression of kidney disease. We will discuss the safety results, demonstrating a well-defined, clinically manageable safety and tolerability profile. Finally, the totality of evidence support a favorable benefit-risk for bardoxolone in the treatment of Alport syndrome.

In a moment, Dr. Brad Warady will provide a background on Alport syndrome and the need for therapy. Next, Dr. Colin Meyer and Dr. Nathan Teuscher will discuss our phase 3 study design. Dr. Meyer will then present our clinical efficacy and safety data. And finally, Dr. Glenn Chertow will provide an overview of the benefit-risk of bardoxolone in patients with Alport syndrome. Additionally, our Reata functional area experts and the following external subject matter experts are

with us to help answer your questions today.

I will now ask Dr. Brad Warady to speak about Alport syndrome and the need for effective treatment.

Applicant Presentation – Bradley Warady

DR. WARADY: Thank you, Dr. Chin.

I'm Brad Warady. I'm the director of the Division of Nephrology and the director of Dialysis and Transplantation at Children's Mercy Kansas City and professor of pediatrics at the University of Missouri Kansas City School of Medicine.

I've cared for children and adolescents with Alport syndrome throughout my career in nephrology, which spans nearly 40 years. I'm also a member of the Medical Advisory Committee of the Alport Syndrome Foundation. I've served as an advisor to Reata over the course of Study 1603 phase 3, and in turn I am a paid consultant to Reata Pharmaceuticals. However, I have no financial interest in the outcome of this meeting.

Alport syndrome is a rare, serious, and debilitating disease. It's an inherited form of

chronic kidney disease, and it's caused by mutations in type IV collagen genes COL4A3, COL4A4, and COL4A5. It affects an estimated 30,000 to 60,000 patients in the U.S., with an estimated 14,000 patients diagnosed in the U.S., and it causes progressive chronic kidney disease.

In addition to the kidney disorder, patients with Alport syndrome experience deafness, eye abnormalities, and the emotional burdens associated with chronic kidney failure. Alport syndrome accounts for 3 percent of pediatric and 0.2 percent of adult patients who develop end-stage kidney disease annually. Thus, this clearly is a very rare disorder, that patients with Alport syndrome have a high lifetime risk for progression to kidney failure.

Why does kidney failure occur in patients with Alport syndrome? As mentioned earlier, we're starting with the genetic insult, and at least currently we can't change the genetics. But on top of that genetic insult, we have inflammation, and that inflammation leads to glomerulosclerosis,

interstitial fibrosis, and ultimately fibrosis of most, if not all, of the previously functioning kidney, with the subsequent development of end-stage kidney disease in many of these patients.

The current standard of care for patients with Alport syndrome includes the use of ACE or ARBs therapy. While this therapy does have some impact on slowing the progression of CKD, most of these patients continue to progress despite the therapy, and some patients do not even tolerate the therapy, becoming hypotensive, a complication leading to discontinuation of that treatment.

Most important is the recognition that RAAS inhibition modulates GFR by addressing hydrostatic pressure, but it does not directly impact inflammation, which is the key driver of kidney function decline. Other approaches to the management of CKD and end-stage kidney disease include diet modifications and restricted fluid intake, interventions that are understandably challenging for many, and especially for adolescents.

Finally, as a result of the many clinical complications experienced by these patients, they require care from a variety of disciplines, including physicians, nurses, social workers, dietitians, audiologists, psychologists, all to address the clinical and psychosocial burdens that accompany Alport syndrome.

Here are the four different inheritance patterns of Alport syndrome and the associated risk of end-stage kidney disease. I want to bring your attention to the bottom row where, as you can see, the risk of end-stage kidney disease and the need for either dialysis or a kidney transplant in those with the most severe Alport syndrome -- namely males with X-linked disease and males and females with autosomal recessive disease -- is 100 percent.

All of these individuals will progress to kidney failure, and for females with X-linked disease, up to 25 percent of those patients will also develop kidney failure. In addition to the substantial risk for end-stage kidney disease, patients with Alport syndrome experience a more

rapid decline in kidney function than patients with many other forms of kidney disease.

Here we see the average annual fall in GFR, or disease progression rate in mLs per minute, of patients with a variety of kidney disorders. The first four groups of patients have a fallen GFR of around 2 mLs per minute per year. This includes diabetic CKD patients, hypertensive CKD, patients with polycystic kidney disease, and children with CAKUT, congenital anomalies of the kidney and urinary tract, the most common disorder associated with kidney failure in children.

Two mLs per minute is much slower than what we see in patients with Alport syndrome. For all patients with Alport syndrome, children and adults, you can see the fallen GFR is nearly 5 mLs per minute per year, more than double the rate of the other forms of CKD. And as you can see on the far right, the Alport syndrome pediatric population enrolled in Study 1603 phase 3 experienced a remarkably high pretrial rate of eGFR decline of 10.7 mLs per minute per year.

Shown here is the five-year historical pretrial fall in GFR for the overall Study 1603 phase 3 cohort in gold and the same data for the adolescent patients alone in purple. Zero years represents the initiation of Study 1603 phase 3, and end-stage kidney disease is represented by the dotted horizontal gray line.

If these same patients followed the same trajectory of kidney function declines over subsequent years, following the initiation of Study 1603 phase 3, on average, the pediatric patients would progress to end-stage kidney disease in less than 5 years and all patients would develop kidney failure in only 9 years.

At the same time, it's important to recognize, as demonstrated here, that an intervention that can slow the rate of kidney function decline, even by as little as 1 to 2 mLs per minute per year, has the potential to delay the development of end-stage kidney disease. For this reason, we assess eGFR regularly to monitor kidney function and track disease progression in patients

with chronic kidney disease.

While traditional endpoints in trials that enroll larger CKD populations included clinical outcomes such as end-stage kidney disease, or a 40 to 50 percent decline in eGFR, the National Kidney Foundation, FDA, and EMA recognize the need for alternative eGFR-based endpoints, particularly for clinical trials in rare diseases or earlier stages of CKD.

As a result, the NKF, FDA, and EMA working group performed a meta-analyses of observational studies and clinical trials and validated that beneficial treatment effects on eGFR, as little as 0.75 mLs per minute per year assessed over 2 years, were associated with reductions in the risk for kidney failure, and FDA now accepts eGFR change as a validated surrogate for clinical trials in CKD to measure disease progression.

This is extremely significant to patients because of the increasing array of adverse clinical manifestations that develop with progression from mild to moderate CKD to end-stage kidney disease.

A decline in eGFR impacts the clinical manifestations patients experience with CKD. Patients who entered Study 1603 phase 3 had eGFR values of 30 to 90 mLs per minute, corresponding to stage 2 or stage 3 CKD, where they demonstrated some proteinuria, fluid retention, and maybe hypertension.

As eGFR declines for stage 5 CKD, which is synonymous with end-stage kidney disease, there are additional clinical manifestations: anorexia acidosis, anemia, and growth delay in children. The patients are fatigued and suffer from a poor quality of life, as many end up requiring chronic dialysis. And as some of you well know, the medical and psychosocial burden associated with dialysis for any patient, let alone an adolescent, cannot be overemphasized.

From the medical perspective, I must add that the prevalence of cardiovascular disease is markedly increased in both adults and children on dialysis. In addition, employment, school attendance and performance, family dynamics, future

goals, and more are all affected by the need for dialysis, and depression is an all too common result.

When children and adults develop end-stage kidney disease, there's also an associated decreased life expectancy for those patients on dialysis. The data on this slide, generated from the database of the United States Renal Data System, represents the estimated years of life expectancy lost for patients by the age of end-stage kidney disease onset.

I highlighted here the ages of 15 through 29 years instead of the age range when the vast majority of individuals with the most severe forms of Alport syndrome develop end-stage kidney disease, and you can see that in this population of patients, their loss of life expectancy is an average of almost 40 years. Their lifetimes are basically cut in half.

Understandably then, in addition to the medical impact of Alport syndrome, there are often significant psychosocial implications associated

with this disorder. At the 2018 FDA Patient-Focused Drug Development meeting, individuals with Alport syndrome voiced their concerns. They emphasized that anxiety, depression, fatigue, and hearing loss most negatively impacted their daily living.

Almost three-quarters of the patients said that the disease interfered with their daily life, and one-quarter of them reported having anxiety or depression related to the fear of developing kidney failure. And on a personal note, the vast majority of my patients with Alport syndrome and moderate-to-severe CKD are seeing a psychologist for just this reason.

Not surprisingly, these patients also related how they are most interested in a medication that would slow their decline in kidney function, because in their mind, it's not if, but it's when will they develop kidney failure? In short, new therapies are needed for Alport syndrome. There is no approved effective treatment.

As I've shown you, this is a rare, serious, and debilitating disease, which often presents in childhood. The rapid decline in kidney function has a significant impact on patients' quality of life and, in fact, leads to reduced life expectancy. And I think it goes without saying that if these patients could have available to them a therapy that has even a small treatment effect and that slows progression by as little as 1 to 2 mLs per minute per year, it could result in a meaningful delay to kidney failure. Having this option would, without question, provide profound medical and psychosocial benefits to patients with Alport syndrome.

Thank you for your attention, and now I'd like to turn the presentation over to Dr. Meyer.

Applicant Presentation – Colin Meyer

DR. MEYER: Thank you, Dr. Warady.

Good morning. I'm Dr. Colin Meyer, chief research and development officer at Reata Pharmaceuticals. I'll now discuss key elements of the study design of our phase 3 Alport syndrome

trial.

As Dr. Chin discussed in our pre-IND interactions, the FDA proposed a phase 2/3 study design with a two-year treatment duration and inclusion of off-treatment eGFR endpoints. We incorporated all of the FDA suggestions into this study design and conducted the three trials shown here that are central to our NDA.

Study 1603 phase 2, an open-label trial that enrolled 30 patients and had the same treatment and visit schedule as the phase 3 trial, while this was a two-year trial, the first 12 weeks established preliminary efficacy and safety in this patient population in gated enrollment in the phase 3 trial.

The pivotal Study 1603 phase 3, a randomized, double-blind, placebo-controlled, two-year trial, enrolled 157 patients, which provides the primary evidence for the NDA, and Study 1803, an ongoing, open-label, extended-access trial, which allows for evaluation of longer term safety.

The endpoints and design of Study 1603 phase 3 are consistent with recent findings from the NKF, FDA, and EMA. As discussed by Dr. Warady, even small treatment effects on eGFR, a validated measure of disease progression, can translate to a beneficial effect on clinical outcomes in CKD. The primary endpoints for our trial assessed on-treatment changes in eGFR over a two-year duration.

For agents that have an acute pharmacodynamic effect, the working group recommended obtaining a before-treatment eGFR value and eGFR values after withdrawing treatment to assess for any persisting effect on kidney function that would represent slowing of disease progression. Study 1603 evaluated this off-treatment endpoint twice after one and two years of treatment.

To assess both the on- and off-treatment eGFR effects with bardoxolone, Study 1603 phase 3 included two 48-week treatment periods and two 4-week withdrawal periods, shown in yellow between

weeks 48 and 52 and weeks 100 and 104. A total of 15 eGFR values were collected throughout the study period, as noted by the solid black dots near the top of the slide.

For patients who discontinued treatment, we obtained an off-treatment eGFR value 4 weeks after their last dose. Patients were randomized 1 to 1 to receive bardoxolone or placebo, starting at 5 milligrams once daily and titrated in the first 6 to 8 weeks to reach their target goal dose of 20 or 30 milligrams. We included off-treatment periods after both years of treatment because during our pre-IND meeting, the FDA indicated that the year 1 data might support accelerated approval.

As noted earlier, FDA stated that the 4-week, off-treatment eGFR endpoint at week 104 would be critical for demonstrating efficacy and supporting full approval. To characterize the on-treatment effects that would inform use in clinical practice, we included on-treatment eGFR assessments at weeks 48 and 100. To address FDA's guidance, we incorporated the off-treatment eGFR

assessments at week 52 and 104, 4 weeks after drug withdrawal. Other exploratory endpoints included a patient-reported outcome, the Patient Global Impression of Change, or PGIC, and frequency and time to first event in a composite of adverse kidney outcomes.

Study 1603 phase 3 enrolled patients with a genetic or histological confirmation of Alport syndrome who were 12 to 70 years of age. Based on feedback from the FDA, we allow patients with a wide range of kidney function, including eGFR values between 30 and 90 mL per minute, which represents CKD stages 2 and 3.

Patients with UACR up to 3500 milligrams per gram were eligible to participate in the trial and were required to be receiving standard management with RAAS inhibitors unless contraindicated. Based on learnings from Study 903, we excluded patients with clinically significant cardiovascular disease or BNP greater than 200 picograms per mL at baseline.

Our earlier trials informed dose selection

in our Alport syndrome program. Study 902 was an open-label, dose-ranging study in patients with type 2 diabetes and CKD that studied 6 doses of bardoxolone up to 30 milligrams. Increases in eGFR were dose dependent and maximal at 15 to 30 milligrams, with an appropriate safety profile. The efficacious dose was dependent upon baseline UACR.

Study 903 used a fixed 20-milligram dose. One key learning from the trial was that dose titration could optimize patient tolerability and allow for careful monitoring. These learnings informed the dosing schemes used in all studies conducted after Study 903.

I will briefly summarize our key regulatory discussions regarding the off-treatment duration. After our 2016 interaction, where FDA stated the importance of the week 104 off-treatment endpoint, the first discussion of the adequacy of the off-treatment duration occurred in January 2020 in connection with FDA's review of the year 1 data.

We did, however, discuss this topic in 2018

at an end-of-phase-2 meeting for ADPKd phase 3 study, which uses the same treatment duration and off-treatment eGFR endpoints. We provided PK and clinical data, much of which is included in section 9.3 of our briefing book, and the FDA stated that it was reassured by the data supporting the 4-week withdrawal period.

Dr. Nathan Teuscher will now present these and other data that we used to justify the duration of the off-treatment period.

Applicant Presentation – Nathan Teuscher

DR. TEUSCHER: Thank you, Dr. Meyer.

Good morning. I'm Dr. Nathan Teuscher, vice president of Integrated Drug Development at Certara. I am a paid consultant to Reata Pharmaceuticals, and I have no financial interest in the outcome of this meeting. I will discuss the data and methods used by Reata to justify the off-treatment duration used in Study 1603.

These are hypothetical eGFR profiles for three different drug effect scenarios following treatment for 100 weeks followed by a washout

period. The placebo group, in gray, declines over time due to natural disease progression. A drug with only acute PD effects is shown as the green dotted line, and a drug with both acute and disease-modifying effects as the purple dash line.

The ability to accurately discriminate the contribution of these two effects is dependent upon the duration of the clinical study. Analysis that includes only the data after chronic administration is not capable of differentiating the green and purple lines. The most robust scientific approach to address this question is to also analyze data that only includes one of the effects.

The same hypothetical eGFR profiles from the prior slide depict drug treatment for 8 weeks. The green and purple lines representing the acute PD effects only and acute and disease-modifying effects, respectively, overlap and are identical. Therefore, this short duration study represents a clinical model of the acute PD effects because there has not been time to accrue longer disease-modifying effects.

The acute PD effects are most easily identified using short-term clinical studies. Reata conducted two short-term clinical studies to define the duration of acute eGFR effects, and we believe that the data support the 28-day washout period. In contrast, the FDA used a PK/PD model based on long-term data to evaluate the acute eGFR effects.

Bardoxolone has a pharmacokinetic half-life of 48 hours in short- and long-term studies, and there are no active metabolites. As shown in this plot, 14 days after the last dose, approximately 99 percent of the drug is cleared and bardoxolone plasma levels would be well below the window of pharmacologic activity based on nonclinical pharmacology studies. Therefore, a short-term study with a minimum washout of at least 14 days should give insight into the pharmacodynamic effect washout period.

This table shows the summary eGFR measurements for the 98 patients enrolled in Studies 801 and 1102, both short-term studies of 4

and 8 weeks in treatment duration. These short-term studies are not confounded by disease progression or disease-modifying effects. The on-treatment change from baseline values show acute increases in eGFR, and the 4-week off-treatment change from baseline values, in the last column, show complete resolution of this effect. These results provide strong evidence that the acute eGFR effects resolved within 28 days, or 4 weeks, after treatment discontinuation.

This plot shows over a thousand individual eGFR values post-withdrawal from 652 patients with various forms of CKD from the integrated summary of safety database. Off-treatment eGFR values are shown from 1 to 42 days after withdrawal.

As you can see, over the first 14 days post-withdrawal, the eGFR change resolves, and the best-fit line shows no association between eGFR change and days post-dose after 14 days. Importantly, between days 28 and 42, the eGFR change from baseline is constant, suggesting that after week 4, there is no further change in eGFR.

The FDA used a PK/PD model to extrapolate beyond the observed 28-day data for estimation of the time to eGFR effect resolution. The FDA PK/PD model was based on data from the long-term study, 1603, and the intermediate term study, 005. Both of these studies have sufficient treatment duration to accrue disease-modifying effects.

Importantly, the FDA model did not include eGFR from short-term Studies 801 and 1102. Thus, the single eGFR effect estimated in the FDA model likely includes both acute eGFR effects and disease-modifying effects, which can confound the interpretation of the FDA model results and extrapolations.

This plot is a simulation of the mean response for Study 1102 predicted by the FDA model based on the information provided in the FDA briefing document. The blue and gray lines represent the bardoxolone- and placebo-predicted eGFR change, respectively, and the observed mean data are shown by the black dots.

The simulated values during the washout

period at week 12 are higher than the observed values, suggesting overprediction of the acute pharmacodynamic washout because the model was built on data that included both acute and disease-modifying effects. Similarly, for Study 801, the simulated values during the washout at week 8 are higher than the observed values. Taken together with Study 1102, this suggests the FDA model does not accurately predict the observed acute eGFR washout.

I'll now hand the presentation back to Dr. Meyer.

Applicant Presentation – Colin Meyer

DR. MEYER: Thanks, Dr. Teuscher.

In summary, we respectfully disagree with the FDA regarding the adequacy of the off-treatment period. We have demonstrated that observed clinical eGFR data most reliably support the adequacy of the 28-day off-treatment duration. The two-year design is an appropriate length to determine both the acute and chronic effects of the drug. The primary endpoint reflects the treatment

effect in clinical practice and the key secondary endpoints were included at FDA's request to assess for slowing of disease progression.

I'll now discuss the clinical efficacy data. I will share the data demonstrating the effectiveness of bardoxolone in patients with Alport syndrome, including the pivotal Study 1603 phase 3 results, as well as supportive data from Study 1603 phase 2 and Study 1803.

The pivotal trial was a global, multicenter study that enrolled patients at 48 sites and 6 countries. Two-thirds of patients were enrolled in the U.S., and a central lab analyzed eGFR data for key efficacy endpoints. The evolving COVID-19 pandemic occurred during the last 9 months of the study and complicated study conduct.

COVID-19-related measures were required to preserve patient safety and to maintain data collection in the study despite temporary site closures, travel restrictions, and logistical challenges. These measures included implementing home health visits, adjusting study visit

schedules, and allowing flexibility in the week 100 and week 104 eGFR collection windows.

We enrolled a population that was representative of the overall Alport syndrome population. Demographics were balanced between the two groups. We randomized 23 adolescent patients representing approximately 15 percent enrolled patients, and most patients had X-linked disease. The baseline characteristics were also representative of the overall Alport syndrome population and were balanced between treatment groups.

Upon study entry, patients had impaired kidney function. Even though the mean UACR was low, most patients were receiving RAAS inhibitor therapies and blood pressure was well-controlled. As shown in the bottom row of the table, the overall trial population was progressing at an average annual rate of eGFR decline of approximately 5 mL per minute. 157 patients were randomized into the ITT population.

More discontinuations occurred in the

bardoxolone arm than the placebo arm primarily in the first year. After 48 weeks, 78 percent of patients randomized to bardoxolone remained on treatment compared to 89 percent of patients randomized to placebo.

At week 100, roughly one-third of patients randomized to bardoxolone had discontinued study drug. Due to our efforts to maintain follow-up in the trial, once patients discontinued treatment, we obtained end-of-study follow-up at week 104 for 98 percent of all participants.

The reasons for treatment discontinuation are shown on this slide; 26 patients randomized to bardoxolone and 13 patients randomized to placebo discontinued treatment during the two-year trial; 10 patients randomized to bardoxolone discontinued due to adverse events, and no more than 2 patients discontinued due to any one type of adverse event. Seven bardoxolone-treated patients discontinued due to protocol-specified criteria primarily due to management of aminotransferase increases, which were not associated with liver injury.

I will now walk you through the analysis methodologies. The primary endpoints compared the effects of treatment after 48 or 100 weeks. We analyzed eGFR changes from the on-treatment periods using a mixed-model repeated measures or MMRM approach. The model included all eGFR values collected through 48 or 100 weeks irrespective of study drug administration, and missing data were not imputed.

The key secondary endpoints evaluated the off-treatment eGFR change on 1 or 2 years of treatment to assess for effects on kidney disease progression. Because these endpoints compared mean changes in eGFR at discrete time points -- that is 4 weeks after stopping drug in year 1 or year 2 -- an ANCOVA was specified to compare changes from baseline in eGFR at 52 and 104 weeks or 4 weeks after the last dose for patients who discontinued study drug. In this analysis, we imputed missing eGFR data based on the treatment group. Because the year 2 off-treatment analysis assesses the effect of long-term exposure, we

prespecified the analysis to only include patients who dosed in year 2. Patients who discontinued in year 1, after only short-term exposure to drug, were excluded in the year 2 off-treatment analysis.

This figure represents all eGFR values collected in Study 1603 phase 3 through week 100. The columns represent the study weeks and the rows represent individual patients. For the bardoxolone group, patients who had eGFR values collected while receiving treatment are shaded in dark blue and eGFR values collected after treatment discontinuation are shaded in light blue.

Since we followed intention-to-treat principles, the primary analyses included all available eGFR values collected over time, regardless of whether patients were receiving treatment or not. Missing eGFR observations are shown in the white cells and missing data were not imputed.

For example, at week 100, 84 percent of bardoxolone patients had eGFR values and 16 percent had missing eGFR observations. However, all

patients had eGFR values collected throughout the two-year study period that contributed to the primary efficacy endpoints.

Study 1603 phase 3 met its primary endpoints with statistically significant and clinically meaningful improvements in eGFR relative to placebo. Treatment with bardoxolone resulted in a relative preservation of eGFR of 9.5 mL per minute at week 48 and 7.7 mL per minute at week 100 in the ITT population.

To better characterize response across all patients, we prespecified a cumulative distribution analysis for changes in eGFR at week 100. Here we showed the percentage of patients in each treatment group with the corresponding eGFR changes at week 100, denoted on the X-axis. Treatment with bardoxolone shifted the cumulative distribution of change from baseline in eGFR.

Not surprisingly, most patients randomized to placebo experienced a worsening of kidney function. Ninety percent of placebo-treated patients progressed more compared to

bardoxolone-treated patients. Across the full spectrum of responses, a treatment benefit was observed with bardoxolone relative to placebo in the year 2 primary endpoint.

We observed relative on-treatment eGFR improvements with bardoxolone at week 100 across all prespecified subgroups, including age, sex, UACR and eGFR categories, ACE inhibitor and ARBs, and genetic subtypes. Similar results were observed for the key secondary off-treatment analysis.

We conducted multiple sensitivity analyses to see how assumptions in the prespecified analysis and any missing data could affect the primary efficacy conclusions. The prespecified analysis model included a covariate that accounted for differences in treatment exposure for patients who discontinued drug early. While we realize the limitations of including a post-randomization factor, exclusion of this treatment duration covariate showed similar results for the primary endpoint.

We also analyzed the primary endpoint using controlled-based multiple imputation. In this analysis, missing eGFR values in the bardoxolone group are imputed with placebo values. This analysis showed a similar statistically significant treatment effect.

Lastly, we used a simple ANCOVA analysis to evaluate eGFR change at week 100 and showed a treatment effect consistent with the year 2 primary input results, demonstrating that the study results were robust to various analytical methods.

This figure shows all eGFR values collected over the two-year study period. The key secondary analyses compared off-treatment eGFR changes after one or two years of treatment using ANCOVA. So in the year 2 key secondary endpoint, the off-treatment eGFR values included in the analysis are the ones highlighted in this column, light blue for bardoxolone and light gray for placebo.

In the bardoxolone group for patients that completed 100 weeks of treatment, these were the eGFR values collected at week 104. For patients

that discontinued treatment early in year 2, these were eGFR values collected approximately 28 days after last dose. Together, 56 patients randomized to bardoxolone and 59 patients randomized to placebo had observed eGFR values that contributed to the year 2 key secondary endpoint.

Missing eGFR observations for the year 2 key secondary analyses are shown in white cells, and missing values were imputed using treatment-based imputation in the ANCOVA model. This primarily includes patients who discontinued in year 1 and did not dose in year 2. Nevertheless, we continued to collect eGFR values for many of these patients, and despite being off drug for over a year, as you can see on the far right, we were able to collect eGFR values at the end of study for 96 percent of patients.

The study met its key secondary off-treatment endpoints. After a 4-week off-treatment period, patients randomized to bardoxolone had a statistically significant preservation of eGFR compared to placebo at

weeks 52 and 104. These data demonstrate that bardoxolone has a beneficial effect of slowing disease progression.

Now, it's important to remember that based on the observed PK/PD profile of bardoxolone, we chose a targeted 4-week duration for the off-treatment period in the key secondary endpoints. As shown on this slide, we collected eGFR values over a range of days, from 14 to over 70 days post-dose. We analyzed the off-treatment eGFR values by weekly post-dose increments.

We saw no association between the number of days post-dose and the magnitude of the off-treatment eGFR values for either treatment group. Off-treatment eGFR values collected in the earlier part of the analysis window, in the left two columns, were not higher than values that were collected later, on the right. If the acute eGFR effects were still present during this period, we would see a negative trend over this duration, which was not observed.

Importantly, we see here that the timing for

collection of off-treatment eGFR values in Study 1603 phase 3 did not affect the difference between treatment groups or impact interpretability of the study's key secondary efficacy results, demonstrating a slowing of disease progression.

We also conducted several sensitivity analyses to probe the reliability of the key secondary results. In particular, we performed a tipping-point analysis to see how missing data could have affected [inaudible] results. Bardoxolone patients with missing off-treatment eGFR values at week 104 would have had to have declined an average of 14 mL per minute from baseline. This decline would be unlikely.

Still, we wanted to explore the likelihood of this happening. Again, the tipping-point threshold required to lose significance minus 14 mL per minute is much lower than the mean eGFR changes in the bardoxolone or placebo arms, which were minus 4.5 and minus 8.8 mL per minute, respectively.

Recall that data from patients who

discontinued in year 1 were not included in the year 2 key secondary analyses. However, we actually obtained off-treatment eGFR data 4 weeks after the last dose for 16 of the 21 bardoxolone patients. All of the eGFR values in the bardoxolone arm would have had to have been below this red line for the results to lose significance. Their off-treatment eGFR values show that did not happen.

Finally, we performed additional sensitivity analyses that explored alternate analytical or imputation methods. As seen in this forest plot, all of these analyses showed similar treatment effects. The final analysis used all off-treatment eGFR values collected at the end of study, as close to week 1 of where it's possible. This included data from 96 percent of patients, including patients who discontinued in year 1, whose mean duration off-study drug was 87 weeks, resulting in a dilution of the treatment effect.

In some of these analyses, the treatment effect was not statistically significant, but

continued to favor bardoxolone, and confidence intervals overlapped with results of the prespecified analysis. The consistency of the treatment effect across the collective sensitivity analyses supports the Study 1603 phase 3 conclusions and the key secondary endpoint.

In regards to the impact of COVID-19 in the trial, the FDA noted in their briefing document that there was a difference in the eGFR change in the pre- versus post-COVID periods. Only a small number of patients finished the trial in the pre-COVID era, making comparisons with those sort of patients difficult.

We noted that the bardoxolone-treated patients had similar treatment effects relative to baseline in both time periods, as highlighted on the slide. The apparent difference in treatment effect across COVID-era subgroups was therefore driven by the different rates of decline in the placebo group. We noted some imbalances in baseline characteristics between these two periods, which likely contributed to this, and the eGFR

differences between these two periods do not affect the overall reliability or interpretability of the trial.

We observed the largest treatment effect at weeks 100 and 104 in the adolescent subgroup. Adolescent patients treated with bardoxolone had statistically significant placebo-corrected improvements of 13.8 and 14.6 mL per minute at weeks 100 and 104, respectively, demonstrating slowing of disease progression in these patients with the greatest risk progression to kidney failure during their lifetimes.

Whereas treatment with bardoxolone preserved kidney function, patients treated with placebo, shown here in gray, lost approximately 15 mL per minute by weeks 100 and 104. Given the mean baseline eGFR for these adolescents, the observed decline rate in the placebo group would translate the need for dialysis or transplantation in approximately 5 to 7 years. During the trial, 2 adolescent patients randomized to placebo, but none randomized to bardoxolone, progressed to

end-stage kidney disease.

Here we see the trajectory of mean changes in eGFR over two years for the ITT population in Study 1603. The gray line shows the placebo group, which showed progressive eGFR decline over the course of two years. The bardoxolone group is in dark blue.

The trajectory for eGFR in year 1 shows some loss of acute eGFR effects, particularly between weeks 12 to 36. In year 2, the trajectory of eGFR beyond week 76 in the ITT population reflects, in part, the inclusion of patients who discontinued treatment. Still, we saw a meaningful separation between treatment groups after year 1 and year 2.

To quantify how eGFR changes over time can translate to a divergence between bardoxolone and placebo patients, we performed an analysis to evaluate chronic eGFR slopes. Study 1603 phase 3 was not designed to evaluate a conventional slope analysis over two years primarily due to treatment interruptions between year 1 and year 2, so we used a piecewise linear model to evaluate individual

patient trajectories within each year. This showed a divergence between treatment groups when considering a chronic slope in year 2.

Let's examine the area in this red box more closely. The year 2 chronic slope was minus 4.3 mL per minute per year for bardoxolone compared to minus 5.8 mL per minute per year for placebo in the ITT population. This represents a slowing in the loss of kidney function of 1.5 mL per minute per year, which is also consistent with slowing disease progression.

The divergence in chronic slope in year 2 is also supported by the eGFR trajectory observed through three years of treatment for patients in the open-label extension study, 1803. These are the data for the patients with Alport syndrome who have had the longest duration of bardoxolone treatment, who enrolled in Studies 1603 phase 2 and 3, and continued in the open-label extension study, 1803, which is ongoing.

Nineteen patients have reached three total years of treatment with bardoxolone. The data for

these patients over time show a pattern in year 1 and 2 that is similar to the bardoxolone group in Study 1603 phase 3. Notably, the eGFR trajectory observed in year 2 continued in year 3, and these data demonstrate maintenance of a beneficial treatment effect through three years of treatment.

This slide summarizes the totality of data evaluating rates of eGFR change. On the left, when we consider off-treatment eGFR analyses, the two-year total off-treatment eGFR slope -- which is an annualized extrapolation of the off-treatment year 2 key secondary endpoint -- shows a slowing in the rate of eGFR loss of 49 percent per year.

When we assess individual patients using all week 52 and week 104 off-treatment eGFR values in a longitudinal off-treatment analysis, we see a similar effect. On the right, the on-treatment chronic slope analyses in year 2 show a 25 percent reduction in the rate of kidney function loss in the ITT population.

This effect is even larger in patients who remained on bardoxolone, the as-treated population,

with a 34 percent slowing of disease progression. Reduction in the rate of disease progression with bardoxolone across these various analyses, both on and off treatment, show bardoxolone is effective in slowing the loss of kidney function in patients with Alport syndrome.

Finally, we prespecified an analysis of events in a kidney failure composite. Bardoxolone reduced the number of adverse kidney outcomes. We also surveyed how study patients felt when treated with bardoxolone. The blue bar shown here is a validated patient-reported outcome tool called the Patient Global Impression of Change. It is a 7-point scale that asks the patient how much their illness has improved or worsened.

As you can see in the table below the scale, in addition to significant improvements in eGFR relative to placebo, treatment with bardoxolone also significantly improved how patients felt.

In summary, Study 1603 phase 3 met its year 1 and year 2 primary and key secondary results. The magnitude of these effects were

clinically meaningful, both on and off treatment. Our eGFR slope-based analyses, both on and off treatment, demonstrated a slowing of disease progression with bardoxolone treatment, indicating these treatment benefits will be maintained over time.

In conclusion, these data provide substantial evidence of efficacy that bardoxolone slows the progression of CKD in Alport syndrome. Multiple sensitivity analyses demonstrated consistency of the results. These benefits were observed on top of standard of care, and the results are generalizable to the Alport syndrome population.

Two additional Alport syndrome studies showed consistent results, while also providing evidence that bardoxolone can preserve kidney function for up to 3 years. These results represent a clinically meaningful benefit in adults and adolescents with this rapidly progressive form of CKD.

Turning now to safety, I'll now present the

key safety data from pivotal Study 1603 phase 3. I will cover the relative safety information for bardoxolone, including adverse events from our Alport syndrome development program, special safety topics of interest, our key safety elements of our proposed label, and our pharmacovigilance plan.

Bardoxolone, has a comprehensive safety data set from trials enrolled more than 3,000 patients with over 2,200 patients exposed, and the safety profile is well characterized. Prior CKD experience informed risk mitigation strategies implemented in the Alport syndrome development program.

To avoid heart failure previously observed in Study 903, in all trials conducted since 2012, we narrowed eligibility criteria and increased monitoring during the first few weeks of treatment. In addition to more frequent monitoring, we implemented flexible dose titration to accommodate differences in individual patient tolerability. Bardoxolone safety profile in Alport syndrome was generally consistent with prior trials.

The overall adverse event profile for the pivotal Study 1603 phase 3 was similar across adults, adolescents, and other subpopulations. There were no deaths, and there were no fluid overload or cardiac serious adverse events in the bardoxolone-treated patients. The majority of AEs were mild to moderate intensity and tended to occur within the first 12 weeks.

The number of patients who reported an SAE in the bardoxolone group was approximately one-half that reported in the placebo group, and no SAEs were reported in adolescent patients treated with bardoxolone. Discontinuation due to adverse events were higher in the bardoxolone group, and no more than 2 patients discontinued due to any one adverse event.

These are the commonly reported adverse events with bardoxolone. Those highlighted in blue are those that we've identified as adverse drug reactions and are included in the proposed label. Several of the ADRs and common AEs have been well characterized and won't be discussed as safety

topics of interest.

Fewer bardoxolone-treated patients reported an SAE compared to placebo. SAEs reported by two or more patients are shown in this table, including kidney failure events, which were balanced across treatment groups. Overall, there were no imbalances in SAEs.

Symptoms of Alport syndrome are not just limited to the kidney and often include depression and anxiety, as well as hearing and vision disturbances. These non-kidney manifestations affect patients' daily lives, even before they reach kidney failure. Adverse events for all of these categories were reported less frequently in bardoxolone-treated patients.

With over 2,200 patients with various types of CKD exposed to bardoxolone in trials, we've observed several common adverse events. We've divided them into areas of clinical interest shown here. I'll first cover the most frequently reported adverse events. Some adverse events are hypothesized to be related to the pharmacological

effects of bardoxolone, as I'll explain. Nrf2 regulates multiple pathways, and many observed clinical findings with bardoxolone may be explained, at least in part, by the presumed mechanism of action.

Muscle spasms are the most common AE reported with bardoxolone. They were mostly mild to moderate in severity and not associated with increases in creatine kinase or other evidence of muscle injury. They typically present as lower extremity muscle cramps, similar to a charley horse. Flexible dose titration helped to resolve them, and only 2 patients discontinued.

Hyperkalemia events were all mild or moderate in severity, and nearly all events were reported in patients receiving concomitant ACE inhibitors or ARBs. Hyperkalemia is a known side effect of this class of drugs. None of the events were serious or resulted in study drug discontinuation.

Although increased albumin in the urine, as assessed by UACR, can be a marker of injury,

bardoxolone's pharmacological effect on eGFR can also increase UACR in a manner that differs from disease progression or injury. The combined effects of increasing filtration rate and decreasing albumin reabsorption explain the increases in albumin excretion seen with bardoxolone.

We have shown in nonclinical studies that increases in single nephron GFR are not associated with increased intraglomerular pressure and do not affect glomerular permeability to albumin, demonstrating the integrity of the filtration barrier remains unchanged. Additionally, we have also shown that bardoxolone decreases the expression of megalin, the primary protein involved in albumin reabsorption in the proximal tubules.

This plot shows UACR over time. Consistent with prior trials of patients with pre-existing albuminuria, treatment with bardoxolone increased UACR in patients with Alport syndrome. After an early increase that is accounted for by the increases in eGFR, UACR generally remains stable

through two years of treatment.

The stabilization of UACR while continuing treatment, and its return to baseline after two years of treatment and withdrawal of drug, is not consistent with glomerular damage. Injury to the glomerular filtration barrier will be expected to cause a continued increase in UACR over time that does not return to baseline or placebo after withdrawal, which was not observed. Importantly, the increases in UACR are not associated with accelerated eGFR loss.

We analyzed patients by quartiles of UACR change at week 12, shown in the middle column, and assessed eGFR changes on and off treatment after two years, in the right two columns. The quartile of bardoxolone-treated patients with the largest UACR increases at week 12 had the largest on-treatment and off-treatment eGFR changes relative to the other quartiles of bardoxolone-treated patients and all placebo quartiles after two years of treatment. These data are consistent with a UACR profile that is due to

the drug's pharmacologic effect and is opposite of a pattern of injury.

Small but reversible increases in BNP were seen with bardoxolone treatment, with mean diets remaining below the upper limit of normal. Importantly, the increases on BNP are not associated with blood pressure elevations or fluid-overload adverse events. Overall, fewer cardiac adverse events were reported in the bardoxolone group compared to placebo group.

Blood pressure was unchanged relative to placebo through 2 years in Study 1603 phase 3. Moreover, in a thorough QT study in healthy volunteers, at doses up to 80 milligrams, we have shown that bardoxolone does not affect blood pressure.

As mentioned earlier, we saw an increase in heart failure events in Study 903 and associated increases in blood pressure, including 24-hour ambulatory blood pressure monitoring that was assessed in a subset of patients. After Study 903, we implemented risk mitigation across all trials,

and in a trial of patients with pulmonary hypertension, we conducted 24-hour ambulatory blood pressure monitoring, as shown on the right. In this trial, we saw no increases in blood pressure, supporting that a risk mitigation strategy could be effective.

Prior to initiation of our Alport syndrome program, our Japanese partner, we initiated clinical development in patients with diabetic kidney disease. In their phase 2 402-005 study, they implemented a risk mitigation plan be developed in carefully monitored patients during the 16-week trial. Weekly serial troponins were assessed and showed no elevations.

Additionally, no adverse findings were observed in serial echos, and blood pressure remained stable without evidence of heart failure. This study was instrumental in supporting our reinitiation of development in CKD.

Across all CKD studies conducted after Study 903, that have exposed more than 600 patients and implemented these risk mitigation strategies,

we have not observed any cardiac SAEs. Further, we have not observed any mean elevations of blood pressure, and the number of exposed patients is meaningfully greater than the bardoxolone arm in Study 1603 phase 3. These data provide evidence that the risk of severe fluid overload requiring hospitalization, as well as less severe manifestations such as increases in blood pressure, can be mitigated.

Regarding weight loss, clinical models of diabetes and obesity have shown that bardoxolone and its analogs reduce total body fat content and preserve lean muscle mass, and these effects are mediated by Nrf2-dependent changes in lipid metabolism and fatty acid oxidation. In clinical studies, decreases in body weight with bardoxolone were accompanied by reductions in waist circumference without changes in total 24-hour excretion of urinary creatinine, consistent with loss of fat and not muscle.

Patients randomized to bardoxolone experienced weight loss relative to baseline and

placebo, which is consistent with prior trials. This plot shows weight changes by baseline BMI subgroups with the patients randomized to bardoxolone, with higher BMI shown in white squares and lower BMI in blue squares. Decreases in weight were more pronounced in patients with higher BMI. Mean changes in body weight were minimal in adolescent or bardoxolone-treated patients who had generally continued along their growth curves for both height and weight.

We have shown in multiple nonclinical studies that Nrf2 activation regulates ALT and AST production in multiple organs, and the clinical profile of aminotransferase increases in Study 1603 is consistent with pharmacological induction of gene expression rather than injury. FDA's review also came to similar conclusions.

Here on the left, we see the profile of ALT over time. These increases peaked approximately 2 weeks after patients reached their final dose, were transient with mean values coming back down while patients continued treatment, and the

increases were also reversible and returned to baseline in the two off-treatment periods. Importantly, these increases were associated with reductions in total bilirubin, as seen on the right, and across all studies, there were no cases of Hy's law.

We are collecting longer term data in Study 1803, an open-label extension study. This study has enrolled 96 patients and has demonstrated no new safety signals with up to three years of treatment. There have been no treatment-related serious adverse events reported to date, supporting longer term safety with bardoxolone.

Based on the safety findings, we have proposed careful monitoring [inaudible – audio break] of the label. Because the Study 903 in patients with diabetic CKD was discontinued due to excess heart failure events in patients treated with bardoxolone, we contraindicated use in patients with a history of heart failure.

Also, in the warnings and precautions section, we instruct physicians to assess BNP prior

to treatment initiation and to monitor for sudden weight gain and other signs and symptoms of fluid retention, which may proceed CHF, in accordance with the American Heart Association heart failure guidelines. Treatment should be discontinued if patients develop CHF.

Aminotransferases should be assessed prior to treatment initiation and during the first few months of use. Patients should discontinue the drug if large increases in aminotransferases or parameters consistent with Hy's law are observed, with frequent monitoring until resolution and before rechallenged. Finally, weight should be monitored if unexplained or clinically significant weight loss occurs. Patients should discontinue drug and be evaluated.

A proposed pharmacovigilance plan also includes expedited reporting of postmarketing cases of liver impairment, as well as severe cases of CHF and unexplained weight loss leading to BMI of less than 18.5, risk communication and education, and the medication guide.

We proposed a postmarketing registry to follow at least 500 patients for five years, providing additional safety data and select efficacy outcomes. Finally, we have outlined a pediatric study in patients with Alport syndrome, age 8 [inaudible] and above, as part of our European pediatric plan commitment.

In conclusion, bardoxolone has a well-characterized and manageable safety profile in patients with Alport syndrome. AEs are generally mild to moderate in severity, reversible with treatment discontinuation, and not life-threatening. Fewer SAEs were observed in bardoxolone-treated patients compared to placebo, and there were no deaths. There were no increases in blood pressure, no imbalances in AEs associated with fluid status, and no SAEs for heart failure in patients randomized to bardoxolone.

In the ongoing, longer term study, 1803, we've observed no new safety signals. The data demonstrate a similar AE profile across adults, adolescents, and other subpopulations. Across our

entire safety database, we've observed no cardiovascular safety signals in studies conducted after Study 903. Further, we have characterized the profile of UACR changes, which is not consistent with kidney injury.

Overall, the safety data from the Alport syndrome development program is consistent with and supported by our comprehensive safety database and a conservative proposed label and monitoring plan.

I'll now introduce Dr. Glenn Chertow, who will present the benefit-risk assessment for bardoxolone in Alport syndrome.

Applicant Presentation – Glenn Chertow

DR. CHERTOW: Thank you, Dr. Meyer.

My name is Glenn Chertow. I am a professor of medicine, and by courtesy, professor of Epidemiology and Population Health, and former chief of the Division of Nephrology at Stanford University School of Medicine.

I have been treating adult patients with Alport syndrome for nearly 30 years. I was the steering committee co-chair and site investigator

of the BEACON trial. I will provide a benefit-risk assessment of the use of bardoxolone in treating patients with Alport syndrome. I am a consultant to Reata, and I've been compensated for my time. I have no financial interest in the outcome of this meeting.

We begin from a place of great medical need. Alport syndrome typically leads to rapidly progressive chronic kidney disease and a high risk of kidney failure in a generally young patient population. There are few existing therapies known to be of benefit.

These are limited to the angiogtensin converting enzyme inhibitors and angiotensin receptor blockers. Although ACE inhibitors and the ARBs are effective at slowing progression of chronic kidney disease, they do not generally prevent or arrest progression. Most patients will progress to kidney failure, albeit slower than they might have otherwise.

We know that delaying the progression of chronic kidney disease to kidney failure not only

forestalls the need for transplantation or dialysis, but can preserve functional capacity and, importantly, health-related quality of life. The National Kidney Foundation, together with the FDA and EMA, showed that a difference of even 1 or 2 mL per minute per year, if sustained, could result in extended dialysis and transplant- free survival.

The data demonstrate a number of clinical benefits with bardoxolone, a therapy with a novel mechanism of action. We recognize that the mechanism of bardoxolone is unique among approved agents or agents being evaluated in chronic kidney disease. We have become accustomed to the narrative that kidney function inexorably declines. We have not seen other agents that increase kidney function acutely and preserve kidney function chronically.

In Study 1603, we saw preservation of kidney function; that is higher eGFR on treatment and sustained benefits off treatment. The changes in estimated eGFR compared to placebo were not only statistically significant but also clinically

meaningful. Bardoxolone was safe and efficacious in adults, as well as in adolescents.

I should point out, of course, that in this clinical trial, aimed to evaluate disease-modifying effects, the study drug was discontinued. However, in clinical practice, we tend not to interrupt therapy in this way. Rather, if patients are faring well, we continue therapy. Importantly, we have seen that the benefits of bardoxolone were sustained over three years.

The observed benefit with bardoxolone and the magnitude of the effect on eGFR, both on and off treatment, should translate to a beneficial effect on delaying disease progression.

Based on the starting eGFR for trial participants and the rates of progression of eGFR seen in Study 1603, even using the more conservative off-treatment estimate annualized from the year 2 key secondary endpoint -- again, if sustained -- the effect of bardoxolone could translate into a multiyear delay in time to kidney failure. For patients who remained on treatment,

this effect could be more profound.

This has additional benefits when one considers the severe shortfall in deceased donor organs. In my region of the country, waiting times exceed the life expectancy of nearly all older patients requiring dialysis, approximately 10 years; and for younger patients, like those with Alport syndrome, delaying progression might mean the difference between a single pre-emptive kidney transplant, lasting throughout middle age or beyond, and the need for two or more kidney transplants, and the need to start or restart dialysis.

We must evaluate the risks of bardoxolone in the Alport syndrome population, which were not serious or life-threatening and were clinically manageable. Elevations in the aminotransferases were generally observed within the first 8 to 12 weeks, transient in nature, and not accompanied by increases in total bilirubin or clinical evidence of liver injury.

Muscle spasms, which have been seen

consistently in studies with bardoxolone, are rarely severe and often wane over the course of several weeks. There was a decrease in body weight, which was proportional to the baseline BMI. In other words, obese adult patients tend to lose more body weight than non-obese patients. Adolescents treated with bardoxolone appear to maintain their individual growth curves.

While albuminuria tends to increase early in the course of bardoxolone treatment, the increase is not sustained and is proportional to the rise in eGFR. In the pivotal 1603 phase 3 study, and all CKD studies conducted after BEACON, there were no increases in mean systolic or diastolic blood pressure, serious cardiovascular events, or deaths.

Monitoring patients with Alport syndrome for these and any other potential adverse effects is feasible in nephrology practices. Adult and pediatric nephrologists typically serve as either the primary or principal care physician for patients with Alport syndrome.

We evaluate blood pressure and volume status

at every follow-up visit for these patients. We routinely measure laboratory data, including assessments of liver enzymes and total bilirubin, as well as kidney function and electrolytes. We also commonly measure UACR or UPCR, urine protein to creatinine ratio, to monitor progression of disease in response to therapies, including ACE inhibitors or ARBs.

The frequency of clinic visits increases as chronic kidney disease advances to stages 3b, 4, and 5. In early stage Alport syndrome, at least on the adult side where I practice, we might see a patient once or twice a year, whereas patients with more advanced disease are typically seen every 2 to 3 months.

In summary, bardoxolone offers the potential to sustain kidney function and reduce the progression of kidney disease for several years without requiring either dialysis or kidney transplantation, as suggested by the on-treatment, as well as the off-treatment effects. Balanced against the potential risks, which are clinically

manageable, it is my clinical perspective that the benefits of bardoxolone outweigh the risks and offer a much needed therapy to patients with Alport syndrome and the physicians who treat them.

I'll now turn the presentation back to Dr. Meyer, who will provide concluding remarks.

Applicant Presentation – Colin Meyer

DR. MEYER: Thank you, Dr. Chertow.

Bardoxolone offers a novel and effective approach to treating patients with Alport syndrome who have high-risk progression to kidney failure often at a young age. We have demonstrated through multiple analyses that bardoxolone slows the progression of kidney disease in patients with Alport syndrome, and the treatment effect, both on and off treatment, is large and clinically meaningful.

We as the sponsor are committed to the Alport syndrome community and to the safe use of bardoxolone for a post-approval registry, risk management plans, and documentation of long-term outcomes. We hope to work with the agency to bring

the first treatment option to these patients, their families, and their treating physicians. We thank you for your careful consideration.

Clarifying Questions

DR. LEWIS: We will now take clarifying questions for Reata. Please use the raised-hand icon to indicate that you have [inaudible], and remember to lower your hand by clicking the raised-hand icon after you've asked your question. When acknowledged, 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'm going to begin the first question. If the sponsor could please bring up slide C-17. In an orphan drug application, which has often a

surrogate outcome, and this one that there's some controversy about, the totality of data is important. The preclinical data, the mechanism of action, and hypothesis are very important.

I have several questions about slide C-17, and conclusions. I have read all the references listed under the slide and I think a couple others that were not in the briefing document. My first question revolves -- and this would be a yes or no answer. In the diabetic study that was done, BEACON, there were no diabetic animal model studies done prior.

Zoja, which is listed here as 2010 and 2013, unfortunately after the BEACON trial was well and almost stopped, did a diabetic rat study which showed loss of weight, increased blood pressure, increased albuminuria, glomerulosclerosis, and increased LFTs.

I was unable to locate any use of bardoxolone in one of the animal models of Alport. So my first question is, was such a study done, and if so, could you share the data?

Secondly, the claim is made that there is no effect on intraglomerular pressure. The Ding 2013 reference shows an increase in filtration fraction with no change in regional plasma flow. The most evidence-based explanation for that would be an increase in intraglomerular pressure, which would be associated with an increase in albuminuria.

A definitive study to decide what is really happening in the glomerulus -- and obviously intraglomerular pressure increases, as the sponsor has acknowledged, are bad -- would be a micropuncture study. Were micropuncture studies done with bardoxolone?

Thirdly, the hypothesis, which is novel, that there's an increase in glomerular surface area, I was unable to find any other examples of any drug that did increase in glomerular surface area, or intervention of any sort, or that was associated with a benefit. If there is such a thing, please share with the committee.

Lastly, I'm unaware of examples of drugs that caused an increase in albuminuria that have

been demonstrated to show a benefit in chronic kidney disease, and if there's an example, could you please share with the committee?

So I guess that's four quick questions. Please keep to yes, no, or as short as you can.

DR. MEYER: Thank you, Dr. Lewis. We acknowledge that the mechanism is novel. And while we have not conducted studies of bardoxolone in models of Alport syndrome, we have conducted numerous studies in other chronic models demonstrating antifibrotic effects.

DR. LEWIS: It's ok; just yes or no. No is fine.

DR. MEYER: We have not done --

DR. LEWIS: No is fine. I'm sorry. We're late. Go ahead.

DR. MEYER: We have not done micropuncture, but we've done 2-photon laser microscopy, and we are unaware of other drugs that have been shown to increase the surface area.

DR. LEWIS: Okay. Thank you.

And lastly, drugs that increase albuminuria

but have been demonstrated to preserve kidney function.

DR. MEYER: We are unaware, but note that the profile is unique and different in agents that are associated with injury or disease progression.

DR. LEWIS: Thank you.

I think the first person with a question is Dr. Palevsky.

(No response.)

DR. LEWIS: Dr. Palevsky, please unmute.

DR. PALEVSKY: Thank you. I was in the process of unmuting as you asked; Dr. Paul Palevsky.

Maybe I missed it, but I did not see a description of methodology for eGFR calculation and whether it was based entirely on serum creatinine or whether you used other established markers such as cystatin C. My one reason for concern is the associated weight loss, and it would be important to know whether there's any data on change in creatinine generation associated with the weight loss that occurs over time.

My third question relates to slide CE-22, which is the plot of the eGFR change. And I note that when drug is reinstituted after week 52, the increase in eGFR from the off-drug period appears to be substantially less than at year 1, which raises concern that the pharmacodynamic effect of the drug had not worn off over those 4 weeks.

Can you please address that that issue? Thank you.

DR. MEYER: Yes, I heard several questions from you. I'll first start by addressing your question about assessment of kidney function.

We acknowledge that it's important to accurately assess kidney function. Slide up. Prior to our initiation of our Alport syndrome, our Japanese partner conducted a phase 2 study, a placebo-controlled, over 16 weeks duration in patients with diabetic CKD.

As shown on the left, there was an increase in inulin clearance, so obviously independent of serum creatinine, and that change was correlated with the change in estimated GFR per

creatinine-based assessments. Furthermore on the right, in that same study, they collected 24-hour urines to demonstrate that there was no change in excretion of 24-hour urines. We've also demonstrated that in three other trials.

In regards to how it was calculated in the Alport syndrome trial --

DR. PALEVSKY: Before you go on with regard to that, you said that's 16 weeks rather than a more prolonged course of 48 weeks, where there may have been more weight loss, and therefore more change in creatinine generation.

Do you have data at a 48-week time point?

DR. MEYER: No, we do not have data at a 48-week time point, but we have it at 16 weeks here and other time frames that show no evidence of any changes in excretion of creatinine. To answer your question directly about eGFR assessment, in the Alport syndrome trial, CKD-EPI was used for adults and Bedside Schwartz equation was used for kids.

DR. PALEVSKY: But there are multiple CKD-EPI equations. You just used the

creatinine-only equation.

DR. MEYER: That is correct.

DR. PALEVSKY: Do you have data on cystatin C?

DR. MEYER: No, cystatin C was not collected.

Then to address your question about weight, slide up. As I mentioned earlier in the presentation, we did see weight loss in the study, and it was dependent upon baseline BMI. Shown here is the eGFR change stratified by those subgroups, and you can see that at the end of the trial, there's very similar eGFR change despite the large differences in weight for these patients; so demonstrating that the change in serum creatinine is different than the change in weight.

Then to address your question about washout, if we could pull up the scatter plot; the week 104 data, on the left here, this is all eGFR values that contributed to the key secondary analysis, and on the right is all except these four outliers.

Dr. Teuscher, can you please comment on

this?

DR. TEUSCHER: Nathan Teuscher. After the washout, there's no continuing change in eGFR after day 14. It's very flat, even the wide distribution of data.

If we could go back to CE-22 also, which was the original question, it's important to note that there is disease progression. The difference between the peak of the bardoxolone-treated and the same time point for placebo is quite similar, even though it doesn't look like the rise is as much.

What you can see is that the bardoxolone is providing, already at year 1, some benefit, and then that distance between placebo is maintained once treatment reinitiates.

DR. PALEVSKY: Thank you.

DR. LEWIS: Dr. Merz?

DR. BAIREY MERZ: Thank you. Dr. Noel Bairey Merz. This is a question for Dr. Meyer.

If we could go to slide CE-6, it demonstrates two bardoxolone subjects progressed to end-stage kidney disease compared to zero in

placebo. If you read the fine print, however, there were 3 patients in placebo that progressed and an additional one in the active arm. I presume that they went on to dialysis or kidney transplant.

How do you handle intention to treat in that situation, as well as the imputation? What were the strategies to mitigate this problem? Thank you.

DR. MEYER: Dr. Chin, can you please address the question?

DR. CHIN: Melanie Chin, Reata Pharmaceuticals. In the intention-to-treat analyses, we included all eGFR values collected up until the point the patient discontinued from the study due to reaching end-stage kidney disease. For the analysis of the primary endpoint, we did not impute for missing data.

DR. BAIREY MERZ: Thank you.

DR. LEWIS: Dr. Mendley?

DR. MENDLEY: Thank you. This is Susan Mendley.

Dr. Meyers, in slide CS-20, you stated that

adolescent patients generally continued along their baseline growth curves for height and weight. But when I reviewed the Reata-provided briefing materials -- on page 155, section 9.9, figure 54 -- I note that at least three, and perhaps four, of the adolescent males had failure of age-appropriate weight gain such that they fell off their growth curve and crossed two or more percentile lines, generally considered a pathologic growth pattern.

Can you provide any data to this committee to reassure us, or patients, or parents that this pattern of failure to gain weight in a normal fashion does not increase the risk of stunting in a population already at risk for growth failure? Thank you.

DR. MEYER: We recognize the limitations of the small data set and are committed to collecting additional data in a postmarketing setting and recommend careful guidance. And I'd like to have Dr. Brad Warady specifically comment on these data and to address your questions.

DR. WARADY: Brad Warady. Slide up, please.

So as mentioned, there were some crossing of lines in the adolescents on bardoxolone, not dissimilar from what occurred in the placebo population. I think it's important to recognize that when one looks at the bardoxolone patients, again, who were a smaller number, their average height at baseline was already 171 centimeters and their average weight was 65 kilos. These individuals, who were a mean age of 15 years, were in large part fully grown.

Slide up, please. This is the data for the adolescents on bardoxolone to look at their weight over the course of the study, and you can see, for the most part, their weights were maintained and they did not demonstrate a significant weight loss, which was seen in some of the adult individuals who had very high BMIs.

So again, this is something that would clearly need to be monitored long-term in patients who are treated, like we do for all CKD patients who are followed up in the clinics.

DR. LEWIS: Thank you.

Would everyone please put their hands down who have had their questions answered?

Our next panel member with a question is Dr. Butler.

DR. BUTLER: Thank you very much. This is a question for Dr. Meyer, slide CE-11. Realizing that smaller numbers make interpretation difficult, I was just wondering if you can comment on your interpretation of baseline eGFR and whether there is a trend of less benefit with advanced lower GFR.

DR. MEYER: We would expect that patients with a lower GFR and more irreversible loss of kidney function would have a smaller treatment effect. So when we can account for the baseline GFR, the relative change is closer but, yes, there is less treatment effect. We do note, however, that it still favors bardoxolone, and I'd like Dr. Chertow to comment on this treatment effect.

DR. CHERTOW: Thank you. Glenn Chertow. I would just say that the treatment effect is clinically meaningful in both groups.

DR. BUTLER: Thank you.

DR. LEWIS: Thank you.

Dr. O'Connor? And please remember to state your --

DR. O'CONNOR: Dr. Christopher --

DR. LEWIS: -- thank you, Dr. O'Connor. Everybody remember to state their name first.

DR. O'CONNOR: Dr. Christopher O'Connor here, and this is a question for Dr. Teuscher, and the slide that corresponds to figure 32, page 96 of the briefing document, regarding the natriuretic peptide levels.

Thank you for taking a serious mitigation effort for the current trial, the CARDINAL trial, after showing an increase in heart failure in the BEACON trial. And while we have normal natriuretic peptide levels at baseline -- if you could pull that slide up that corresponds to figure 32 -- it appears that the drug actually increases natriuretic peptide levels within this intranormal range, which also has important prognostic significance in preclinical heart failure and other

cardiovascular disease. Then during the washout, the natriuretic peptide level comes down, you reinstitute the drug, it elevates again, and washout, it comes back down.

Are you familiar with animal studies that have shown that this class of drug could have direct myocardial injury effects? And the second question is, was there any asymmetric post-randomization withdrawal of RAAS inhibition between the treatment and placebo group?

DR. TEUSCHER: To answer your second question first, there is no evidence of asymmetric withdrawal of RAAS inhibition. To answer your first question -- slide up -- we do have direct evidence from animal studies with close bardoxolone analogs that demonstrate that there is increased BNP expression that's associated with reduced cardiac hypertrophy. This is consistent with the metabolic effects that BNP has beyond the effects on fluid -- slide up -- and we actually see differential expression, or BNP levels, in the Alport syndrome phase 3 trial.

Shown here are BNP levels by baseline BMI subgroup. In the patients who had higher BMI, if you lost more weight, we saw larger increases in BNP.

I'd like to have Dr. Bangalore comment on the clinical profile of BNP that we saw in our Alport syndrome trial.

DR. BANGALORE: Hi. Sripal Bangalore, interventional cardiologist, NYU Medical Center. I'm a paid consultant for Reata Pharmaceuticals, and I have no financial interest in the outcome of the meeting.

I think it is important to clearly differentiate BEACON from the Alport syndrome patients, who are much younger, and their BNP profile baseline was significantly lower than that of BEACON. I think that being said, given the fact that these patients will be on these medications for a long time, and some of them may develop a profile similar to BEACON, the risk mitigation measures that outline close monitoring of fluid status, blood pressure, monitoring for any

elevation in blood pressure, and close monitoring of heart failure, I think should maximize the benefit, at the same time, decreasing the risk of these patients.

DR. LEWIS: Thank you.

Dr. O'Connor, does that answer your question?

(No audible response.)

DR. LEWIS: I think we'll move on to Dr. Nachman.

DR. NACHMAN: Yes. Thank you. Patrick Nachman. I have a couple of questions regarding the patient population that was included in the phase 3 trial.

Particularly, I did not see, either in the briefing material or today's presentation, any analysis based on genotype. Reata made a big point, a very important point, that patients who are either X-linked hemizygous males, or have autosomal recessive disease, have a significantly higher risk of progressing to ESKD. I have not seen analysis based on this.

I know that the analysis has been made for adolescents versus I did not see the exact number of patients who are males with X-linked or male or female who had autosomal recessive.

That's question number 1, and that pertains to Dr. Butler's question from before. Again, most of the benefit seems to be related to patients who start with a well-preserved GFR and minimal albuminuria, so the two questions are interrelated.

My third comment, if I may, pertains to slide CE-11, which seems to correspond to the Reata briefing material, figure 19, but the two are not exactly the same. There are some significant differences in the reported benefits and confidence intervals between the two.

If you could comment on why the two are so different, specifically for patients with UACR more than 300 for X-linked Alport syndrome and for low GFR. Thank you.

DR. MEYER: Thank you for your questions. I'll address your question about X-linked versus non-X-linked. Shown here on this slide, CE-11,

this is the forest plot of data from the primary endpoint at week 100, so the on-treatment analysis, and you see that there are clinically meaningful effects in the X-linked patients and the non-X-linked patients. Overall, there are 23 male X-linked patients in the bardoxolone group and 21 male X-linked patients in the placebo group.

I believe you are referring to BD-38. Slide up. This is a similar forest plot, but this is for the key secondary week 104 analysis, so once patients had withdrawn drug. And we still see a clinically meaningful treatment effect in the X-linked, as well as the non-X-linked patients.

We recognize that there is a larger treatment effect in patients with earlier stage disease, but these patients progress very rapidly, as highlighted in the pediatric patients. So in our view, it's optimal to get to them before they have too much irreversible loss of kidney function that bardoxolone could not affect.

DR. LEWIS: Thank you.

Did that answer all your questions,

Dr. Nachman?

(No audible response.)

DR. LEWIS: We'll go on to Mr. Paul -- Dr. Nachman, yes?

DR. NACHMAN: Yes. Thank you.

DR. LEWIS: We'll go on to Mr. Paul Conway.

MR. CONWAY: Thank you, Doctor.

My question is actually for Dr. Meyer. In looking at the FDA briefing materials under the appendices 61, page 39, I was a little bit intrigued about the back and forth that had occurred with FDA, and I'm interested in your perspective or some clarification on why the company chose not to engage with FDA at the end of the second trial. Because there appears to be, based on footnote number 2 there, a fair amount of correspondence back and forth on eGFR, and I'm just interested, in your own language, your description of that.

DR. MEYER: Yes. We had numerous interactions with the division about multiple CKD programs in this time frame. I think that provides

helpful context.

In 2016, at our pre-IND meeting, we actually proposed a phase 2 study for our Alport syndrome study, and in the meeting, the division recommended a phase 2/3 approach that included a two-year treatment duration and two off-treatment periods. I was present at that meeting. We engaged in dialogue with the division; it was collaborative. And in the end, they acknowledged our design.

We submitted our protocol to the division. In our study-may-proceed letter, they noted that the week 104 endpoint, following a 4-week drug treatment withdrawal period, would be critical for evaluating efficacy and supporting approval.

As I was mentioning in my presentation, we had a parallel program in polycystic kidney disease, where we engaged with FDA for an end-of-phase-2 meeting in February of 2019, and this was approximately a year and a half into enrollment of the pivotal phase 3 Alport syndrome trial, and we had a same, basically, proposal for the design, two-year treatment duration, two

off-treatment periods, with a 28-day window.

In that meeting, individuals in the meeting at FDA inquired about the sufficiency of an off-treatment period, so we specifically discussed the 28-day topic. We reviewed data, much of the same data that Dr. Teuscher reviewed, and then we submitted it to them as they requested, and they said they were reassured by that data.

They then, a few months later, asked for an end-of-phase-2 meeting for Alport syndrome. So once again, a year and a half into the conduct of the phase 3 trial, we had just discussed the design, and we thought we had addressed all of FDA's comments, and we didn't discuss the Alport syndrome trial again until after we reviewed the year 1 data with them.

So just to clarify, there was a lot of back and -forth. We were listening to FDA, and we incorporated all recommendations from them into our trial.

MR. O'CONNOR: Thank you. That answers my question.

DR. LEWIS: Thank you.

Dr. Palevsky?

DR. PALEVSKY: Paul Palevsky; two additional quick questions. It occurred to me, in response to one question, you said there was no differential use of RAAS blockade. Was there any use of SGLT2 inhibitors during the course of the trial? And if so, was there any differential use between treatment arms?

Then the second question, in your briefing documents, you talk about the effect of bardoxolone on regulation of expression of megalin, which is involved in proximal tubular protein reabsorption.

Do you have any data to inform us as to whether the changes in proteinuria are due to increases in glomerular protein leak or change in tubular reabsorption? Thank you.

DR. MEYER: This is Dr. Meyer, and to address your first question quickly, no patients within the Alport syndrome trial were using concomitant SGLT2 inhibitors.

Regarding your second question, we've

performed many nonclinical studies to probe the effects on proteinuria. Clinically, it's hard to differentiate between the increases in GFR and the megalin contribution, but we do see both effects experimentally. We do see that associated with increases in single nephron GFR, using 2-photon laser microscopy, that there is not an increase in permeability in wild-type animals or animals with diabetic kidney disease.

Most importantly, clinically, we see return to baseline in the two off-treatment periods, and I'd like to highlight the pediatric albuminuria data. Despite the limitations of a small N, we actually did see progression in the placebo-treated adolescent patients.

Slide up. While in the adults there was no progression -- it's a relatively flat line -- here, this is only the adolescents, gray or placebo treated. Over the course of two years, you can actually see about a doubling of proteinuria. With the bardoxolone-treated adolescent patients, we actually see some variabilities, slight increases

early, but by the end of the trial, albuminuria is actually lower in the bardoxolone-treated adolescent patients.

So this perhaps is the best way to interrogate -- in patients who have the most fragile kidneys, the most severely rapid disease -- if bardoxolone would have any adverse effects on albuminuria and kidney function in the clinical setting. In, obviously, the eGFR-based data, this subgroup had one of the largest between-group difference as showing preservation of kidney function.

DR. LEWIS: Thank you.

I have a quick question. Do you have a slide of the magnitude of the acute effect based on the baseline eGFR? And while you look for that slide, I'd like to let Dr. O'Connor ask his question. And, Mr. Conway, I think you want to put your hand down.

Dr. O'Connor?

DR. O'CONNOR: Yes. This is Dr. O'Connor; a quick question.

Was there any concern by the Data Safety Monitoring Board, throughout the trial, with some of the emerging adverse safety signals, particularly around the liver function studies, the UAC, the BNP? And did the Data Safety Monitoring Board agree with the interim analysis and breaking the blind to present to the FDA a potential expedited review?

DR. MEYER: The data monitoring committee, that oversaw the trial on an unblinded basis, had obviously access to the insights that we've generated and data supporting the profile of LFTs, as well as BNP. They did specifically look for any changes that were outside of the pharmacologic profile that we've observed, such as actual cases of liver failure or emergence of fluid-related heart failure, which was not seen, and there were no concerns raised on the conduct of the trial.

The FDA proposed the study design, which included a one-year off-treatment period that could support accelerated approval. That was prespecified in the protocol, in the statistical

analysis plan, and we had a specific data access plan that limited the number of people who had access to the information. So that was prospectively defined and shared with the data monitoring committee, as well as the FDA.

DR. O'CONNOR: Dr. O'Connor, quickly. Could you send us the minutes from the DMC?

DR. MEYER: Are you requesting it from us, the sponsor?

DR. O'CONNOR: I assume that you have the minutes --

(Crosstalk.)

DR. MEYER: We have --

DR. O'CONNOR: -- of the DMC now that the trial's over.

DR. MEYER: Yes, and we provided that, all minutes, to the FDA in our NDA.

DR. O'CONNOR: Okay. Then we can get it from the FDA. Thank you.

DR. LEWIS: Do you have the slide of the magnitude of the acute effect based on eGFR available yet? If not, we can do it over the lunch

break.

DR. MEYER: I have that available.

DR. LEWIS: Oh, great. If you'd just show it. Thanks.

DR. MEYER: You can see here that the dark blue shaded squares on top are the patients who had baseline eGFR greater than 60, and those patients that had baseline eGFRs of less than or equal to 60 are shown in the open squares, and those patients tended to have slightly lower acute increases.

DR. LEWIS: Dr. Nachman, our last question.

(No response.)

DR. LEWIS: Dr. Nachman, you want to unmute?

DR. NACHMAN: Yes. Sorry. I muted myself by mistake. Patrick Nachman again.

I would like to come back to this baseline eGFR and baseline albuminuria issue, and figure 19 on page 64, and slide CE-11. So I stand corrected from my previous comment, that one is off treatment and one is on treatment. But especially when you look at the off treatment, it looks like the benefit of bardoxolone in patients with a GFR of 60

or less, or less than 60, is not existent; and for patients with a UACR of 300 or more, the benefit is small and the confidence intervals cross the zero line.

So my question is, does the sponsor think that there is going to be a -- is there a GFR or a proteinuria level at which you think that treatment is not beneficial, and if so, what would it be? I mean, looking at figure 19, it looks like there's really very little benefit if the GFR is below 60 or there is substantial proteinuria.

DR. MEYER: Yes. We note that there is a smaller treatment effect in patients with lower GFR. We also note that there's a meaningful treatment effect in patients with high albuminuria at baseline, so patients who progress fairly rapidly. And we also acknowledge that, due to this relatively small trial and a rare disease, it's hard to make firm conclusions about subgroup analyses.

We did have a post hoc finding in patients with low GFR; that it appeared that many of those

patients were not at their goal dose. And when patients are at their goal dose, those patients tend to have a better treatment effect.

Slide up. To illustrate this point in just the overall population, goal dose versus not goal dose, the gray line is placebo. The patients who were after goal dose at the end of the trial are in blue at top, dark blue, and the patients who were below their goal dose were in light blue.

You can see that the patients who are at their goal dose had a much larger treatment effect on and off drug, and one important finding from the trial is that it's important for patients to be at their goal dose. So we believe that it's up to the individual treating physician to determine, with the patient, if the drug is appropriate to them, and that the drug likely should be used across the eGFR range.

DR. LEWIS: Thank you.

I would like to acknowledge Dr. Thompson.

(No response.)

DR. LEWIS: Dr. Thompson?

(No response.)

DR. LEWIS: Dr. Thompson?

(No response.)

DR. LEWIS: Dr. Thompson, I was told you had a question or had a comment. Maybe after the break?

DR. THOMPSON: I actually do not have a comment. This is Dr. Thompson.

DR. LEWIS: Oh, okay. Sorry.

Well, panel members, unfortunately because we had a late start and had very good questions -- and I want to thank all the panel for their questions -- we are behind schedule. If it's ok with you guys, can we do a 5-minute break to try to catch up some of that time?

So it's roughly 12:09; let's say it's 12:10. We'll return at 12:15. We will take a quick 5-minute break, a little bit more, 6 minutes. 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 12:15.

(Whereupon, at 12:11 p.m., a recess was taken.)

DR. LEWIS: We will now proceed with the FDA presentation, starting with Dr. Lars Johannesen.

FDA Presentation – Lars Johannesen

DR. JOHANNESEN: My name is Lars Johannesen, and I'm a clinical analyst in the Division of Cardiology and Nephrology. I'll be presenting the FDA review team's findings of bardoxolone's efficacy and safety, together with Dr. Dali Zhou, the statistical reviewer from the Office of Biostatistics.

I want to start the presentation by stating the four AC points to consider. The first point is whether CARDINAL phase 3 was adequately designed to assess for an effect on the progression of chronic kidney disease in patients with Alport syndrome.

The second point is whether the available data indicate that bardoxolone methyl slows the progression of chronic kidney disease, and whether it is reasonable to conclude, based on the available data, that bardoxolone methyl will reduce

the risk of progression to kidney failure when used chronically in patients with Alport syndrome.

The third point to consider is do bardoxolone methyl's effects on albuminuria, blood pressure, or other parameters raise concern about its long-term efficacy and/or safety in patients with Alport syndrome. The fourth and last point to consider is what are the implications of bardoxolone methyl's effect on body weight of pediatric patients?

The remainder of the presentation is divided into three parts. Challenges with interpretation of the efficacy results from CARDINAL because of bardoxolone's reversible pharmacodynamic effect will be discussed in the first part of the presentation. This includes a discussion of the adequacy of the 4-week washout to support the off-treatment analysis, as well as the results of an analysis of the impact of eGFR values collected outside the SAP-defined analysis window on the off-treatment analysis.

The second part of the presentation will

discuss overall safety findings and cover safety issues identified during review and related to heart failure, increases in albuminuria and blood pressure, decreases in weight, and the potential implications on the growth and development in pediatric patients. The third part of the presentation is benefit-risk assessment.

I will now discuss some of the challenges with interpretation of efficacy results from CARDINAL. The CARDINAL phase 3 study provided the pivotal support for efficacy for bardoxolone to slow the decline in kidney function. The primary endpoint was the on-treatment difference at the end of each year; that is at weeks 48 and 100, and the key secondary endpoint is the off-treatment difference following a 4-week washout at the end of each year at weeks 52 and 104.

Both the primary and key secondary endpoint are based on a surrogate endpoint, that is eGFR, and the results are shown on this slide. Overall, the trial met its prespecified primary and key secondary endpoints, however, because of

bardoxolone's reversible pharmacodynamic effect, the primary endpoint does not inform whether there's a fixed or irreversible slowing of the rate of decline in renal function. The key secondary endpoint could potentially show a decline in kidney function, provided the 4-week washout duration is adequate.

In the next couple of slides, I'm going to show you hypothetical treatment patterns on eGFR to illustrate challenges with interpretation of eGFR for drugs with reversible pharmacodynamic effects.

The figure on this slide illustrates the treatment pattern for a drug that only has a reversible pharmacodynamic effect in blue. The X-axis on this figure is time in years and the Y-axis is eGFR. On treatment, there is an increase in eGFR, but the rate of decline in eGFR over time, that is the slope, is identical for the placebo group in gray and the treatment group in blue.

After stopping treatment, the reversible pharmacodynamic effect is washed out, represented by the red square, and there's no difference in

eGFR between the two treatment groups. If the treatment group difference is measured too soon after stopping treatment, that is before the reversible pharmacodynamic effect has resolved, a treatment group difference could be observed, which is reflective of the reversible pharmacodynamic effect and not a slowing in decline in eGFR on treatment.

On the next slide, I will show an example of a treatment pattern for a drug with both a reversible pharmacodynamic effect and a slowing in decline in kidney function. The orange line represents a treatment pattern for a drug with both a reversible pharmacodynamic effect and a slowing decline in kidney function.

For this treatment pattern, there is a slower rate of decline in eGFR, or a less steep slope on and off treatment. The slower rate of decline translates to an increase in the difference over time on treatment, and therefore a larger difference between the orange and the gray line at the end of the treatment period as compared to the

blue and gray lines. Unlike the reversible pharmacodynamic effect only, the blue line, a drug that slows disease progression will have a detectable difference off treatment, represented by the orange line.

The detectable off-treatment difference is because the drug slowed the rate of decline in eGFR on treatment, which translated to an increase over time in the treatment group difference. In clinical trials, endpoint selection is critical for drugs with reversible pharmacodynamic effects because the endpoint should differentiate between a reversible pharmacodynamic effect from slowing the rate of progression.

At the pre-IND meeting, the review team indicated that the endpoint would need to capture an effect of the irreversible loss of kidney function, and that post-treatment assessments of kidney function would be needed to differentiate bardoxolone's pharmacodynamic effect on kidney function from its effect on disease progression.

During the course of development, the review

team grew concerned about the timing of the applicant's post-treatment assessment and whether it was adequate to differentiate the pharmacodynamic effect on kidney function from its effect on disease progression, and voiced this concern to the applicant.

Next, I want to discuss the challenges with interpretation of the off-treatment increase in eGFR and the adequacy of the 4-week washout. Our main efficacy concern is whether the observed effects on eGFR are indicative of an effect on disease progression in patients with Alport syndrome.

As shown by the primary endpoint, there is an increase in eGFR on treatment at weeks 48 and 100, the left panel, however, this on-treatment difference cannot be interpreted as a drug effect on disease progression because of the positive pharmacodynamic effect. Because the study included a washout at the end of year 1, it is not possible to conduct an on-treatment slope analysis to show a slowing in decline in eGFR on treatment.

Similar to the primary endpoint, there is an increase in eGFR at weeks 52 and 104, the right panel, the key secondary endpoint of CARDINAL. This endpoint has the potential to show slowing of the decline in kidney function.

An attenuation in the treatment group difference was observed off treatment, which is attenuated further in sensitivity analysis that Dr. Dali Zhou will discuss later in the presentation. However, the interpretation of this endpoint depends on the adequacy of the 4-week washout to resolve the reversible pharmacodynamic effect.

In the next few slides, I will show you why the review team believes that the pharmacodynamic effect is not washed out by 4 weeks. I'll start with the applicant's main justifications for the 4-week washout and why the review team did not find these points compelling.

The first justification is based on the time course of resolution of other pharmacodynamic markers, such as changes in liver enzymes. We do

not agree with the assumption that the time course for eGFR will follow the time course of other pharmacodynamic markers that are not related to renal function.

The second justification is based on bardoxolone's pharmacokinetics and exposure-response analysis, which assumes that eGFR changes are directly proportional to bardoxolone concentration. We do not believe that this assumption is consistent with observed data or the proposed mechanism of action, activating the Nrf2 pathway and expression of genes involved in modulating inflammation, oxidative stress, and cellular energy metabolism.

The third justification is based on a polled analysis of short-treatment duration studies, that is less than 8 weeks, suggestive of adequacy of 4 weeks in patients with CKD and type 2 diabetes. However, it is unclear how these observations from short-duration studies in a related patient population translates to the current setting and the interpretation of findings in CARDINAL.

Notably, the applicant's justification excluded the TSUBAKI study, which is the only study with serial off-treatment sampling of eGFR. TSUBAKI was a phase 2 study in patients with CKD and type 2 diabetes. The study included 16 weeks of dosing and 12 weeks of off-treatment sampling of eGFR.

In this figure, I am showing the time course of eGFR as indicated by the dashed lines and bardoxolone concentration as indicated by the solid lines for the TSUBAKI study. If you would focus on the time of steady-state bardoxolone plasma concentration, the solid lines, at the last dose titration, as indicated by the blue rectangle, you observe that despite having reached steady-state concentration, eGFR, as shown by the dashed line, continues to increase over the following weeks with maximal effect occurring around week 16. This delay is indicated by the "onset delay" arrow.

Now focus on the off-treatment period, which is shown by the "offset delay" arrow. You can see a delay between bardoxolone concentrations, the

solid line, which are essentially gone by week 20, and the slower decrease in eGFR, the dashed line. eGFR appears to wash out around 8 weeks in TSUBAKI, which is longer than the 4-week washout implemented in CARDINAL.

Results from TSUBAKI therefore suggests the 4-week washout in CARDINAL might not have been sufficient. The delay in onset and offset changes in eGFR appear consistent with the purported mechanism of action of bardoxolone, including activation of the Nrf2 pathway and expression of various genes.

To assess the adequacy of the 4-week washout implemented in CARDINAL, the review team developed a fit-for-purpose PK/PD model. The PK/PD model incorporates the decline in kidney function and allows for a delay in the onset and offset in eGFR relative to bardoxolone concentrations. The advantage of a PK/PD modeling approach is that it allows for integrating all available data to characterize the time course for resolution of the reversible pharmacodynamic effect following

discontinuation of treatment.

Model diagnostics and external validation confirmed that the model adequately describes the time course of eGFR in patients with Alport syndrome, and key findings will be shown on the next two slides.

The PK/PD model was developed based on TSUBAKI and CARDINAL phase 3 data. Data from CARDINAL phase 2 and Study 1102 -- a short-duration treatment study in patients with CKD and type 2 diabetes -- were used as external validation data. The model was able to capture off-treatment eGFR across all four studies, as shown by the overlapping confidence intervals between the observed data, in black, and the model-predicted values, in orange. This comparison includes Study 1102 in the right-most panel, a short-term study indicating that the model captures off-treatment eGFR in this study.

As you heard earlier from the applicant, they stated that the model does not capture the observed data in Study 1102. However, I'd like to

point out that the comparison I'm showing is based on eGFR calculated consistently across studies. It looks like the applicant is using MDRD calculation, but it's not clear since we're not able to reproduce their findings.

It is our opinion that the model captures the off-treatment eGFR of both long-term and short-term studies in patients with CKD, type 2 diabetes, and Alport syndrome. I'll be happy to discuss any questions the committee would have on the modeling results and differences between our results and what the applicant has presented.

The PK/PD model captures the time course of eGFR in the CARDINAL phase 3 study shown, which is shown in the figure on this slide. The observed eGFR at each time point is shown as mean 95 percent confidence and connected by the dashed line. Bardoxolone is shown in blue and placebo in gray. The model-predicted time course is shown by the solid line and shaded area. The model was able to capture the general time course of changes in eGFR well in both treatment groups, but slightly

underpredicts the peak increase around week 12.

The PK/PD model has two important findings. Firstly, the model indicates that the increase in eGFR observed with bardoxolone treatment is limited to a reversible pharmacodynamic effect only, and there is not a slowing in the rate of decline in kidney function.

Secondly, the model indicates the duration of the 4-week washout in CARDINAL phase 3 is insufficient to resolve the reversible pharmacodynamic effect of bardoxolone. When the model is used to extend the time of washout, the reversible pharmacodynamic effect on eGFR observed with bardoxolone has mostly resolved around week 110 or around 8 weeks after treatment stops. Additional statistical analysis related to the off-treatment analysis will be presented later by Dr. Dali Zhou.

In summary, the key secondary endpoint, the off-treatment difference between bardoxolone and placebo following a 4-week washout, is intended to support showing a slowing in decline in kidney

function. However, the interpretation of this endpoint depends on the adequacy of washout duration.

The PK/PD model predicts the washout of reversible increase in eGFR to be longer than the 4-week washout implemented in CARDINAL, therefore, bardoxolone does not slow the rate of decline in kidney function.

Next, my colleague, Dr. Dali Zhou, will discuss the sensitivity analyses on the impact of the analysis window.

FDA Presentation – Dali Zhou

DR. ZHOU: Hi. My name is Dali Zhou, statistical reviewer for bardoxolone. I will present the advocacy issue regarding the impact of the year 2 off-treatment endpoint analysis window and the corresponding sensitivity analyses.

As discussed by Dr. Johannesen on the prior regulatory advice, the most appropriate outcome to assess is an off-treatment eGFR analysis based on eGFR values collected after any acute PD effect has resolved. Thus, we will focus on the year 2

off-treatment endpoint in this section.

The year 2 off-treatment endpoint is changed from baseline in eGFR at week 104. This endpoint achieved statistical significance with a least square mean difference of 4.4 and p-value of 0.02. However, this analysis, based on observed data from 80 percent of the patients, is quoting a substantial amount of actual observed data.

As shown in the second row, 20 percent of patients were excluded from the analysis in total. The exclusion rate is imbalanced between the two arms. Percentage of patients excluded in bardoxolone almost doubles that in the placebo arm.

Among these excluded patients, 25 patients were excluded because they discontinued treatment permanently in year 1 and did not take any dose in year 2. These patients had available off-treatment eGFR values collected, but the data were not used in the analysis. They were considered as missing and were imputed under the missing-at-random assumption.

That being said, the imputation considers

them as if they would perform similarly as the patients in the same treatment arm who continued the study treatment to year 2. The inclusion/exclusion of the data used in this analysis was based on the applicant's defined analysis window, which will be further explained in the next slide.

Here is the applicant's definition of the week 104 off-treatment analysis window defined as at least 14 days after last dose in year 2. Two issues related to this analysis window definition that we think are critical are listed here.

Firstly, the last dosing year 2 in this definition excluded the 25 patients who discontinued treatment before year 2. As mentioned, these patients had available observed off-treatment eGFR values. Secondly, the study was designed with a 4-week, 28 days washout period. However, the analysis window used a 14-day cutoff value, meaning that the off-treatment eGFR values in the analysis would have been collected between 14 days and 28 days after last dose, which was

before the 4-week washout period ends.

The next three slides provide more information for these two issues. For the first issue related to the analysis window, the excluded 25 patients were explained in this bar chart. The left two bars in the gray box show that 25 patients discontinued treatment permanently in year 1. Note that the number of patients that discontinued treatment in year 1 is imbalanced between the two arms, 16 in bardoxolone versus nigh in placebo.

All of these 25 patients had available off-treatment eGFR values collected at least 14 days after last dose. Twenty-two of them stayed in the trial until the end of year 2 and had eGFR values collected at follow-up visits. These 25 patients did not take any dosing in year 2; thus, were excluded from the prespecified year 2 off-treatment analysis.

The right two bars show that 125 patients continued to be treated through year 2. We call them year 2 dosed patients for simplicity. Most of these year 2 dosed patients discontinued treatment

at week 100. All of these patients took at least one dose in year 2. These were the patients whose off-treatment eGFR observations were included in the prespecified year 2 off-treatment analysis.

In total, this bar chart shows all 150 patients with available off-treatment eGFR values regardless of treatment discontinuation, which consists of 96 percent of all randomized patients. We call these 150 patients all available patients.

Because one of the keys to reduce bias in randomized clinical trials is randomization, to stay as close as possible to all randomized patients reflects the intention-to-treat principle, which minimizes bias. So the review team considers it important to analyze all available patients instead of just this year 2 dosed patients. When 25 patients were excluded, the patients used in the analysis may no longer be a good representation of all randomized patients. Thus, the analysis between groups is not a randomized comparison anymore and may introduce bias.

For the second issue related to the analysis window, a 14-day cutoff was used for a 4-week washout. As discussed earlier by Dr. Johannesen on the adequacy of the 4-week washout period, it is not clear if a 4-week, 28-day washout was long enough for the reversible PD effect on eGFR to be fully resolved.

The applicant defined analysis window used a 14-day cutoff to collect off-treatment eGFR values, resulting in even a shorter washout period of 2 weeks. The eGFR values collected with this 14-day cutoff includes values collected between 14 days and the 28 days after last dose. These eGFR values were possibly collected before the PD effect on eGFR has fully resolved, which could potentially bias the comparison in favor of bardoxolone.

Let me further illustrate the groups of patients with off-treatment eGFR values collected using the prespecified 14-day cutoff versus a 4-week, 28-day cutoff. This bar chart shows all 150 available patients with off-treatment eGFR

values collected at least 14 days after last dose.

To the left of this solid black line are the patients with off-treatment eGFR values collected less than 28 days after last dose. To the right are the 111 patients with off-treatment eGFR values collected at least 28 days after last dose, which consists of 71 percent of all randomized patients; though not all patients had a full 4-week washout period before their off-treatment eGFR values were collected because of the visit window definition.

Analysis on these 111 patients, using a 28-day cutoff, are more likely to rule out the potential bias caused by the PD effect on eGFR. Therefore, the agency requested some sensitivity analyses in addition to the prespecified sensitivity analysis for the year 2 off-treatment endpoint.

The prespecified sensitivity analyses only included the year 2 dosed patients, but did not include the observed off-treatment eGFR values for those 25 patients who discontinued treatment in year 1, and those analyses mainly focused on

assessing the missing data assumption.

The agency requested sensitivity analyses and took into consideration the off-treatment eGFR data collected from all available patients instead of using only year 2 dosed to patients. So it took into consideration those 25 patients who discontinued early but stayed in the trial to preserve the integrity of the randomization under the intention-to-treat principle.

The agency requested sensitivity analyses also focused on assessing the impact of the analysis window by performing analysis to compare treatment effects between using the 14-day cutoff and the 28-day cutoff. The results are shown in the next two slides.

The first set of sensitivity analyses were performed on year 2 dosed patients. Just for comparison, the results of the main prespecified year 2 off-treatment analysis is included in the first row. As a reminder, by the definition of the analysis window, the main analysis used a 14-day cutoff to collect off-treatment eGFR values, and

the excluded observations were imputed by assuming the patients who discontinued treatment in year 1 or loss to follow-up behaved similarly as the available year 2 dosed patients in the same treatment arm.

The first sensitivity analysis was an observed case analysis performed on the same set of patients as main analysis without imputation. This analysis includes 80 percent of all randomized patients. Because the prespecified year 2 off-treatment analysis imputes data under the assumption that the excluded patients behave similarly as year 2 dosed patients, the treatment effect in observed case analysis is similar to that of the main analysis.

The second sensitivity analysis used a 28-day cutoff. Patients with eGFR values collected between 14 days and 28 days after last dose were excluded. Results show that the treatment effect becomes smaller when the 28-day cutoff is used. Note, this analysis used observations from only 55 percent of all randomized patients.

Within these two sensitivity analyses, we consider the second sensitivity analysis with the 28-day cutoff provides a better estimate of the true treatment effect since this analysis is more likely to rule out the PD effect. The second set of sensitivity analyses were performed on all available patients regardless of treatment discontinuation. Similarly, we included the results of the main analysis in the first row for comparison.

The sensitivity analyses were also performed without imputation. The first sensitivity analysis used all 150 patients with available earliest option and eGFR values collected at least 14 days after last dose. This consists of 96 percent of all randomized patients and reflects the intention-to-treat principle. Results show that the treatment difference becomes smaller when all available patients were used.

The second sensitivity analysis used a 28-day cutoff and included 111 patients with eGFR values collected at least 28 days after last dose.

This consists of 71 percent of all randomized patients. As can be seen from the results, if all available patients, regardless of taking a dose in year 2 or not, were considered and used only off-treatment eGFR measured at least 28 days after last dose, the treatment difference is 0.8, and almost disappeared compared to the main analysis.

In this set of two sensitivity analyses, the first analysis is based on the intention-to-treat principle and better estimates the true treatment effect than the main analysis. The second analysis used a 28-day cutoff based on all available patients. Although some patients were excluded, results from this analysis is more likely to rule out the bias from unresolved PD effect.

From these four agency requested sensitivity analyses, we can see that, when equal, only the eGFR values collected at least 28 days after the last dose, the treatment difference becomes smaller. When all available patients were considered, regardless of treatment discontinuation, the treatment difference becomes

smaller or almost disappears.

Note, for each patient who discontinued treatment early, multiple off-treatment eGFR values could have been collected. For example, in this figure, if a patient discontinued treatment at week 24, the first eGFR value could have been collected at or around 28 days after treatment discontinuation, and the last eGFR value could have been collected at or around 104 weeks after randomization at the follow-up visit.

The four sensitivity analyses shown above used the change from baseline to the first off-treatment eGFR values. If the last off-treatment eGFR values collected at or around week 104 were used, the treatment differences shown in the above table are smaller or becomes negative.

In summary, the results from the agency requested sensitivity analyses provide more information from the data collected. The results show that if the 28-day cutoff is used for the analysis window, treatment effect becomes smaller. If the 28-day cutoff is used, and when data from

all available patients were taken into consideration, treatment effect almost disappeared.

However, there are limitations on these agency requested sensitivity analyses. These analyses are observed case analyses, and some of them excluded a considerable number of patients. These analyses should be considered as exploratory only, but not conclusive.

Thank you, and now let me turn it back to Dr. Johannesen.

FDA Presentation – Lars Johannesen

DR. JOHANNESEN: Thank you, Dr. Zhou.

Next, I'll present an overview of the safety database and overall safety findings. The safety evaluation focused on the CARDINAL phase 3 study, which included 157 patients with Alport syndrome and is supplemented by BEACON, a phase 3 study which included 2185 patients with stage 4 CKD and type 2 diabetes.

Notably, BEACON was terminated early due to a numerical imbalance of all-cause mortality and higher rates of fluid overload related serious

adverse events, including heart failure in the bardoxolone arm.

In CARDINAL phase 3, there were no deaths and concerning imbalances in serious adverse events. There were more discontinuations reported in the bardoxolone group for increases in liver enzymes, BNP or NT-proBNP, and acute kidney injury based on pooling of related adverse events using customized medical query.

Adverse reactions observed with bardoxolone in CARDINAL and BEACON are shown in the figure for bardoxolone in blue and placebo in gray. Each bar represents the percentage of patients reporting the event. In general, the adverse event profile is similar between CARDINAL and BEACON, with some notable exceptions.

There were no heart failure events in CARDINAL and no imbalances in the percent of patients reporting peripheral edema. CARDINAL was designed to exclude patients with risk factors associated with heart failure, such as patients with elevated BNP at baseline and patients with

prior hospitalization for heart failure event.

More patients in CARDINAL reported elevated NT-proBNP or BNP levels. In BEACON, however, BNP levels were not routinely monitored while on treatment and were collected at week 24 in a subset of patients. More patients in CARDINAL reported elevated liver enzymes, which I'll discuss more on the next slide.

Bardoxolone also caused changes in a variety of laboratory parameters and vital signs. Increases were observed for NT-proBNP/BNP; liver enzymes; urinary albumin creatinine ratio or UACR; ferritin; albumin; serum potassium; and blood pressure. Decreases were observed for serum magnesium; creatinine kinase; hematocrit; hemoglobin; and body weight. The mechanism of these observed changes are not understood.

Bardoxolone also caused an increase for the liver enzymes AST and ALT. The increase in these liver enzymes did not coincide with an increase in bilirubin and no Hy's law cases were observed. The increase in liver enzymes subsided with continued

dosing and resolved during the washout, suggesting a possibility of enzyme induction without significant liver injury.

Next, I want to discuss the risk of heart failure with bardoxolone. Although there were no heart failure events in CARDINAL, heart failure remains an important safety issue, and heart failure was observed in the BEACON study. BEACON was designed to determine if bardoxolone was effective at delaying the progression to end-stage renal disease in patients with an eGFR between 15 and 30 mL per min and type 2 diabetes.

In BEACON, heart failure occurred within the first 4 weeks after randomization with a statistically significant hazard ratio of 1.8. BNP was not routinely measured during the BEACON trial, but there were substantial elevations in BNP at week 24.

CARDINAL phase 3 was designed to exclude patients with high risk for heart failure based on the findings of BEACON. Patients were excluded with a history of heart failure hospitalization,

cardiac disease, and elevated baseline BNP greater than 200. Furthermore, patients with eGFR less than 30 mL per min were excluded.

Despite enrolling patients with low risk for heart failure, there were still increases in NT-proBNP and BNP with bardoxolone treatment. It is not clear if the lack of heart failure events in CARDINAL is generalizable to the patient population with Alport syndrome who will be taking bardoxolone.

The next few slides discuss the observed increases in albuminuria and blood pressure with bardoxolone. In both CARDINAL phase 3 and BEACON, bardoxolone increased albuminuria as measured by urinary albumin creatinine ratio or UACR. Increase in albuminuria is associated with adverse kidney and cardiac outcomes.

The figure shows the time course of UACR of bardoxolone in blue and placebo in gray. During both years, there's an increase in UACR relative to baseline and placebo, and UACR decreased during the washout period, as indicated by the shaded areas.

An increase in UACR was observed in the pediatric patients and in patients with baseline UACR below and above 300 milligram per gram. The observed increase in albuminuria raised concern about potential adverse effects on long-term kidney function.

Bardoxolone has been shown to increase blood pressure. Drugs that cause sustained increases in blood pressure, even small increases in blood pressure, are associated with adverse cardiovascular effects. The FDA recommends ambulatory blood pressure monitoring, or ABPM, to detect small, but clinically meaningful, increases in blood pressure that can be missed with clinic blood pressure measurements.

An ambulatory blood pressure monitoring study was conducted in a subset of patients in BEACON, and the study showed that bardoxolone increased systolic blood pressure by a mean of 5 millimeter mercury, which is larger than what was detected with clinic blood pressure measurements.

There was no clear signal for a blood

pressure increase in CARDINAL. However, the absence of a signal, based on clinic blood pressure measurements, does not provide reassurance that bardoxolone does not increase blood pressure in patients with Alport syndrome because the lack of blood pressure detection could be due to the blood pressure measurement methodology used in CARDINAL.

The last safety issue that I want to discuss relates to the observed decrease in weight. A decrease in body weight was observed in CARDINAL and BEACON. The figure on the right shows the time course in weight for bardoxolone in blue and placebo in gray for CARDINAL based on the safety population. The mean decrease in weight were apparent by week 6, continued through week 12, and tended to plateau after week 12. The mechanism for the weight loss is not well understood.

On this slide, I'll be showing a time course of weight in pediatric patients. You can see that an increase in weight in the placebo subgroup, the gray line, relative to baseline, and no change in weight in the bardoxolone subgroup, the blue line.

It's difficult to draw definitive conclusions about weight changes in pediatrics because the size of the pediatric subgroup is small, 11 patients in the bardoxolone group and 12 patients in the placebo group. Any treatment group differences in body weight raise concerns about the impact of bardoxolone on the growth and development in pediatric patients.

Lastly, I want to discuss the benefit-risk assessment of bardoxolone. The FDA review team recognizes that Alport syndrome is a rare, serious condition with an unmet need and no approved therapies. However, for the reasons discussed in this presentation, the FDA review team does not believe the submitted data demonstrate that bardoxolone is effective in slowing the loss of kidney function in patients with Alport syndrome. Therefore, the review team does not believe bardoxolone has been shown to have clinical benefit.

Bardoxolone causes changes in a variety laboratory parameters and vital signs and increased

the risk of heart failure in BEACON in a different patient population with more advanced kidney disease. The mechanism underlying these changes is unclear. These considerations raise concern for safety and long-term efficacy.

CARDINAL excluded patients with severe chronic kidney disease, eGFR less than 30 mL per min, who are more proximate to kidney failure. In principle, a treatment that causes a large fixed increase in eGFR that persists on treatment could delay initiation of dialysis in a population proximate to dialysis; however, the rationale for starting such a therapy at an earlier stage of disease is unclear. Moreover, whether such a strategy is effective and results in a benefit that outweighs the risk would need to be prospectively studied in a target population.

The FDA review team working on this application is shown on the slide. Thank you for your attention.

Clarifying Questions

DR. LEWIS: Thank you, and I appreciate that

you went under time as well.

We will now take clarifying questions for FDA. Please use the raised-hand icon to indicate that you have a question, and remember to lower your hand by clicking the raised-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 your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

My first question is with Dr. O'Connor.

DR. O'CONNOR: Thank you. Dr. O'Connor. This is a question for Dr. Zhou.

On slide 25 -- thank you for performing these important sensitivity analyses -- would it be fair to say that while the point estimates are

lower in your sensitivity analyses from the prespecified sponsor main analyses, the point estimate that you found, which is lower, it is really not significantly different than the main analysis findings, given that they fall within the confidence intervals of the main analysis point estimate? Thank you. That's the end of my question.

DR. THOMPSON: Hi. Thanks. This is Aliza Thompson, and I'm going to be moderating the questions for FDA. We will certainly direct this one to Dali.

Dali, can you respond?

DR. ZHOU: Yes. Hi. This is Dali, the statistical reviewer.

In slide 25, the sensitivity analyses with the 28-day cutoff excluded some patients -- more patients than the main analysis, and they provided the least square mean difference of 2.6 versus 4.4. It is smaller, but we did not compare these two analyses using any former test or anything, so we cannot say it is significantly smaller than the

4.4, but just want to use this exploratory analysis to show the FDA committee about the result when using the 28-day cutoff.

DR. O'CONNOR: But it falls within the confidence interval, so would that mean that it's within the expected fluctuation from the main analysis? Thank you.

DR. THOMPSON: Dali, can you address that?

DR. ZHOU: I don't know.

DR. THOMPSON: This is Aliza Thompson. Maybe you are in fact asking a different question, but I think the purpose of some of these analyses were, as well, to explore the time window being used and whether it was sufficient. But I'll stop as well.

DR. LEWIS: Thank you.

Mr. Conway?

Dr. O'Connor, please --

MR. CONWAY: This is Paul Conway.

DR. LEWIS: Go ahead, Mr. Conway.

MR. CONWAY: Thank you very much, Chair.

My question is also on slide 25. And at the

top, I'd say thank you to the FDA for including a reference on pages 9 and 10 of your briefing document about the NKF and the Alport Syndrome Foundation session that was held, and the patient insights, obviously, that were revealed in that.

On slide 25, in looking at it, I understand this is exploratory analyses, but the figure of 2.8, I'm wondering how would you describe that to a patient that has Alport syndrome? What is that data basically saying to that patient who's looking at this trial and listening to this today? What does that data show?

DR. THOMPSON: Right. If we could please show this slide for all to see.

(Pause.)

DR. THOMPSON: And I apologize. We may need to take a minute pause. It looks like some of our members may be disconnected. Some of us also aren't seeing a display of slides, so I think we may be having a little bit of a challenge here.

DR. LEWIS: Why you take that minute, I will make a comment.

I'm very involved with many of these endpoint suggestions, and there are numerous references to that in the sponsor's briefing document. For example, on the 0.75 mLs per year benefit, if it's a consistent effect -- it would be fair to say unless a consistent effect over time is plausible or shown by the data, a 2-mL difference in GFR would not be clinically significant or meaningful to a patient.

DR. THOMPSON: Dr. Lewis --

(Crosstalk.)

DR. LEWIS: Go ahead.

Do you have your slide, Dr. Thompson?

DR. THOMPSON: Yes. I think we now have our slide up and our other members on the team. Maybe I can offer some comments from a clinical perspective, and then also just want to note, Dr. Lewis, that we have another statistician who can respond to a prior question. So if we can revisit that question as well at some point, that would be great.

Just maybe to take a step back, I just want

to speak to how we think about GFR decline as a surrogate endpoint. If you think about it, typically in our trials, the size of the treatment effect, in terms of the absolute size that we see in a trial, can be very small. So our assumption about whether that 2-mL per minute per year difference will translate into a clinically meaningful effect on progression to kidney failure assumes that that treatment effect will continue to accrue over time across the various stages of the disease. So the curves continue to diverge over time.

That's the concept behind it. So just looking at one time point and noting two differences, that doesn't necessarily tell you -- and what you need to understand -- whether that's continuing to accrue over time across the various stages of disease.

Does that answer your question or do you need additional clarification?

MR. CONWAY: No, that answers it. Thank you.

DR. THOMPSON: Dr. Lewis --

DR. LEWIS: Dr. Thompson --

DR. THOMPSON: -- should we return -- go ahead.

(Crosstalk.)

DR. LEWIS: Yes, I do.

DR. THOMPSON: I apologize.

Jialu, can you respond to the earlier question?

DR. ZHANG: Hi. This is Jialu Zhang, the FDA statistician from Office of Biostatistics.

Can you hear me?

DR. LEWIS: Yes.

DR. ZHANG: Okay.

(Automated message.)

DR. ZHANG: Can you still hear me?

MALE VOICE: Yes.

DR. LEWIS: Yes.

DR. ZHANG: I hear a message that it disconnected.

Okay. Getting back to the earlier question, I believe the question was, in the main analysis,

the estimate is 4.4 with a confidence interval 0.7 to 8.1. And then one of our sensitivity analyses using the 28-day cutoff showed a point estimate of 2.6 and whether we would consider the two are different.

Let me just clarify. The confidence interval of 0.7 to 8.1 measures the uncertainty for the estimate of that 4.4 in the main analysis. We are not able to do a formal comparison in terms of how this sensitivity analysis, the point estimate, how that would differ from the 4.4.

So like Dr. Zhou said, this is just to provide some additional information in terms of the point estimate in a sense that it gives you a sense of the magnitude of the treatment effect. The confidence interval of each estimate provides the uncertainty around that estimate.

I hope that clarifies the question.

MR. CONWAY: Yes, it does.

DR. LEWIS: Dr. Merz?

DR. BAIREY MERZ: Thank you. Noel Bairey Merz. I have a similar question as prior for

Dr. Zhou, again, on slide 26.

We were told in the morning that they had 94 percent follow-up status of all participants for their intention to treat. So my question is, in your all subjects used, how were the end-stage chronic kidney disease participants -- were they included or not? They would have been on dialysis or received a transplant? Thank you.

DR. THOMPSON: Dali, can you please address?

DR. ZHOU: Yes. I suggest you refer to the analysis with the 14-day cutoff. That includes 150 patients. I didn't check if patients are on dialysis or end-of-stage renal disease, but for the 150 patients, the eGFR values collected for them, used in this analysis, are the earliest eGFR values 14 days after their last dose. So it's not necessarily at the end of study, but it could be close to the last dose. It could be close to the time when they stopped study treatment.

DR. BAIREY MERZ: Thank you. I would suggest that we should know that. Thank you.

DR. LEWIS: May I help with that a little

bit? There are not very many ESRD events, so I'm not sure it's going to impact much. But often you could use an eGFR of less than 15 as a value for someone who went on dialysis if you didn't have a proximate in time close value.

Did either of you in your analysis do that for the ESRD patients?

DR. THOMPSON: Dali, can you address? If not, Jialu?

DR. ZHOU: I think I can. I haven't done that analysis. Did you refer to the composite endpoint that the sponsor provided earlier this morning, or another, something different?

DR. LEWIS: I think the composite endpoint --

(Music playing.)

DR. LEWIS: Wow, I hear music. Somebody must have put us on hold, yes.

The composite endpoint is different and it includes three things. But one way to handle if you're doing a GFR analysis, people who kind of crash into dialysis, or whatever, have a recent GFR

that's less than 15 is to assume anyone on dialysis has a GFR less than 15.

I bet you didn't do that, and I bet the sponsor didn't either, but I'm just asking. And I think that's what Dr. [inaudible – audio break] -- how you used ESRD patients; how you counted them for GFR.

I'll let you think about it just for times' sake because I think I might be confusing you more than I'm helping you.

Dr. Palevsky?

(No response.)

DR. LEWIS: Can you guys hear me?

DR. PALEVSKY: Thank you.

DR. LEWIS: Great.

DR. PALEVSKY: So given all of the questions about whether the pharmacodynamic effect wears off within the 4 weeks, one other way to look at outcomes would be to do a slope analysis of the data on treatment. The sponsor did discuss the slope analysis, but it was limited to the year 2 data.

Has the FDA looked at this and looked at an analysis of slope, incorporating both year 1 and year 2 data, beyond treatment data?

DR. THOMPSON: Thanks.

Dali, do you want to answer this? And, Lars, do you have any comments?

DR. ZHOU: Yes. This is Dali, statistical reviewer. I think I can answer this first, and if anyone has additional comments, they can answer maybe later.

Due to the study design with the washout period at end of year 1, patients were put off treatment during week 48, then to week 52. The conventional total eGFR slope analysis over the 2 years is not appropriate.

DR. PALEVSKY: Although, could you do an analysis censoring the data from the week 48 to week 52, when the medication was restarted, since the pharmacodynamic effect, one would expect, would be fully reversible in both directions?

DR. THOMPSON: Dali, please feel free to respond. I believe Lars may also have some

additional comments.

DR. ZHOU: Okay. Firstly, an adequate estimate of the slope could provide some information about treatment effect. However, because of the trial design, the patients were off treatment for 4 weeks, it's not clear the PD effect, how it affects the estimate, and it's not clear if the piecewise linear mixed-effect model is a robust and unbiased estimator of the second year chronic slope.

There are some unknown factors like the change point should be prespecified for that analysis. And importantly, with the unignorable and imbalanced recent data, results would be hard to interpret. So the patients available in year 2 are not a good representation of all randomized patients anymore, and if you only use those patients that have year 2 measurements, this is not a randomized comparison anymore.

(Crosstalk.)

DR. PALEVSKY: What about [indiscernible] comparisons?

DR. THOMPSON: And maybe just to jump in for a second, Dali, perhaps we could have Lars comment.

DR. ZHOU: Yes.

DR. THOMPSON: Lars?

DR. JOHANNESEN: Lars Johannesen, clinical analyst. Can you hear me?

DR. PALEVSKY: Yes.

DR. JOHANNESEN: Thank you. I had some audio issues on my end. I'm going to try to go to slide 16. Oh, sorry. There's a bit of a lag here.

Looking at this slope over time, across all the data, it was included in the PK/PD model. When we included an interaction that attested for a difference in the rate of decline between treatment arms in the model, which considers all the data across both years, we do not see a difference between the two treatment arms.

I'm showing here on slide 16, which I hope you can see now, both the observed and the model for the data, it looks like the slope is fairly similar between treatment arms, which is what the model's indicated as well. I hope this addresses

the question.

DR. LEWIS: May I make a comment while you have the -- actually, on page 71 of the briefing document of the sponsor, they state that the slope is actually worse than placebo between weeks 12 and 36 of the first year; so after the supposed PD effect and before the washout.

I don't know if you want to confirm that or not. I will say slope analysis with this number of patients is probably a super reliable thing. But did you look at the first year, and did you confirm what the sponsor said on page 71 about the first year?

DR. THOMPSON: Dali or Lars, can you comment?

DR. ZHOU: This is Dali. I didn't look at this year 1. I don't know if Jialu knows if there is a result.

DR. ZHANG: Hi. This is Jialu Zhang. We have not confirmed that year 1 slope analysis. In essence, we don't believe such slope model is helpful in a sense, based on the data and the

design of this study.

DR. LEWIS: Thank you.

Dr. Palevsky, did we get at your answers? I will refer you to page 71 in the briefing document so you can at least see what they said.

DR. PALEVSKY: Actually, the data on page 71 was what prompted my asking the FDA if they had looked at this.

DR. LEWIS: Okay. Thank you. Good.

Dr. Butler?

DR. BUTLER: Thank you, Dr. Lewis. This is Javed Butler.

Do we know whether the natriuretic peptide elevation signal was largely limited to those with eGFR less than 60 or was seen in both groups? Thank you.

DR. THOMPSON: Lars, can you answer that question?

DR. JOHANNESEN: Lars Johannesen, clinical analyst. I did not do that analysis.

DR. BUTLER: Okay. Thank you.

DR. LEWIS: Well, remarkably, I again want

to thank the FDA for getting us back on time. If there are no further questions -- I'm getting typed a message.

Dr. Nachman, I see your hand is up. We will take your question.

DR. NACHMAN: I have a question, but maybe not to the FDA, and I don't know if this is the right time to ask it.

DR. LEWIS: No, it is the right time. Since we have a few minutes, I will allow the question to the sponsor, and to make their answer brief, please.

DR. NACHMAN: Patrick Nachman again.

I'm having a little bit of a hard time wrapping my brain around the concept. A lot of the discussion we're having is whether the effect of the study drug is purely a pharmacodynamic/ hemodynamic effect, as opposed to an effect of the drug on inflammation, on fibrosis, and on the hypothesized increase in glomerular surface area.

The question that I have is, if we think that this is an effect on what's going on in the

kidney, from the fibrosis, or inflammation, or the surface area level, would we expect such a big washout effect in 14 days or 28 days? It seems to me that we're using different arguments for different things, and that they're not completely aligned with each other.

That's the end of my question. Maybe glomerular experts or Reata experts could comment on that, or Dr. Lewis.

DR. MEYER: This is Colin Meyer. I'd be happy to respond. There are two distinct effects with bardoxolone. In animal models, we've demonstrated that the acute increases are due to effects on surface area. We can't prove that in humans, but showing the slide here from FDA 16, those initial increases we believe are that effect. An effect on fibrosis would take months and months and months to accrue.

I'd like to point out that the time to peak here is exacerbated by the titration scheme. In all of our modeling, we see a direct relationship for the acute effects to plasma levels. So the

acute effect manifests within 2 weeks of patients reaching their final dose, and then when patients washed out the drug, that effect is lost.

So yes, it is a large effect, and based upon the rate of progression of patients in the Alport syndrome trial, which is about 4 and half mL per minute per year, with the slowing of progression of 50 percent, which is a very large slowing of progression, that's still only a few mL per minute accumulation on the chronic effects over time.

So all of our data are consistent with demonstrating that the drug is washed out within 14 days, which is why we justified the window the way we did.

DR. LEWIS: Does that answer your question, Dr. Nachman?

DR. NACHMAN: In part.

DR. LEWIS: I think our comments to each other about it will be when we get to the questions from the FDA, if that's ok. I think that will be the more appropriate time for me to comment. Okay?

(No response.)

DR. LEWIS: Alright.

We will now break for lunch. We will reconvene at 2:15 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 join at around 2 p.m. to ensure -- as we learned this morning, it's very important you are connected before we reconvene at 2:15 p.m. Thank you.

(Whereupon, at 1:29 p.m., a lunch recess was taken.)

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

(2:15 p.m.)

Open Public Hearing

DR. LEWIS: We will 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 is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written and oral statement to advise the committee of any financial relationship that you may have with the applicant, its product, and if known, its direct competitors. For example, this 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 this 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 speak only when recognized by the chairperson, and thank you for your cooperation.

We have a large number of speakers today. Each will be limited to three minutes. I apologize

in advance. To be fair, I will stick to the clock. So if I interrupt you, again, my apologies, but it is only fair to stick to the clock.

Speaker number 1, your audio is connected now. Will speaker number 1 begin and introduce yourself? Please state your name, organization you may represent for the record.

MS. DeLUCCA: Hi. My name is Afton DeLucca. I don't represent a specific organization, just myself and my family. I have no financial relationships with any party associated with this hearing.

As I said, my name is Afton DeLucca. I'm from Madison, Alabama. I'm an Alport syndrome patient and the mother of an Alport syndrome patient, my 6-year-old son, Cameron. Alport syndrome has impacted multiple generations of my family, including my grandmother, two of my uncles, my mother, myself, and my son.

I've overcome a lot of misinformation and bias as a female with Alport syndrome. Before finding a nephrologist who suspected that I was

experiencing more than a UTI, my family was told that women were not affected by this disease; they are simply carriers. This belief is misinformed at best, and at worst, life-threatening.

While I'm empowered by the information I've gained through my diagnosis, the knowledge that I live with a condition that could rapidly worsen at any time and has no curative treatment has caused me both anxiety and depression at times.

The stress is further compounded by the fact that many of my doctors have never treated a patient with Alport syndrome before, having only read about it in medical textbooks. Consequently, many of the physicians have not taken the possibility of disease progression or the need for preventative treatment options seriously in my case.

In addition to advocating for my own health, I'm also relentlessly focused on making sure my son gets the best possible care. In my experience, the treatment protocols for children are often just as misunderstood as those for adults.

I believe that the approval of an Alport specific treatment option would increase physician awareness of this rare disease and provide them with a safe and effective treatment to offer their Alport patients. Approval would also mean that my son has the opportunity to manage his condition with an effective oral medication instead of invasive procedures like dialysis and kidney transplant that both of my uncles endured throughout their 20s. It could potentially buy him years, or even decades, of health that his great uncles didn't have.

The approval of bardoxolone would offer our family a chance to free ourselves from a legacy of organ failure at a time when Cameron, representing the youngest generation of my family, should be focused on finding his place in the world instead of finding a new kidney and bearing the burden of a new disease, a lifetime of organ rejection medicines, being permanently immunocompromised, and always worrying about losing the organ.

With those additional years of health,

Cameron would continue to pursue his love of basketball, writing science fiction stories, and American Ninja Warrior training to the best of his abilities. Approval would give me hope for the future, both as a patient and as a mother. Thank you for your time and the chance to share my family's story.

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.

MS. BONEBRAKE: My name is Lisa Bonebrake. I have no financial relationships to disclose. I'm 55 years old and have X-linked Alport syndrome. I'm the parent of two young men. It's my youngest son age, 19, who inherited my genetic mutation for Alport syndrome.

As a tween and teen, Alport syndrome swiftly took away my son's identity, self-confidence, and quality of life. Doctors emphasized the only way to slow disease progression was for Grant to take

ACE and/or ARB medications. Though blood pressure was naturally very low, the increasing doses of these standard-of-care medications complicated his life at every turn. He took ice packs to school and tried to hide them under a shirt to keep himself cool enough not to get dizzy. If he stood up too fast or exerted a bit of energy playing a game or sports, he would crawl to the grass or someplace safe to pass out.

It was a daily challenge for him to wake up. The fatigue was constant. Due to illness, fatigue, and stress, Grant missed school so often that at one point he spoke of how our family would be better off if he was no longer on this earth. For him, at age 14, life was far too hard and without enough joy.

Because these medications were not making a difference in his lab results and were affecting his quality of life, we were motivated to seek out a clinical trial. Grant and I began the CARDINAL study on the same day together four years ago.

Within several months, Grant's lab results

improved enough that the PI asked how we felt about taking Grant off his ACE medication. His blood pressure was so low it was dangerous for his other organs, let alone that frequent passing out.

The change was almost immediate. He started feeling stronger, less tired and stressed, and able to be physically active. His outlook and emotional health improved significantly. For us, participating in this study has been about time. It gave Grant time to get through his high school feeling well, keep up with peers, and get into an excellent college.

After four years of feeling good on the study, really good, Grant's labs began to be concerning this past August. End-stage renal failure came within three months. He began dialysis two weeks ago. His older brother has stepped forward to be his living donor. Transplant surgery is imminent, but during those four years, Grant became stronger, and so did his brother, now older than 18 and able to be willing and a qualified donor.

I continue to do well on this study, and I'm hopeful that I won't spend my retirement years on dialysis. The study has also given me time, time to be strong enough to get my kids off to college and to now work full-time at a very meaningful job, helping other families with Alport syndrome.

As Alport families await novel therapies and potential genetic cure, so many are suffering and deserve an alternative to the standard of care, which often is not tolerated or barely tolerated. There are other therapies currently being studied. Perhaps bardoxolone will be a complement to them or a bridge. My family believes that other families should have access to bardoxolone to give them time as well. In fact, I wish I had more time today. There is so much more to --

DR. LEWIS: Thank you.

MS. BONEBRAKE: 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.

MS. LARA: My name is Charri Lara. I am a patient. I have participated in the study, been paid a stipend, and reimbursed for my travel. I live in the rural area of Lander, Wyoming.

My brother and I were diagnosed with Alport syndrome in the '70s, inherited from my mother. My brother was a pioneer in kidney research under Dr. Tom Starzl. He lived on the 7th floor of the Colorado Medical Center during these studies. My brother's first transplant was at the age of 13 by Dr. Starzl. This transplant lasted about 13 years. His second transplant lasted until his death in 2016.

My sister, dad, and I lived in Wyoming, and my mom and my brother had to live in Denver during those times. I still don't know how my parents could have afforded to run two households with only my dad working during this time. We would drive to Denver every Friday night, after my dad got off work, to spend the weekend with my mom and Tim. When Tim had to go on peritoneal dialysis, my

parents were trained on how to operate this machine. We had to run dialysis on Tim at her home in Wyoming since there were no dialysis units available.

We recently found a journal that my brother had kept during this time of his life. His writings were very detailed about the emotions that he had during this time. He was very grateful for the research that Dr. Starzl did for this disease. He would write that he knew when Dr. Starzl would come around late in the evenings, as there would be cigarette butts in his toilet.

I would never have participated in a clinical study like the CARDINAL trial with an investigational drug if it hadn't been for my brother. My brother would have participated in this study without a thought. He knew what he'd lived with at such a young age and wouldn't want anyone else to go through what he had to.

I began this study three years ago for my brother. I would love to see the opportunity for change to the life of young boys that live with

Alport syndrome. If this drug can extend the life of one's kidneys in order to postpone dialysis and transplant, what a success that would be. My brother died from cancer from the long-term effects caused by the anti-rejection drugs. Had he been able to put off having a transplant at such a young age, we could have had him around longer than the 51 years that we did.

When I started this study, my GFR was 35, and I'm very proud to say it is at 49. Because of this improvement, I am hopeful that I will be able to delay the need for transplant and the terrible effects of anti-rejection drugs; hopefully delay long-term side effects like cancer until much later in life. Please consider these views when deciding what might be a meaningful benefit that would support approval of this drug. Thank you very much for your time.

DR. LEWIS: 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.

MR. SEYMOUR: Good afternoon. My name is Phil Seymour. I'm a configuration manager for an aerospace company, and I live in Orange County, California. I have no financial connections to disclose.

I'm 58 years old, and I've lived with Alport syndrome all my life, although I was not diagnosed until my mid 30s. At the time, my kidney function was over 50 percent. Despite continuous monitoring and taking a variety of medications, my kidney function declined to near stage 4 CKD around five years ago, all despite my treatment of Alport's, which has been taking ACE or ARB, monitor my labs, see my nephrologist every six months, eat healthy, and pretty much cross my fingers.

This is one of a decades-old kidney failure, risk mitigation process and treatment, a never-ending daily regimen of a plethora of prescriptions and over-the-counter medications. That was all I had, at least until I became aware of the CARDINAL trial in 2017. And with the approval from my nephrologist, I successfully

enrolled in a phase 2 trial at the local Los Angeles site.

In CARDINAL, I was able to take the highest allowable dose of the bard trial drug, and the results have been amazing, and even bewildering. For the first time ever, my kidney function actually improved. When I started the trial drug, my eGFR was just around 30, yet during the next few years, I was able to improve my eGFR up to the mid 40s.

To me, this meant that my parts and my kidneys were not truly scarred and unusable, as so many Alport patients experience, but were actually increasing their functionality. My outlook on life shifted. I began to envision more travels with my wife and a chance to visit family members without enduring extreme medical precautions.

At work, I've been able to delay for years any discussion of extended time off I'd need to take when I was procrastinating transplant surgery. Just like being out of school can cause a student to fall behind, I worried that being out of work

would cause me to be bypassed for projects, become inconsequential, or even be let go. With my wife permanently partially disabled, I've become the sole income earner for my family. Thus, avoiding dialysis and transplant is critical to our financial stability.

The only persistent side effect to this trial drug that I've encountered has been increased muscle cramping that can be minimized with proper hydration. The side effect cost is quite acceptable to me, and beyond cramps, the single events of high-liver enzymes and boosted NT-proBNP values were determined to be inconsequential or not indicative of organ decline.

I have indeed already seen a bountiful delay of 45 years of my disease progression for which I owe to bard and to the clinicians involved in the trial. My permanent medical condition diminishes my happiness, especially if it affects me to the point where I need to lessen or give up some of my life's hopes and desires. This new drug has indeed shifted my outlook towards the positive. I've

gained years of improved health, and I am pleased with my future trajectory. Thank you.

DR. LEWIS: 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.

MS. SMITH: Good afternoon. My name is Cassandra Smith, and I am only representing myself. I am a patient with Alport syndrome, a mother of two patients with Alport syndrome, and a registered nurse. I'm here today to speak with you regarding bardoxolone methyl and the treatment of our rare disease and its potential impact on patient-declined quality of life.

While pharmacodynamics, the study design, and [indiscernible] have largely been discussed today, I just humbly ask that we recenter our thoughts on those who are directly impacted by today's decision, such as myself and my children.

I ask you to reflect on my daughter, Aaliyah, pictured here. She's 10 years old, and she loves ballet, painting, and her brothers, most

of the time. She has Alport syndrome. And I ask you to reflect on my son, Miles, also pictured here. He is 5 years old and he adores his big sister, his Nintendo, and his mom, and he also has Alport syndrome. And I ask you to reflect on me and the other patients presenting to you today while making your decision, who are the names and the faces, and even the voices of the numbers that have been displayed on our screen. And I ask you also to reflect on yourselves and your own lives.

Please take a moment and imagine with me. What were you doing at 18 years old? Were you finishing high school, pursuing college, or a career? What were you doing at 24? Were you perhaps falling in love or starting a family? What were you doing at 30?

Each of these lived experiences are not easily captured or reflected by data, yet they are some of the most impactful revered moments of our lives. But for patients with Alport syndrome, including many of my own family members, these moments can be limited, or even halted, by

moderate-to-severe renal disease, renal failure, dialysis, and/or transplantation like we've heard today, and the many downstream psychosocial effects such as anxiety, depression, and socioeconomic concerns that arise from the cost of medical treatment and even missed work days, all things that I've experienced myself.

But what if we could delay renal failure even by a short time frame? What impact will this have on quality of life? That to me is the primary question that I have been exploring with this medication.

So for my daughter, I believe this would allow her to pursue her dream of becoming a professional ballerina, and I believe it will allow my son to pursue love and a family of his own without renal failure halting his plans. And as for me, I believe it would give me more time at the bedside as a nurse and in the lives of my children as their mother.

Although this is not a perfect world and no drug comes without risks, I believe that approval

of bardoxolone methyl in the treatment of our rare disease would provide those of us living with Alport syndrome with more time, more time prior to renal failure, more time for the opportunities we all wish for our loved ones and even have for ourselves, leading to an overall increased quality of life. Thank you.

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. LANDWEHR: Thank you. Good afternoon. My name is Ryan Landwehr. I'm representing myself, and I have no financial ties to the process. I reside in San Diego, California, and I'm a 43-year-old X-linked Alport syndrome patient. My story's a little different than other patients, as I have been blessed with two living donor transplants over the last 25 years.

My story begins with unexplained hearing loss at the age of 6 and a confirmed Alport

diagnosis at age 12. I was told I would need a kidney transplant as a young adult, but a specific time line was unknown. There were no treatments and no studies to participate in; just simply living life until my renal failure set in. I was extremely scared.

Renal failure reared its ugly head at the most inopportune time, my senior year of high school. I was devastated. I was a talented athlete with offers to play in college, but I watched those offers vanish as I had to prepare to save my life. Thankfully, my body held on, and I was able to stave off transplantation, including any need of dialysis until the following fall after high school graduation. And more importantly, I was one of the lucky ones with a compatible living donor ready to go, my mom.

Despite needing to adjust to this new lifestyle of religious medication routines, follow-up appointments, and living every day with a healthy mindset, I went on to graduate college and have a pretty successful business career. Life was

moving on and was at its peak, both professionally and personally, which was about 10 years post-transplant, when then my transplanted kidney begin to fail. My world was shattered once again.

It was happening quickly with little time to prepare for a second transplant. I began a life on dialysis, a truly unpleasant experience and one I wish every patient can avoid. However, in the darkness of dialysis, a bright spot emerged. I received news that another living donor was compatible, this time my older sister. So at the age of 31, I received the second gift of life.

I'm an extremely optimistic person, so I look at my second transplant as the biggest blessing yet. An entirely new life that I couldn't even have imagined emerged from all of this, and I've certainly made the most of it.

Despite my transplant success, we need drugs like bardoxolone to help patients keep their native kidneys longer. Adding treatments like bardoxolone will help Alport patients get further into their adult life, become more emotionally and physically

prepared for transplantation, and most importantly, get past many crucial life events that young adults face early on.

I experienced firsthand the challenges of being a young transplant recipient, so I know that any delay of disease progression and transplant would benefit patients like me. I support the approval of bardoxolone methyl for Alport syndrome patients. Thank you.

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. LAGAS: Hello. I am Sharon Lagas, the co-founder of the Alport Syndrome Foundation and I have no direct financial relationships to disclose. I'm a patient with CKD stage 3. I'm a caregiver for two of my three children who also have Alport syndrome. Ours is a third generation of our family affected by this disease. Seven family members are facing significant life challenges and the

possibility of an early death.

Today, I speak on behalf of the Alport syndrome community and its 9700 registered members. We wanted to emphasize we have a significant unmet need and no FDA-approved treatment. This was documented in the voice of the patient report from our patient-focused drug development meeting held in 2018 and summarized in the document we provided in the docket for this meeting.

Alport syndrome is uniquely devastating because it causes young adults, mostly male, to go into renal failure during critical times in their lives. Imagine starting college, or a career, or a family, and having that derailed because of this disease, or even losing your life at the age of 31 like two of our members did recently, both male and female.

The current off-label standard of care does not stop disease progression and is poorly tolerated by many patients. Many young adults deal with high potassium due to the standard of care, which significantly impacts their lives and

involves regular visits to the emergency room. Patients also report that they cannot tolerate the effects of even the most minimal dose of ACE or ARBs, causing them to be excessively tired or even faint during their daily activities.

Alport syndrome patients need new therapies to maintain their kidney function and their quality of life. You are hearing from patients participating in the CARDINAL and EAGLE trials that have directly benefited from bardoxolone methyl. Some have been on drug for four years. These patients report higher energy levels, increased kidney function, and prolonged delay of renal failure, allowing them to participate in their lives and accomplish goals they did not think they would achieve.

Without novel therapy, many Alport syndrome patients are guaranteed earlier renal failure, which leads to a poorer quality of life and potential for earlier death. Families like mine have watched generation after generation of their loved ones deal with this disease and its

devastating challenges and losses.

For this reason, our patients have a high tolerance for less certainty about the treatment benefit, even when faced with risks involved with a new drug. This is because any delayed progression, even if measured in short years, is valuable time in a patient's life; time to complete high school or college, get married, start a career or family, before facing renal failure that forever changes one's life and the lives of their family. Thank you.

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.

MS. REED: Hello. My name is Janine Reed, and I have no financial ties here. Thank you for the opportunity to share what I've experienced while taking bardoxolone and what this drug has meant for me. I live north of Battle Creek, Michigan on a small sustainable farm. I'm 68 years

old, and I'm a retired dialysis nurse.

I was first diagnosed with Alport syndrome in 1974. At that time, my diagnosis was based on symptoms and a family history of several affected family members over three generations, including my mother, two uncles, my grandmother, and a great uncle. Later, my diagnosis was confirmed through biopsy and genetic testing.

I began the CARDINAL study in October of 2018 at the University of Michigan with a GFR of 38. Despite 45 years with a slow decline in my kidney function, after just three months of beginning the CARDINAL study, my GFR improved to 74. In the two washout months during the study, my GFR drifted back down into the 50s. Once I resumed taking the drug, my GFR improved again.

When my renal function improved, so did my overall energy and well-being, to the point of being able to resume walking and running 30 miles per week, bicycling, and managing a large vegetable garden, which is a noticeable difference from gardening or walking only an hour at a time once in

a while. I also have the energy and motivation to volunteer with Alport Syndrome Foundation, National Kidney Foundation, and Pierce Cedar Creek Institute. My retirement years have become dynamic.

While on bardoxolone, I've experienced three side effects: weight loss, muscle cramping, and an oral lichenoid reaction. All of these side effects have been tolerable when compared to stage 3 fatigue or losing my kidney function. The obvious choice for me is to continue on bardoxolone.

If bard was no longer available to me, I would anticipate that my kidney function would once again decline to the point of needing dialysis or transplantation some time in the next few years, causing a significant change in my overall health and adding a financial burden for myself and my family.

Having a treatment for Alport syndrome is not just important for my own health, but also for the health of my affected family members. I'm especially concerned for my daughter who has

inherited X-linked Alport syndrome from me that currently has very limited treatment options without bardoxolone. I would ask, as you make your decision, that you carefully consider the input from those of us who have had the opportunity to take bardoxolone. Thank you.

DR. LEWIS: Thank you.

Speaker number 9 has withdrawn.

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.

MS. MARTIN: Hello, and thank you for the opportunity to speak today. My name is Maddison Martin. I have no financial disclosures to make. I'm a 22-year-old Alport patient who lives in Connecticut.

I was diagnosed with Alport syndrome at age 4, which was a shock to my parents because I'm the only one in my family with kidney problems. Shortly after my diagnosis, I was started on an ACE inhibitor, enalapril, which I took twice a day. I

remained on this medication for most of my childhood and adolescent life, as this was and remains the standard care for Alport syndrome.

While my kidney function remained stable for most of my childhood, it slowly started to progress in my early adolescent years. As a result, my nephrologist would increase my enalapril, eventually working up to 30 milligrams daily. At 18 years old, while in college, I went into acute renal failure as a result of dehydration and the high dose of enalapril that I was on. My kidney function bounced back after this episode but was never the same, and my body could no longer tolerate the ACE inhibitor.

Over the next two years, my kidney function began its steady decline until 2019 when I underwent an altruistic living donor kidney transplant at the age of 20 years old. I am fortunate that I had the opportunity to receive a donor kidney from my high school attendance secretary, however, because of my young age, it is likely that I will need another kidney transplant

in my lifetime.

Unfortunately, the CARDINAL clinical trial was not available to me when I was younger. By the time I knew about the trial, I was already well on my way to needing a transplant. While the ACE inhibitor may have slowed my progression for 14 years, the Alport patient community needs a more reliable treatment option, as this current standard of care for those with Alport syndrome is not a viable long-term solution.

Without a true sustainable treatment option, I'm fearful for my own children who will likely inherit this disease from me. The only treatment available to me failed and transplants are hard to come by, which is evidenced by the 13 people that die each day waiting for a kidney.

I know I'm not alone when I say I hope studies like this one on bardoxolone methyl can provide Alport patients with a more sustainable and tolerable treatment option. Thank you again for allowing me the opportunity to speak to you all 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.

DR. KASHTAN: My name is Clifford Kashtan. I'm an emeritus professor of pediatrics and pediatric nephrology at the University of Minnesota, with an extensive record of research, education, and advocacy concerning Alport syndrome. I've no current financial relationship with Reata.

My goal today is to describe the current treatment of Alport syndrome and the need for safe and effective therapies to improve the outcomes achievable by the current standard of care.

When I began my career in pediatric nephrology in the 1980s, Alport syndrome was considered a condition treatable only by dialysis and kidney transplantation. That changed in the early 2000s with the demonstration that early treatment of transgenic Alport mice with an ACE inhibitor dramatically suppressed their kidney

disease.

Retrospective studies of men and boys with Alport syndrome have shown that early treatment with ACE inhibitors delays the onset of kidney failure by 10 to 20 years compared to patients who do not receive such treatment. A recent prospective study showed that treatment of children with Alport syndrome with an ACE inhibitor delayed the onset of proteinuria, a well-established marker of kidney disease progression in Alport syndrome. Based on these observations, treatment with ACE inhibitors has become the standard of care for Alport syndrome.

Despite the dramatic delay in onset of kidney failure achievable with ACE inhibitor treatment, many treated patients will nevertheless develop kidney failure at a relatively early age. In European men with Alport syndrome, early ACE inhibitor treatment increased the median age of kidney failure from 22 years to 40 years, while in Japanese men with Alport syndrome, early ACE inhibitor treatment increased the median age of

kidney failure from 16 to 28 years. Thus, there's clearly a need for safe therapies that can be added to ACE inhibition to further delay the onset of kidney failure in patients with Alport syndrome.

One of the attractive features of ACE inhibitors therapy is its relative safety. Adverse effects are generally mild and reversible, often responding to dose adjustment rather than discontinuation of treatment. Ideally, new agents for the treatment of Alport syndrome also have mild reversible adverse effects.

Alport syndrome is rarely a fatal disorder, at least in countries with universal access to high-quality care for kidney disease. Compared to patients with other forms of kidney disease, patients with Alport syndrome have less dialysis and associated mortality, and patient and graft survival after kidney transplantation for Alport syndrome are generally excellent. These favorable outcomes should be at the forefront of analyses of the balance of risk and benefit for new treatments for patients with Alport syndrome.

In conclusion, despite the demonstrated benefits of ACE inhibitors in delaying kidney failure in patients with Alport syndrome, there is a need for new add-on treatments to further delay kidney failure while minimizing additional risk. Randomized clinical trials that test the efficacy and safety of new agents in Alport patients receiving the standard of care represent the optimal approach to developing more effective treatment for Alport syndrome. Thank you.

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.

MR. DUNLAP: Thank you for allowing me to speak today. My name is John Dunlap. I have no financial connection to any company. I do not represent any company, only myself and my family. Again, my name is John Dunlap. I'm vice president of a recycling company, and I am from Nashville, Tennessee. I'm 35 years old, and I was born with

Alport syndrome. My mother had Alport syndrome and my 8-year-old daughter, Nora, has Alport syndrome.

As you all know, Alport syndrome is a rare kidney disease. Rather than being a kidney disease caused by eating or lifestyle habits, it's a congenital disease imprinted in our genes. We didn't ask for this, but it was the cards we were dealt.

I first discovered I had Alport syndrome when I was 22 years old after deciding to get a biopsy on my own. Growing up, I saw a pediatric nephrologist, but I was lumped in with a broad category of kidney disease patients, never having the opportunity to explore specific treatments for Alport syndrome. Even today, as medical science and technology advances, many nephrologists still lean to their proclivity of generalized medication. However, if bardoxolone were approved, there would be now an option specific to the rare disease that affects my family and I.

At 24 years old, I had emergency open-heart surgery to repair a rare side effect of an aortic

aneurysm caused by Alport syndrome, then I had a kidney transplant when I was 28 years old. While raising three children and working full-time, two years later, I had two full-blown strokes that I thankfully recovered from. It was difficult and exhausting. Additionally, I suffer from 60 percent hearing loss.

I want to do everything I can to help prolong this inevitability for my daughters. This is why I'm here today to advocate. If I had treatments like this when I was 8 years old, my developmental stage would have been easier to navigate. I struggled while in high school, college, early married life, and when trying to start a family in my early 20s. I grew up playing soccer, but I had to deal with constant fatigue and constant issues.

Nora, my daughter, is an avid softball fan. She hit three home runs this last season alone. She enjoys hiking, mountain climbing, and we even go whitewater rafting. She's a natural athlete, but with specific medication like bardoxolone,

hopefully she won't have to deal with the fatigue issues and medical issues that I struggle with. I want her to excel at things that she loves despite having this illness. My hope is that Nora can use this drug one day to allow her to develop into adulthood without the anxiety of kidney transplant literally behind her every step of the way.

Nora is the light of my heart, and many times she was the reason I kept going even when I was at my lowest point during kidney failure. We only have one life to live, so I ask that you please allow us to treat Nora properly so she can live her best life. Thank you for your time.

DR. LEWIS: Thank you.

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

MR. PAK: Good afternoon. My name is Christopher Pak. I represent myself and have no financial disclosures to make. I'm a 32-year-old transplant patient, and I've been living with

autosomal recessive Alport syndrome for all my life. I'm also a father of a 23-month-old daughter that has chance to be impacted by Alport as well.

My doctors first noticed I had kidney issues at 3 years old, and I was formally diagnosed with Alport syndrome at 9 years old through a kidney biopsy. Growing up was filled with doctor visits, constant blood draws, 24-hour urine tests, ACE/ARB inhibitors, and special diets. All of this was done to slow the progression of end-stage kidney disease caused by Alport syndrome, however, it did not slow the progression enough.

A year after I graduated college, my kidneys failed. I had just started my first job and I wanted to travel the world with my friends. I felt like I was in the prime of my life. All of that was put on hold due to catheter surgery and dialysis. I felt like my life came to a full stop. I was receiving dialysis in the mornings and in the evenings. My schedule revolved around these dialysis sessions.

I was on dialysis for four year years when I

got the life-changing call that I would receive a kidney transplant. However, even this life-changing transplant will not last forever. The average lifespan of a deceased donor transplanted kidney is 10 years.

I wish there would have been some way to delay my progression of end-stage kidney disease. Delayed progression means I could have avoided transplant in the first place or at least have delayed transplant to have the time with the [indiscernible] kidneys I currently have later into life.

After I got my biopsy, I saw my parents get pulled aside by my nephrologist while I was in the waiting room. Looking back, I know this must have been when they received the news that I had Alport. I can only imagine how devastated they were when they heard the news. At the suggestion of my doctors, my parents and I tried different treatments and diets. If we had an option of an Alport specific treatment when I was young, I'm sure this would have eased my parents' concerns.

Now, I am a father and I am in the shoes of a concerned parent. I would give anything so that my daughter does not have to go through what I went through, however, in my lifetime, there are now companies working on Alport syndrome treatments. It might be too late for me, but treatments like bardoxolone and other drugs can give Alport patients a chance to avoid dialysis and transplant altogether. Even the delay of dialysis and transplant would give patients, and maybe my daughter, a better quality and longer life. Each and every day matters. Thank you.

DR. LEWIS: Thank you.

Speaker number 14, your audio is connected now. Will speaker number 14 begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. SPRAGUE: Good afternoon. I'm Stuart Sprague, a nephrologist at NorthShore University Health System and professor of medicine at the University of Chicago. I am an investigator in the CARDINAL and other Reata studies. I have no other

disclosures to make.

I would like to make two main points this afternoon. First, Alport syndrome is a rare genetic disease caused by a defect in type IV collagen production as a result of mutations in the COL4A3, 4, and 5 genes. With advances in testing, we are identifying more patients who have the same genetic defect, such as individuals with thin basement membrane disease and who may be carriers of Alport, or who have progressive kidney disease without the other manifestations of Alport's or being diagnosed with Alport's.

Indeed, the recent bardoxolone studies have helped us understand that there may be a larger population at risk than those who have classically been diagnosed with Alport's. Thus, an effective therapy can slow the progression of disease and could have a considerably larger clinical impact than we thought even a few years ago.

Second, having been an investigator in the CARDINAL study, I want to share my firsthand observations of the patient experience. In

general, patients felt well and essentially had no complaints during both the blinded study and then the open-label extension. Side effects, if they occurred, were mild, and no one dropped out from my site. In fact, I had patients who were so committed to a treatment for Alport's, that even though they were going to college hundreds of miles away, or even overseas and not knowing whether they were on a placebo or the study drug, arranged their schedules in order to see me and not miss any of their study visits.

Additionally, it was clear that there was a decrease in proteinuria in many subjects who also noted feeling better. Even the few subjects who had mild increases in their liver enzymes were not bothered by it and felt very relieved when it corrected and they were able to tolerate a lower dose without problems.

Thus, from my perspective, this drug was extremely well tolerated with minimal to no side effects and had a positive impact both in decreasing patients proteinuria and slowing

progression of disease. Nearly all the subjects I enrolled wanted to know when bardoxolone will be available. In addition, many of them have relatives with Alport's, and they're hoping that they, too, may have access to the compound.

Finally, during the open-label extension study, all the subjects have been very grateful to be part of this study and none have experienced any side effects that concerned either myself or the subjects. With the overall safety data in the effectiveness of bardoxolone in slowing progressive kidney disease in patients without Alport's, I very much hope it gets approved. Thank you very much for your attention and allowing me to speak this afternoon.

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. WILLIS: Good afternoon. I'm Kerry Willis, chief scientific officer at the National

Kidney Foundation. I have no financial relationship with the applicant. On behalf of the foundation, I want to first thank all of the patients and family members who have participated in our efforts to understand the risks and benefits of potential new therapies from the patient perspective and help sponsors and regulatory agencies make clinical trials more patient-centered.

In 2018, we had the privilege of collaborating with the Alport Syndrome Foundation on a patient-focused drug development meeting, which included 140 Alport syndrome patients and caregivers and 9 representatives of FDA. In live testimony and answers to calling questions posed during the meeting, we learned, and you heard today, that the most impactful symptoms of Alport syndrome on daily life are anxiety and depression, fatigue, and hearing loss, and that a major source of anxiety for patients is fear of disease progression and the eventual need for dialysis or a kidney transplant.

When we asked about potential new treatments, 78 percent of patients said they would consider taking a drug that would slow progression of their disease, even if its side effect profile was worse than their current treatment, and 74 percent said that slowing progression was the most important benefit of a new drug, even if it had no effect on hearing loss.

The lasting impressions I took away from the meeting were of urgency and hope. People with Alport syndrome face rapidly progressive decline in kidney function, and with it, a high risk of cardiovascular events and end-stage kidney disease. It was clear, patients want access to a therapy that increases their chances of avoiding these outcomes.

Many meeting attendees were participating in clinical trials of potential new therapies and expressed concern, mixed with optimism, that a specific treatment for Alport would be approved soon.

The positive results of the CARDINAL trial,

showing continued improvements in eGFR with bardoxolone treatment over two years, are consistent with the results of numerous other studies of bardoxolone in other types of kidney disease, which provides additional support that bardoxolone is effective in reducing progression of CKD.

We recognize that not all safety concerns can be addressed in a relatively small, two-year trial. Safety data will need to be monitored if approval is granted and patients will need to be informed of potential risks of long-term use. However, we would ask that the committee bear in mind that given the chance, most Alport syndrome patients will want to try bardoxolone as soon as they can. Thank you for your attention.

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.

DR. SIMON: Thank you for allowing me to

speak today. My name is Jim Simon. I represent myself. As an adult nephrologist at Cleveland Clinic, I have been caring for patients with Alport syndrome for over 10 years and have participated in multiple Alport syndrome trials, including the CARDINAL and EAGLE trials, and was involved early on as a paid subject-matter expert during the design phase of the CARDINAL trial. I also served as a paid consultant for Regulus Therapeutics for the design of the ATHENA trial in preparation for studying AntimiR-21, a drug now studied by Sanofi Genzyme.

First, as you've heard, I cannot stress how important it is to the Alport community that treatment trials are being conducted on their disease. For too long, the disease was misunderstood, misdiagnosed, or outright dismissed. While RAAS inhibition has been shown to slow progression of kidney failure, the potential to have a drug approved specifically for use in Alport syndrome is monumental, to say the least.

Second, and slightly contradictory, I will

admit that I've been a vocal critic of Reata in my discussions with them from the very early stages of the design of the CARDINAL trial for multiple reasons, some of which I'll explain below, but I participated in the CARDINAL trial because it was important to my patients.

Two of bardoxolone's effects on the kidneys, the rise in GFR shortly after starting it and the rise in proteinuria, raised concerns amongst the nephrology community, even as patients got excited to see their GFRs rise. Unfortunately, debates about whether these were beneficial or detrimental effects demonstrated how little is known about the true effects of hyperfiltration in proteinuria.

Bard is thought to increase filtration surface area, suggesting that intercapillary shear stress would not increase, but little is known about any stress on the slit diaphragm this increased flow might create, which is thought to be the true deleterious effect of hyperfiltration.

Likewise, the increase in proteinuria is proposed to be due to downregulation of megalin

activity, leading to reduced proximal tubular stress at the expense of increased proteinuria. This will be very difficult for clinicians to wrap their brains around without definitive proof that it's not detrimental to the kidneys.

Additionally, it takes up to 12 weeks to reach the peak increase in GFR after starting the medication, yet the company was not required in CARDINAL to check GFRs 12 weeks after stopping the medicine to assess its lasting effects. And just as importantly, surprisingly to me, studies on Alport mouse models were not required before this drug was approved for study in humans.

Fortunately, the evidence Reata has presented from its clinical trials suggested that many of these concerns were not borne out. GFR slopes continue to separate over time, suggesting against a purely hemodynamic effect; the increase in proteinuria has been clinically inconsequential in most cases; and it appears to be safe when given to patients without a history of CHF or volume overload.

The data publicly released by Reata appears to show that this drug has a favorable treatment effect and safety profile. As long as the FDA feels that the studies were conducted according to its standards with regards to patient selection, censoring, and data analysis, such that evidence presented by Reata reflects the true effects of bardoxolone on patients with Alport syndrome, I support its approval. 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. WEST: Hi. My name is December West. I am representing no organization, and I have no financial relationship within any organization. My daughter's name is Nhalani. When she was 3 years old, she started to show signs of something was wrong with her kidneys. I noticed she had blood in her urine, and it wouldn't be until five years and three diagnoses later, when she was 8,

that we found out that she was diagnosed with Alport syndrome, which affects her vision, hearing, and kidneys.

We were told by her physician at some point she would need a kidney transplant because of her type of Alport syndrome. She would probably need it sooner than later in life. Nhalani is now 10, and just last week we were told that her creatinine is rising, and that may be because of the ACE inhibitor she is on. Now, they want to do monthly lab work to see if they want to change her medication.

Being able to have another option and possible treatment for her diagnosis would be an answer to our prayers. So approving bardoxolone could possibly help delay our daughter from needing dialysis or kidney transplant and having some sense of normal life.

Nhalani loves to dance, do track and field, and laugh. Nhalani competed in the 2019 Junior Olympics where she placed 6th in the nation for shot put. She also competed in javelin. It was an

exciting and emotional moment because of her accomplishment, but I could not fully enjoy it because in the back of my mind, I wondered if she would be able to do that again.

She also this year got accepted into a performing arts middle school for dance. She has aspirations of one day attending Juilliard School of Performing Arts in New York and competing in the Olympics. As a parent, my job is to help support and to help her achieve her goals. This is why I am here now fighting for the approval of bardoxolone because if she does not get a treatment for her condition, she may not be able to achieve her goals of competing in the Olympics and attending Juilliard.

Just the other day, I saw where a teacher donated her kidney to a young man in the 6th grade with Alport syndrome. Nhalani is in the 5th grade. This young man talked about having to do dialysis 3 times a week for 3 to 4 hours, and his experience of having a kidney transplant. All I could think about was Nhalani. She would miss school, she

would miss dance, she would not be able to practice her track. This is why it is important for you to approve bardoxolone so that my daughter won't possibly have the same experience as that young man. Thank you for your time.

DR. LEWIS: Thank you.

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. PERGOLA: Good afternoon. I'm Dr. Pablo Pergola, an adult nephrologist, and I represent myself. I was an investigator in the CARDINAL study, and I'm a consultant to the sponsor but have no financial gain by the outcome of this meeting. Thank you for the opportunity to speak today.

For over a decade now, I have been using bardoxolone to treat hundreds of patients with CKD of many etiologies, including Alport's, and in many cases I have followed them for several years. I want to share this practical hands-on experience with you, as it does not come across in the data

you have available.

Bardoxolone is well tolerated for short- and long-term use, and as witnessed by the patients that spoke today, generally and importantly, patients report feeling very well while on it, and treatment discontinuations are rare. The current protocols that include progressive dose uptitration allow reaching the optimal dose while minimizing the chances of potential side effects and monitoring the extra renal target effects that are unique to this drug.

Cramps, for example, subside over time while on the drug, occasionally require dose deescalation, and rarely result in drug discontinuation. Transaminase elevations follow a very predictable pattern, level returns towards the upper limit of normal over time, and only sometimes require the late dose uptitration and occasionally dose deescalation. Never have I seen the toxicity associated with transaminase increase.

Furthermore, patient selection and frequent early monitoring resulted in no cases of volume

overload in recent trials, including the CARDINAL study. Even with long-term use, in my opinion, comparing the safety of patients in CARDINAL with those of BEACON is clinically inappropriate because of the marked differences in the populations studied, and also because it negates the improvements made to manage previously observed side effects.

Much of the attention was focused on the off-treatment data that clearly supported, at a minimum, the lack of an underlying detrimental effect of long-term treatment. The observed increase in GFR that is simply being dismissed as a PD effect on GFR is a true treatment effect that is supported by clinical and preclinical data and deserves your full attention and study.

I have followed many patients for years after discontinuation of bardoxolone and I have never observed acceleration of disease progression. It is true that clinicians will need to learn how to monitor patients on bardoxolone, in particular during the dose titration period, but in no way do

I think this should deter us from using it for the treatment of patients with Alport's.

It is my opinion that if you find the efficacy and safety data available acceptable and recommend approval of bardoxolone, used by trained clinicians, it would result --

DR. LEWIS: Thank you.

DR. PERGOLA: -- in successful implementation of this treatment in clinical practice.

DR. LEWIS: Thank you. Your three minutes is up. Thank you.

Speaker number 19, your audio is connected now. Will speaker number 19 begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. SEYMOUR: Thank you for the opportunity to speak today on behalf of the National Center for Health Research. I'm Dr. Meg Seymour, a senior fellow at the center. We analyze scientific data to provide objective health information to patients, health professionals, and policymakers. We do not accept funding from drug or medical

device companies, so I have no conflicts of interest.

We agree with the FDA scientists that although the sponsor met prespecified primary and secondary endpoints, the submitted data do not demonstrate that bardoxolone is effective at slowing the loss of kidney function and reducing the risk of progression to kidney failure, and those are the outcomes that matter most to patients.

In addition to concerns about efficacy, we are concerned about its safety as well. There were so few patients evaluated for safety that data from an earlier trial on people with kidney disease due to diabetes were added to the analysis. However, those previous data were from a study that was terminated for safety concerns due to excess serious adverse events and mortality. Furthermore, bardoxolone may affect blood pressure, potentially leading to cardiovascular risks, but the full extent of that risk is unknown because patients with heart problems were excluded from the study.

We agree with FDA reviewers' concerns that over the long term, the cardiovascular effects, in addition to the effect of albuminuria, could actually accelerate the progression to kidney disease. It is expected that bardoxolone would be taken long term, and thus it is crucial to understand its long-term effects.

Finally, we are very concerned about the small number of children studied. The sponsor is seeking approval for patients ages 12 years and older, but there were only 11 pediatric patients in the treatment arm. We would agree with the FDA reviewers that the sample size is too small to draw conclusions about the effects of the drug on weight or how it might affect development.

We agree that there is an urgent need for therapies for Alport syndrome that can reduce the risk of progression to kidney failure, however, patients deserve drugs that have proven to be safe and effective and with meaningful outcomes. We urge you to consider the balance of potential benefits and risks for long-term use of the drug

during your discussion and vote today. Thank you.

DR. LEWIS: Thank you.

Speaker number 20, your audio is connected now. Will speaker number 20 begin and introduce yourself? Please state your name and any organization you are representing for the record.

MS. KLIND: Good afternoon. My name is Linda Klind, and I'm representing myself and have no financial ties. I reside in McCall, Idaho and recently participated in a 17-week study relating to the efficacy of bardoxolone methyl in the treatment of kidney failure for those at risk of rapid progression. Leading the MERLIN study was Arnold Silva, MD, PhD.

I'm a retired registered nurse active in volunteerism in the community and was diagnosed in 2015 with fibrillary glomerulonephritis, a rare form of chronic kidney disease with negligible treatment options. I participated in the MERLIN study led by Dr. Silva with a goal to titrate to a 20-milligram per day dosage.

While I did not know if I was receiving

placebo or bardoxolone, early in my participation I realized I was feeling notably better. I experienced rather dramatic improvement of symptoms relative to my diagnosis to include significant improvement in lab results, including that my GFR improved from 25 to 40, even prior to reaching maintenance dose. My blood pressure readings were consistently improved, rare in my situation. Intermittent edema, notably in my lower extremities, literally resolved, and for the first time in years, my legs and feet not only looked like they used to, but I was relieved of the pain and discomfort that accompanied the edema.

Shortly after reaching the planned 20-milligram daily dose, I experienced some identified potential side effects, moderate in nature. Leg cramps started about two weeks after reaching maintenance dose. While somewhat uncomfortable, that did not sway my enthusiasm for my overall improvement while participating in the study. Although not always considered an unwanted side effect, gradually throughout the study my

weight decreased by about 5 to 7 pounds with mild loss of appetite and a slight sense of a metallic taste.

In conclusion, participating in the MERLIN study and the invitation to speak today reminded me that my participation might just offer help to others with kidney disease, notably those with Alport syndrome, and that I too might benefit. When asked, following the study by my attending nephrologist, Dr. Amanda Hall, if I would consider taking bardoxolone if offered, my answer was an emphatic yes. Thank you very much for the opportunity to testify today.

DR. LEWIS: Thank you.

Speaker number 21, your audio is connected now. Will speaker number 21 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 an investigator on three clinical studies evaluating the safety and efficacy of bardoxolone methyl in patients with Alport syndrome. I am not financially compensated for my time today.

As a physician and clinical investigator who has participated in clinical studies with multiple sponsors for over 20 years, I am very encouraged by the efficacy of bardoxolone therapy to slow the progression of chronic kidney disease and potentially improve renal function in patients with Alport syndrome. Moreover, bardoxolone is well tolerated by patients with an excellent safety profile, comparable to placebo.

Impressive data on both efficacy and safety of bardoxolone is indeed encouraging for patients with Alport syndrome who previously had no other treatment options and were often faced with an unfavorable long-term prognosis that meant dialysis or renal transplant as the only options for long-term survival.

During the clinical trials with bardoxolone

and Alport syndrome, I witnessed a marked positive change in the patients who went from despair to hopeful that their disease now had a potential treatment that may improve their quality of life and avert the need for renal replacement therapy. Their testimonies have presented me with the greatest reward in my role as a clinician and investigator.

There is the mother of three with declining kidney function and increasing fatigue, with continued loss of functional capacity who tells me, "This drug has given me my life back. I wasn't sure what I was going to do before the opportunity to participate in this trial. I was struggling at work. I was having increasing difficulty to care for my family. I am most grateful for the chance to be in this study."

There is also the student who aspired to compete in collegiate soccer, but because of her Alport disease, she began to lose kidney function in adolescence and waning physical performance on the field. In her senior year of high school, her

chance of playing soccer at the college level was in jeopardy.

She elected to participate in the bardoxolone clinical trial and remained compliant for the past three years, with study medication and clinical visits that requires her to travel from out of state to keep her appointments. Despite her busy college schedule, she tells me, "I would not be where I am today without this therapy. It's given me the ability to continue my education and compete at the collegiate level." She is now in her third year in college and is a starting player on her college soccer team.

I hope you will support the approval of bardoxolone methyl for patients with Alport syndrome and chronic kidney disease. Thank you.

DR. LEWIS: Thank you.

Speaker number 22, your audio is connected now. Will speaker number 22 begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. CAROME: I'm Dr. Michael Carome,

director of Public Citizen's Health Research Group. I previously was a practicing board-certified nephrologist for nearly two decades. I have no financial conflicts of interest.

Public Citizen strongly opposes approval of bardoxolone because the drug has well-established risks of serious harms, but the CARDINAL phase 3 trial failed to provide substantial evidence that the drug slows the progression of chronic kidney disease in Alport syndrome patients. As a result, a favorable benefit-risk profile has not been established for bardoxolone.

Importantly, bardoxolone causes a myriad of diverse biological effects in multiple organs, the mechanisms and implications of which are not well understood in many cases. Combined safety data from the CARDINAL phase 3 trial in AS subjects, and the BEACON trial in subjects with type 2 diabetes and CKD, revealed that bardoxolone was associated with a higher incidence of the following adverse effects, among others: heart failure; increased blood pressure; increased proteinuria; weight loss;

decreased appetite; dygeusia; nausea and vomiting; anemia; hypomagnesemia; and muscle spasms.

Increases in blood pressure and proteinuria are factors that likely augment the risks of adverse cardiovascular and renal outcomes. Notably, the BEACON trial was terminated early after 2185 subjects had been enrolled with a median follow-up of just nine months because of excess serious adverse events in bardoxolone group subjects, including hospitalization or death due to heart failure, cardiovascular deaths, and a composite endpoint of non-fatal MI, non-fatal stroke, hospitalization for heart failure, or cardiovascular death. The CARDINAL phase 3 trial, which unrolled only 157 subjects, was too small to detect any differences in important cardiovascular outcomes.

Given bardoxolone's troubling safety profile, approval of the drug would only be justifiable if there was robust evidence that the drug provides substantial clinical benefit. However, as FDA reviewers explained in detail, the

CARDINAL phase 3 trial data failed to demonstrate that bardoxolone is effective in slowing the loss of kidney function in patients with AS and reducing the risk of progression to kidney failure.

In particular, the statistically significant effects seen with bardoxolone on the primary and key secondary endpoints likely were largely due to reversible pharmacodynamic treatment effects of bardoxolone. FDA reviewers convincingly argue that the duration of the actual washout periods in the CARDINAL phase 3 trial was insufficient to resolve the reversible PD effects of bardoxolone.

In closing, given the available scientific data that shows a lack of substantial evidence of effectiveness and clear risk of serious harm, Public Citizen urges your committee to vote no on question 4 and to recommend that FDA not approved bardoxolone. Thank you.

DR. LEWIS: Thank you.

Speaker number 23, your audio is connected now. Will speaker number 23 begin and introduce yourself? Please state your name and any

organization you are representing for the record.

MR. ALBERT: Good afternoon. My name is Anthony Albert. I'm from Hutchinson, Kansas. We have had our travel expenses paid for, as it is a 4-hour drive for us. I'm here to represent my son, Carson Albert.

My wife and I have four boys, all of them afflicted with Alport syndrome. Our three oldest children have had transplants now and our oldest is on the transplant list. Unfortunately, the CARDINAL drug was not available to them at this time, so I'm going to talk today about my son, Carson.

Carson just turned 17 and is a happy high school junior. Because of bardoxolone, his life is on a much different trajectory from his brothers. Carson has a normal life compared to our son Brenden, who was on hema [indiscernible] with dialysis for two years awaiting a transplant.

Brenden was a top baseball player in his class as he entered high school with a 4.0. He had goals of playing in college and going away, but the

summer before his freshman year, he was put on peritoneal dialysis and became so fatigued, he didn't want to do anything but sleep. His grades dropped from a 4.0 to a 2.6, even though he tried as hard as he could.

It was difficult for my wife and I to see him struggle like that. The lab draws, the lab appointments, even after transplant for nine months, it was nine months before he felt normal. He lost three years of his life.

I can say this with the utmost conviction. Bardoxolone has given Carson his life, and the only downside is some minor muscle cramps every once in a while that can be mitigated with hydration. It has been so minor, he has never complained about them. He only admits to them on appointments when they ask if he has felt any, and he'll say, "Yes, I've had one here or there."

Bardoxolone has given Carson the ability to get a 4.2 grade point average. He'll graduate next semester a full semester early with 18 college credits. He plays varsity tennis. He's a manager

at the student snack shop. He was able to hold down a part-time job this summer. It has given him so much hope for the future. It's so amazing to see the excitement in his eyes when he talks about going to college and the excitement when the mailman brings letters from different colleges asking him to come visit. It has truly been a miracle drug.

I want to tell you that Carson and our family have only had positive experiences with this drug. I know you've seen a lot of numbers and a lot of graphs, but please don't discount the human aspect. There are tens of thousands of Carsons out there that just want a chance to be normal. They just want a chance for a miracle. Please help them. I also want to say thank you to Dr. Warady at Reata, CARDINAL, and the staff at Children's Mercy for allowing Carson to be a part of this amazing project. Thank you very much.

DR. LEWIS: Thank you.

Speaker number 24, your audio is connected now. Will speaker number 24 begin and introduce

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

MR. KINGSBERY: Yes. Hello. My name is Clint Kingsbery. I represent myself and I am not financially compensated in any way for my testimony.

I was diagnosed with Alport syndrome in early 2017. Because I was adopted, no one really understood what was going on with my kidneys or anything else. So it was quite surprising when I went to the doctor with high blood pressure in mid-2016, and they told me that my kidney function had significantly declined. This was quite problematic because I had just started a master's program and it just felt very overwhelming.

Once I had gotten the diagnosis, I did like anyone would and jumped on the internet to start trying to figure out what's going on with me and what does this mean. I found a Facebook support group for Alport syndrome, and I saw that it mentioned the CARDINAL study there. It turned out the CARDINAL study was in my own home city, at

least one of the locations was, so I joined in San Antonio, Texas.

I have been on the CARDINAL study and the open label since May of 2017. I currently still take bardoxolone at this time. When I started, my GFR was in the mid 30s. My creatinine was around 2.1 or so. As of today, my GFR still is in the mid 30s. My creatinine has creeped up to about a 2.6-2.7 now.

Essentially, during this entire time, my kidney function has remained steady and consistent while on the drug, though it did briefly peak into the low 40s when I initially started the drug. Overall, it's been an incredible boon for me and my family. It's allowed me to do many of the things I didn't think I'd be able to accomplish after I initially got my diagnosis. The initial prognosis said that I would probably need dialysis or possibly a transplant within four or five years.

Today I am able to speak before you without that concern thanks to bardoxolone. Sure, there have been some side effects. I've had cramps

occasionally. I lost appetite, and I lost a little bit of weight, about 5 pounds over the last four years, so nothing significant. But it's allowed me to do so many things, like complete my master's degree. I started a PhD. I'm actually an elected official in my city, and I even changed my career because I didn't have to worry about the fact that my kidneys were shutting down.

I can say that my life has changed for the better while being a part of this drug study, and I fear that should the drug not be approved, my kidney function will begin to deteriorate, bringing back all the fears and apprehensions that come with CKD. Thank you for listening to my testimony and my experience with bardoxolone and how it has positively changed my life.

DR. LEWIS: Thank you.

The open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before

the committee, as well as the public comments. We will pause, though, for Dr. Thompson has a comment or answer to a question.

DR. THOMPSON: Thanks, Dr. Lewis. Can you hear me?

DR. LEWIS: Yes.

DR. THOMPSON: Great.

We just need slide 6 pulled up, FDA's slide 6. This is slide 16; if we go to slide 6. Perfect. Thank you.

I just want to thank the speakers during the open public hearing, and in particular the patients and their families for sharing what are very personal and important stories.

I'd asked Dr. Lewis to allow me to provide a comment before the committee moves to discussion because I wanted to clarify and provide further context around some of the questions that came up around slope analyses, which as we heard, FDA didn't do, as well as analyses trying to understand the benefit. As I think we heard from our speakers, some of this may have just appeared like

a lot of analyses and can be hard sometimes to follow the story.

If you look at the slide -- I just want to orient you or remind you -- this slide shows the primary endpoints, as well as the key secondary endpoints in CARDINAL phase 3. The primary endpoints are shown on the left. The year 1 is shown on the top, the year 2 results are shown on the bottom, and then the off-treatment effect is shown on the right with, again, the year 1 results shown on the top and the year 2 results shown on the bottom.

As I said in my opening comments, and I think as you probably are all well aware right now, the outcome that we want to prevent is progression to kidney failure. But the reality is, it's just not really feasible to do that in a feasible clinical trial in many of our chronic kidney diseases. So as you've heard today, we often rely on changes in eGFR as a surrogate endpoint.

I want to point out, though, that a trial provides a snapshot into what's happening to renal

function over some window. But then to really understand the clinical significance in terms of its impact on progression to kidney failure, we have to make a number of assumptions.

One assumption we make is the treatment effect that we're seeing in the trial continues to accrue over time, and how we typically address that issue is via the slope-based analyses. We see that one curve is showing that patients may be declining at 4 mLs per minute per year and the other rate of decline is 8. So in other words, the drug has cut the rate of decline in half. So that's one thing we look out to figure out whether the treatment effect is going to accrue over time.

The other thing we do when we make these extrapolations is we also make the assumption that the treatment effect continues to accrue across various stages of disease. Again, a trial is a snapshot into what's happening to a population. It's a tool.

So how do we satisfy these assumptions about the benefits accruing over time or the benefits

accruing across the various stages of disease? Well, I'll tackle the second issue first.

Typically, what we tell sponsors to do is to enroll a population over a wide range of eGFRs, and we look, post hoc, at subgroup analyses and see whether we're seeing the treatment effect above 60, in the 60 to 40 range, below that, et cetera, just to get a sense of whether it's accruing over time or whether it's just happening in a certain window of the treatment period, because that helps us understand, ultimately, the nature of the benefit in terms of affecting progression to kidney failure.

The other thing we do is we say, again, does it, as I noted, accrue over time? We didn't do these slope-based analyses, but I think that if you look at the slide, you'll get insight into this issue. Again, the left side of this slide shows the on treatment, the right side shows the off treatment.

If you look at year 1 and the LS mean difference between the treatment arms, it's about

5.4. -- the point estimate -- mLs per minute, per 1.73 meters squared. If you look at week 104, it's 4.4. So if the treatment effect accrued over time, you would expect it to get bigger. Right? If you think that each year you're slowing the rate of decline by some amount, then the treatment effect, or the difference between arms, should grow over time.

So while it's true that we didn't do slope-based analyses because we had concerns, from a statistical perspective, about the validity of them, we do think that there are other data that essentially address this issue.

I appreciate your giving me this opportunity to clarify.

DR. LEWIS: Thank you, Dr. Thompson.

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

Dr. Thompson?

DR. THOMPSON: Sure. I just want to say that I very much appreciate the opportunity that you just gave me to provide those additional

clarifying comments and want to yield my time to the committee to allow for sufficient discussion of the issues.

Questions to the Committee and Discussion

DR. LEWIS: Thank you, Dr. Thompson.

The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as 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. I will read the first question.

Discuss whether CARDINAL phase 3 was adequately designed to assess for an effect on the progression of chronic kidney disease in patients with Alport syndrome.

Are there any questions about the wording of the question?

(No response.)

DR. LEWIS: I don't see any hands up. If there are no questions or comments concerning the wording of the question, we will now open the question to discussion.

Dr. Merz?

DR. BAIREY MERZ: Noel Bairey Merz.

As a non-nephrologist, could the nephrologists on our panel tell us why an on-treatment effect is not adequate? For example, as long as patients keep taking their statins, they do well, and there's data for 25 years that when they stop their statins, they don't do as well.

Am I thinking about this correctly? Any nephrologist?

DR. LEWIS: Do the nephrologists want to answer that question?

DR. BAIREY MERZ: Dr. Lewis, you can take it.

DR. PALEVSKY: This is Dr. Palevsky. I'm

happy to jump in.

The analogy that you were drawing was to statin therapy, where altering the cholesterol levels is having an effect on long-term cardiovascular risk, progression of atherosclerosis. In this case, the outcome that's being looked at, which is the glomerular filtration rate, is the actual outcome of the disease process. Patients don't die from the elevated cholesterol itself. Patients with kidney failure suffer renal death when their GFR progresses to a point that it no longer is able to sustain healthy life.

If there is an artifactual change, hemodynamically mediated change, or because of a change in how the marker that's being used -- creatinine for calculating eGFR -- is being affected, it is not changing the natural history of the disease. The perfect example is the effect of SGLT2 inhibitors or RAAS blockers, which will decrease eGFR but alter the long-term slope so that the rate of progression of disease over time is lower, and the point at which end-stage kidney

disease occurs is delayed.

So the question is not whether the creatinine is lower and the eGFR higher, but whether that is going to change when the patient is going to reach end-stage kidney disease and require dialysis, or transplantation, or ongoing life support. If you're just changing the apparent GFR, that's not necessarily going to correlate with changing the outcome of disease.

DR. BAIREY MERZ: Excellent and very helpful.

Dr. Lewis, can I ask one additional question?

DR. LEWIS: Yes.

DR. BAIREY MERZ: Which is a better predictor of that large outcome renal failure, the urinary microalbuminuria, or a creatinine clearance, or a cisplatin?

DR. LEWIS: I'll take a stab at that one. At least in diabetes, albuminuria is a more potent predictor of what's going to happen to creatinine than creatinine itself, so I hope that answers your

question.

DR. BAIREY MERZ: It does. Thank you.

DR. LEWIS: Dr. Moliterno, I believe your question is next.

DR. MOLITERNO: Hey, Julia. Thank you. Yes. David Moliterno. My question, like Dr. Noel Bairey Merz, is just trying to get some bearing here. The question's about adequacy of trial design.

I'd turn it back to the nephrologists. We're talking about an estimated GFR, not a GFR, and then I just heard the term "apparent GFR." So you'll have to tell me how confident you are in estimating GFR, and if they use different formulas, if they used a core lab to measure creatinine, and with such a small cohort, why they didn't use cystatin C.

So that's the first thing, is how confident are we in the design based upon the actual measurement at hand.

Then the second one I'd like your input on is the effect of, say, protein intake. We heard

one patient say they had loss of appetite. We saw some growth curves that look like the kids dropped off a little bit, and I just wonder if any of this has to do with loss of appetite, protein intake, and shifting in lean muscle mass.

Those are my two questions, and it's more to get your sense as nephrologists, your level of confidence or concerns.

DR. LEWIS: Let me try to take a stab at that, and I'd for other nephrologists to comment, too.

First off, full disclosure, in 1990, the eGFR paper, where it shows the calculation in GFR seen on all our lab slips, I was an author on and have been an author on numerous other papers measuring kidney function.

It is a doable kidney function, and I think that, currently, it does, in most cases, correlate with the clinical renal function. So even though the iothalamate GFR, inulin, or cystatin C may differ by a few mLs per minute, and in terms of its accuracy, particularly high GFRs, that is a

cross-sectional difference.

If you look at it longitudinally over time, although there can be some decreases in creatinine production with lower GFRs and stuff, it is probably longitudinally -- over time, comparing one GFR to another, it's reasonably accurate and has been compared in the [inaudible – audio break] trial, iothalamate, in terms of predicting the ESRD outcomes, to be equivalent to iothalamate GFR.

So [inaudible] definition that Medicare uses, and insurance companies use, and that doctors use to begin dialysis.

So I think that it's a fair measurement. I think the question at hand is, is this increased glomerular hyperfiltration, or this increase in GFR, is it a good or bad thing long term for the kidneys that are exposed to it? And I think that comes maybe more into our second question, and I'm glad to comment on it more there.

I will say that serum creatinine, to my understanding, was only measured once at the off-treatment thing. And typically for a trial, I

think, I would recommend -- since there's a lot of variability in the actual measurement of creatinine -- more than one view, at least two, sometimes three, and then doing a geometric mean would have been a better design element.

The protein intake issue, protein intake in the MDRD study was not shown to benefit -- to decrease protein intake was not shown to benefit the decline in GFR, and I don't know that we have any data on protein intake from this trial. We do know that they lost weight, but I don't know if it was related to protein.

I hope that answers your questions, and maybe someone else can take a stab at that, too.

DR. PALEVSKY: Can I jump in, Julia? This is Paul Palevsky.

DR. LEWIS: Sure.

DR. PALEVSKY: I agree with the majority of the explanation and comments that you provided, and certainly over a two-year period, the change in eGFR, sex isn't changing. I presume this was using the older CKD-EPI equation that included race.

Race is not changing. Age is changing by two over the course of time in the adults, where the CKD-EPI equation was being used. So any change in eGFR is, actually, merely reflecting the change in serum creatinine over time.

The assumption, then, is that creatinine production is remaining constant over time and that there is nothing, as a result of either the treatment or disease progression, altering creatinine production. And that does raise a concern for me, given the weight loss. I think the study would have been much stronger if we had a filtration marker, i.e., cystatin C, so that we knew there was no impact of change in creatinine generation on the outcomes.

DR. LEWIS: Dr. O'Connor?

DR. O'CONNOR: Yes. Dr. O'Connor. Regarding the design, I'm curious why more advanced kidney disease patients weren't included in this population so we could get a better idea of what's happening when your GFR is in the CKD 4 range. And number two, I don't understand why the 14-day

window was included in the 4-week washout? Was that prespecified, that we could go as low as 14 days in the washout?

Those are my two questions.

DR. LEWIS: The 14 days was the window, so it was prespecified I guess as a window.

Your first question again was -- would you remind me?

DR. O'CONNOR: More severe kidney disease.

DR. LEWIS: Oh, yes, the more severe kidney disease. I think there are a couple comments about that, and I can only speculate or I can tell you comments.

If you include people with lower GFRs, you have less time to impact on the progression of their disease; that could be argued. But also remember that acute effects are attenuated at lower GFRs so that the benefit, if you will, on the absolute GFR would be bigger in people with higher GFRs. And I think I asked a question of the sponsor, and they [inaudible].

I think that the other factor is that

although this was a population of 40 year olds mean age and the BEACON study was 68, as you know, CKD is a powerful risk factor for HFpEF, and of course many of our patients, as they progress towards lower GFRs in ESRD, they have more HFrEF, so that you, I guess, would have less ability to see an impact on a more high-risk population by excluding people with lower GFRs.

Then again, I'll open it to the other nephrologists for comments.

If there aren't any, Dr. O'Connor, if you would put your hand down.

Dr. Palevsky, you have a question, and thanks for your help with the answers.

DR. PALEVSKY: Yes, not so much a question, but rather the concerns that I have with the design.

Given the acute effects that the drug has on GFR, I was surprised that the primary outcome was the on-treatment change rather than what would be the more clinically meaningful outcome of the off-treatment residual improvement in kidney

function, and designing it with sufficient attention so that we wouldn't have to be arguing as to whether, at the end of the washout period, there had been adequate washout of the pharmacodynamic effect.

So I have some concerns about those aspects of the design, and in particular, the fact that it was only a 4-week washout period, where the maximum bar appeared to be 12 weeks.

DR. LEWIS: I think I had the next question or comment. I'm saying questions because we started out this session a little bit differently with questions, and I actually appreciate the cardiologists doing this because the measurement of kidney function is an extremely complicated issue for nephrologists, even for nephrologists who work in this area, so I really appreciate your questions.

But my comment is very similar to Dr. Palevsky's, which is there were only 157 patients in this trial. Adding an extra visit or two, at which all you would have to draw is a

serum creatinine to better elucidate whether there was any benefit on true-saving GFR or slowing the decline compared to placebo versus just residual acute effect -- which, if anything, might be considered negative; in fact, would be considered negative, I think -- it's hard to understand why not. It wasn't thousands of patients getting an extra visit, it wasn't the hard extra visit, or two, and it was a simple blood test. So that concerns me in the design of the trial.

Another concern I have is excluding people with an increased BNP. I think that that is a hard thing to translate into use by a clinician. Does that mean we monitor BNPs throughout the trial? As you know, BNP is affected by decreasing GFR in terms of part of it being excreted by the kidney. So if the BNP goes up, do we stop the drug?

I mean, it's a very -- first off, it's a worrisome signal, but it's also a very difficult one to operationalize in a clinical practice. So that is another concern I have [inaudible] about the design.

After me is Dr. Nachman.

DR. NACHMAN: I'm sorry, Dr. Lewis. Did you call on me?

DR. LEWIS: I'm sorry. I did call you.

DR. NACHMAN: Thank you. Patrick Nachman here.

You know, it's easy to critique a design four years after the fact, so I'm going to be careful of this. I'm still bothered by whether there could have been stratification, or at least analysis, really truly based on genetics. We know that males with X-linked or patients who are homozygous for autosomal recessive have a significantly worse outlook and potential outcome, but I still haven't seen data to support this. The data that is presented to us as X-linked Alport's versus non-X-linked, to my calculations, includes that about half of those patients would have been women, so they would not have been hemizygous and would have had a better prognosis than their male counterparts.

I don't know that we have been shown data

that shows that this drug has efficacy in the population who would normally stand to gain the most. Is that in the works? That should be feasible. That's a secondary analysis. Even if it was not prespecified, I would argue that it should have been prespecified. Thank you.

DR. LEWIS: Thank you, Dr. Nachman.

Dr. Butler?

DR. BUTLER: Thank you, Dr. Lewis. Javed Butler here.

Very much like Dr. Nachman, I'm also cautious in critiquing a trial that has completed some time ago. But the best that I can understand from reading the paper work is that the primary endpoint was changes in eGFR over a two-year period, and what we have is a modest-sized trial with not an inconsequential minority of patients that withdrew or discontinued for various reasons. Perhaps not everybody was on the dose that they were intended to, and then they are also dealing with missing data for the primary eGFR values over time as well.

I would have expected that there would be a hypothesis and a certain threshold of preservation of eGFR slope that would have been hypothesized, and a certain degree of drug discontinuation built into the power analysis, and perhaps even some adaptive trial design so that at the end of the study, you have a hypothesis that is tested with an adequate number of samples available and patients still on drug, and that makes interpretation a little bit difficult.

DR. LEWIS: Thank you, Dr. Butler.

Dr. Mendley?

DR. MENDLEY: Thank you. I'd like to return to a question of Dr. O'Connor's and a comment of Dr. Nachman.

Dr. O'Connor asked why did you not enroll more patients with advanced CKD, but I need to remind everyone, Alport syndrome is a disease of young patients. In fact, the most rapid loss of kidney function occurred in the adolescents, and they would clearly have the largest potential lifetime benefit.

So my question is -- my concern is -- why only 11 adolescents, especially if you're seeking indication for children over the age of 12? Their eGFR loss was so much greater that you might actually have been able to establish efficacy in that group with more thoughtful design. Thank you.

DR. LEWIS: If you'll all please remember to put your hands down once your question is answered.

Dr. Mendley?

DR. MENDLEY: Yes. I had a question.

DR. LEWIS: Thank you. I just want to be sure you were done.

Dr. Palevsky?

(No response.)

DR. LEWIS: Dr. Palevsky, do you have another question or another comment?

DR. PALEVSKY: I forgot to lower my hand.

DR. LEWIS: Okay.

I believe all hands are down. I will give a moment.

Dr. Gorman is our other nephrologist on the committee. Do you want to make a comment about the

design?

CAPT GORMAN: No. I raised my hand a few times, and I guess someone asked the same question. But I agree. I think they have a great network from the Alport Foundation and different centers, but as Dr. Mendley said, maybe it wasn't representative of the patients that might get the most benefit, quality life out of there. Progression of kidney disease with an imperfect estimate, estimating equations, especially with just creatinine, are imperfect, especially at higher GFR levels.

I know it was done a while ago, and many careers have been made on evaluating more and more complex estimating equations, but at the end of the day they represent estimating equations. I think it was designed as best they could. There are some tweaks they could have done and longer. I think it's also unfortunate that the pharmacodynamic effect of raising GFR, whether that's hyperfiltration or not, complicates it even more. Over.

DR. LEWIS: Thank you very much.

Dr. Cook, as our statistician, do you have any comments about the design?

DR. COOK: This is Thomas Cook. My biggest comment is probably what you had said earlier, that they only measured the eGFR once off treatment. I think had they known then what they now, I would have recommended that they measure it at several time points during their post-treatment period, but only because then we could get a much better sense of when the pharmacodynamic effect goes away when it says [indiscernible], because given what we've seen and from the FDA, it's not clear to me that they ever actually reached that point, and I think that's a pretty crucial analysis that we would need to see to really definitively nail this thing down.

DR. LEWIS: Yes. I certainly agree. We're in agreement on if there was any question about how long it would take the acute effect 12 weeks to get up there and to come back down. It's an easy thing to do.

If there are no more -- one more hand.

Dr. Palevsky?

DR. PALEVSKY: I was just going to point out that even if they didn't do that at the one-year time point, it would have been relatively easy at the end of treatment, after week 100, to have gone out rather than just to week 104, but to go out to week 112 with additional creatinine to demonstrate that there was a persistent improvement in kidney function, and I think that we would be far more convinced if that were the case.

DR. LEWIS: Exactly, and thank you.

Okay. I'm going to summarize what [inaudible]. Again, I appreciate our cardiology colleagues asking for some clarification about the use of eGFR as a measurement. There are some questions about whether eGFR, or one of the other equations or other methods of measuring GFR, might have been more informative.

Also, there was an issue brought up about whether on treatment was an appropriate outcome or whether, really, [inaudible] would have been off treatment so that [inaudible] effect as opposed to

the chronic declining kidney function compared to placebo could have been evaluated.

I think multiple people have questions about what people felt would have been a much improved design, which would be to provide a margin for an adequate washout by further time out, especially after the 104-week visit. There's also a concern expressed by several of the members about the design and not doing an analysis or being prepared to analyze the genetic defect to the Alport syndrome.

Lastly, a question about the 157 patients with a primary input of eGFR being a very modest trial, especially with the differential discontinuation in the bardoxolone group and the complexity of missed data, particularly complex with the one-year washout, and perhaps some trial design that would have allowed a better evaluation of slow preservation may be an adapted trial design.

Lastly, I think a comment that was made was why not enroll more patients with advanced CKD and

why only 11 adolescents. By increasing the number of adolescents, you would also increase your number of people who are having a more rapid decline in GFR and perhaps more relevance to patient outcomes could have been evaluated.

I neglected to read -- and I will now read -- that the applicant is seeking approval of bardoxolone to slow the progression of chronic kidney disease caused by Alport syndrome in patients 12 years of age.

I'm going to read the second question, which is discuss whether the available data indicates that bardoxolone methyl slows the progression of chronic kidney disease and whether it is reasonable to conclude, based on the available data, that bardoxolone methyl will reduce the risk of progression to kidney failure when used chronically in patients with Alport syndrome.

Are there any issues or questions about the wording of the question?

(No response.)

DR. LEWIS: I don't see any hands up. If

the wording of the question is clear, I will open it up for discussion and comments.

(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. Cook?

DR. COOK: One of the things that the FDA said on their sensitivity analysis -- this is Thomas Cook; sorry. For example, Dr. O'Connor asked whether the point estimate that came out of the 52-week analysis within the confidence interval, and I would argue that that's the wrong question. The purpose of a sensitivity analysis, in my opinion, to confirm or validate the primary is to assess whether there is an alternative explanation for what we're seeing other than a plausible effect on the rate of progression of disease.

I think it's pretty clear, from the FDA's set of scenarios that they looked at, that there are probably very plausible alternative

explanations that suggest that in fact what we're seeing isn't a change in the progression of the disease, but rather simply an artifact of the pharmacodynamic effect on GFR.

Thank you. I think that's the end of my comments.

DR. LEWIS: Thank you.

Dr. Nachman?

DR. NACHMAN: Yes. Thank you. Patrick Nachman.

My comments about this question 2 is that we're lumping Alport syndrome, which has a huge spectrum of severity and rapidity of loss of kidney function, as if it were one disease and one patient population. The data is maybe a lot more compelling in terms of risk-benefit for a subset of patients and almost inexistent for the subset of patients with more rapidly progressive disease.

So I don't know, when we're considering the risk-benefit and approval, if there is a way of parsing out at least these two patient populations. Alport syndrome, it's probably syndromes with an S,

and I'm a little bothered by lumping everybody in the same bag. Thank you.

DR. LEWIS: Okay. I think you're asking for an analysis [inaudible] that we didn't see, and I will ask the FDA -- and we're going to go on with more comments -- if they have any information about the impact on whatever cutoffs of GFRs you want to use, based on the population of patients, to address Dr. Nachman's concern.

Dr. Palevsky?

DR. PALEVSKY: I think this question is really the one that's the crux of the decision making that we need to make because we're asked to look at a study as its outcome, a surrogate endpoint asking whether the long-term outcome for these patients will be improved with treatment.

When I read through the materials that were provided before this meeting, I was struck by exactly the point that Dr. Thompson made about the fact that the difference between the treatment and control arms, rather than widening with time, seemed to be narrowing between year 1 and year 2

whether you look at the outcomes on treatment or at the end of the 4-week withdrawal from treatment, which has me very concerned that we're not actually seeing a true beneficial effect.

As much as I desperately want to see a drug that has an alternative mechanism of improving kidney function, whether it's for this relatively rare form of kidney disease or for the more common forms of kidney disease, I'm left quite concerned that the data that we've been provided does not meet the bar of showing that this is going to slow the time to end-stage kidney disease.

Now, the slide that Dr. Chertow put up showing a 20-year delay in reaching end-stage kidney disease is what we're all hoping for, but I think that's an overly optimistic interpretation of this data, and I'm left unconvinced.

DR. LEWIS: I believe I have the next hand up. I think I do.

I think question 2 does come [inaudible] totality of the data that we have, too, in the world, and that [inaudible]. As I indicated

earlier, it concerns me that we have an unprecedented increase in glomerular filtration rate as an acute effect. Whether you call it glomerular hyperfiltration or increased GFR, the explanation for that, I believe, in their own preclinical research of then 2013, with an increase in filtration [inaudible] is most likely increasing intraglomerular pressure, which as far as we know as nephrologists is a negative thing.

The other explanation that they give without doing any micropuncture studies -- which could have been done to address this so we wouldn't be struggling with this question by reading these papers -- is unprecedented, as they said themselves. Their hypothesis is that there is evidence for a glomerular surface area increase, which I recognize that they in the [indiscernible] was visualized, I guess.

We don't have an animal model of Alport's, and, again, it troubles me deeply that in the BEACON study, where the drug was stopped for safety reasons, there was no benefit on ESRD, granted they

only had 7 months and the study was stopped earlier, but there were 96 events. We're also being asked to believe that increased albuminuria, which is a risk factor, cardiovascular as well as progression of renal disease, in this situation is not a negative thing.

On top of all hopes, kind of background data, we're given some information from the actual trial itself; again, their repeated use of the NKF, FDA, EMA data I think is somewhat flawed. First off, I would completely ignore the exploratory analysis of the greater than 30 percent decline of GFR. That analysis would require thousands of patients over many years to be valid because of the acute effect. The devil is really in the details of that report.

The 0.75 mL per minute change over two years being a benefit would only be true if it was consistent over a very long period of time, which I don't think we have confidence in.

The greater loss of GFR in the first year compared to placebo, I do not think the slopes are

adequately powered; it's troubling. You could make an argument that this is just a pharmacodynamic acute effect. Give it to them right before they hit ESRD as a one-time thing and avoid the toxicity, and you get just a little boost. Maybe that would happen. I doubt it. It's a possibility. So I have trouble feeling strongly that this data, the totality of data before us, actually supports the claim.

Let me see if there are any other hands.

Dr. Mendley?

DR. MENDLEY: Thank you. This is Susan Mendley.

The question about the available data, I'd also like to point to the quality of the data. I find the concerns about the adequacy of the washout phase at 28 days truly compelling, considering the gene expression augmentation that's postulated. But I was also very concerned by the large fraction of the final off-treatment measurements, which were obtained at 14 days, or between 14 and 28 days, and that further undermined, in the sensitivity

analysis, the robustness of their findings, and the fact that participants who were only treated in year 1 were not included in the final analysis even though they could have been. They were dropped even though there was an off-treatment available time point.

So those things draw me back to the available data, and I'm concerned whether the available data is really the data we should be relying on. Thank you. That's all.

DR. LEWIS: The FDA might have missed my question. One of our panel had a question with regard to the fact that the patients with Alport's are not all one patient population and that there may be a risk-benefit that is different for a subset of patients, like those with more rapid disease, those with, I guess, lower GFRs. And I wondered if the FDA had done any analysis of the benefit of treatment compared to placebo in people with more [indiscernible] or lower GFRs.

DR. THOMPSON: Dr. Lewis, this is Aliza Thompson. Thank you for repeating your question.

I think for the FDA team, a key issue was the off-treatment period and its adequacy. So I think given the larger concerns with that issue, as well as some of the other issues with the data in terms of how much data we had, et cetera, the robustness of the primary endpoint findings, we didn't do a whole lot of subgroup analyses.

Also, I just want to highlight that this was already a very small population to begin with, understandably so, because this is a rare disease, but it is a good question.

DR. LEWIS: Thank you, Dr. Thompson.

I forgot to put my hand down.

Dr. Cook, do you have a another comment?

DR. COOK: No, actually I have a question maybe for the nephrologists. I forgot to say my name. This is Thomas Cook.

During the open public session, there were a lot of patients who said they took this drug and then they felt a lot better. Their function was better. Is that explainable by this change in GFR or is there some other mechanism by which this drug

might actually make them feel better? Thank you.

DR. LEWIS: Dr. Gorman?

CAPT GORMAN: I had a question about that, too. That's a good point, and I was struck by that as well. I'm not sure that the absolute number of the increase in GFR would make you feel any better. There are other things that go with chronic kidney disease, like acid-base status that might change your appetite or make you feel lousy.

But I was struck -- and this to deal with the design question that wasn't pacifically asked, is that so many people said they had great energy, and they could work again, go to school again, achieve things in sports, but that was never an outcome. The health-related quality of life of which there are good measures and patient-reported outcome measures, again, this study was done a while ago before they became maybe more popular or more likely to be included in studies, but that struck me as a disparity, that really there is no data on that, and that most of the patient and family member testimonials all talked about that.

So I don't think the data that showed -- I don't think, as a pediatric nephrologist, that the minute changes in GFR would correspond to that and, certainly, there was no comparison between placebo and the control. We didn't hear from a lot of the placebo folks.

So I would discount that, and I wish if there was ever a study again on this or other things, that patient-reported outcome measures and quality of life are included. Over.

DR. LEWIS: I think they did actually have something like that, and I'm flipping through it because I also discounted it. But I think they did measure some kind of quality thing.

Dr. O'Connor?

DR. O'CONNOR: Chris O'Connor. [Inaudible], PGA [ph], but I did find there delta between drug and placebo to be modest, the testimonies that were heard.

CAPT GORMAN: Greg Gorman. Can you show me that data? I'd love to see that. I do not see that reading through the briefing materials.

DR. LEWIS: I don't know if we want to take the time to find it because I think -- page 70, Patient Global Impression of Change, PGIC. So they did do something, and the p-value, the difference between the groups was 0.39.

DR. MENDLEY: May I --

DR. LEWIS: I don't know anything about the validity of that thing.

I'm sorry. I didn't hear who spoke.

DR. MENDLEY: I apologize. May I contribute to that conversation you're having right now? I think it's worth --

DR. LEWIS: Who's asking --

(Crosstalk.)

DR. MENDLEY: This is Susan Mendley.

DR. LEWIS: I'm sorry. Who's asking --

DR. MENDLEY: This is Susan Mendley.

DR. LEWIS: Yes. Sorry. I didn't know who was saying that. Sorry.

DR. MENDLEY: I think we must recognize that this study was not blinded. Once patients saw their GFR improve, they were heartened. They saw a

great benefit to that. I don't think we should overlook that experience. All of the patients who spoke to us told us how much of a benefit they perceived from the increase in their eGFR, which came about because they are knowledgeable about and are very attuned to their laboratory findings. So I think we should interpret their experience in that light. Thank you.

CAPT GORMAN: Great point. Great point.

DR. LEWIS: Thank you, Dr. Mendley.

Mr. Conway?

(No response.)

DR. LEWIS: Mr. Conway, you're still on mute.

MR. CONWAY: Thank you very much, Doctor.

I just wanted to take a second to reinforce the point that Dr. Mendley just made, which is not to be discounted, that patient insight data is highly valuable. You have an organization -- two national organizations -- that took the time in 2018 to gather those insights.

I know this does not pivot on that, but I

don't think we should devalue it whatsoever. I do think that in terms of much of the data that's been presented, it's lacking for some of the points that Dr. Palevsky has made quite clearly, and also Dr. Mendley. But this is 2021, and the weight of patient insight data and patient-reported outcome data is critical.

I hope that every applicant who's listening to this conversation today understands that, and understands that the design of trials and the data produced is not just important for the application, but it's important in terms of practical applications and insights for people who are struggling to get an additional month, a year, or two years, or three years of functionality, especially at a younger age. Thanks.

DR. LEWIS: Thank you.

Dr. Gorman, is your hand up because you have another comment?

CAPT GORMAN: No, my fault. I'll lower it.

DR. LEWIS: No problem.

Okay. I'm going to try to summarize this.

I appreciate, Dr. Cook, our statistician, for sharing with us the importance of the sensitivity analysis is to assess whether there's an alternate explanation for the proposed positive effect other than slowing the progression of the disease. He argued that his impression of the sensitivity analysis is that it was likely that there were other explanations.

I think we, again, heard that it may have been valuable to look at the patients. I think we've heard that both based on the genetic basis of their disease, as well as the level of GFR which they were in, in the trial.

Another comment was that it was a surrogate outcome, and it was being used to see if the long-term outcome would be improved. The difference between the control and the bardoxolone grow is narrow, and between year 1 and year 2 it became even more narrow, so that was a big concern.

I think on top of that, another one of the comments was that the missing data, the data that was collected earlier not including patients with

very small [inaudible], who were only receiving drug in year 1 -- in the year 2 analysis, bringing into some question the strength of the results.

I was just making sure I didn't miss anything.

I think the last comment to summarize was, very respectful of all are outside speakers and also very empathetic -- very empathetic, I must say, on myself personally -- to their stories that knowing that your GFR is higher is likely going to impact your feeling of wellbeing.

In future studies, very sophisticated ways of measuring patients feeling better would be recommended. I think it was also mentioned on more than one occasion that the small difference in GFR that is being seen would be unlikely to have a very strong clinical benefit at that moment.

With that, I'm going to go on to discussion question number 3, and first read the question.

Discuss bardoxolone methyl's safety profile.

Do bardoxolone methyl's effects on albuminuria and blood pressure raise concerns about

its long-term efficacy and safety in patients with Alport syndrome?

What the implications of bardoxolone methyl's effect on body weight for pediatric patients?

Does anyone have any issues or questions about the wording of the question?

(No response.)

DR. LEWIS: I don't see any hands raised. So if there are no questions or comments concerning the wording of the question, we will now open the question to discussion.

Ms. Alikhaani?

MS. ALIKHAANI: Thanks. Yes. Hi. Jacqueline Alikhaani here. I myself am a rare disease patient, and there are a lot of disparities in rare disease research. It's complex, it's difficult to find, so I really applaud the sponsor for taking on Alport's.

I'm very sympathetic to the patients, and the family members, and caregivers dealing with this rare disease, and I really think we need newer

and better models for doing rare disease research. We haven't made inroads into that area like I think we need to.

So I've been listening very carefully to everything, with particular interest to all of the discussion between all of the different medical experts and healthcare consumers here today, and I've heard and learned about what are clearly some very challenging research questions, and issues, and outcomes about bardoxolone, and these issues just can't be ignored.

I know that kidney failure is a very bad disease. My mother had it. She was on dialysis, and she died from kidney failure just a few months ago, and my son's friend also has it. It's a devastating disease with a lot of disparities and care for lots of people, particularly for African Americans -- I'm African American -- and other ethnic groups, and women, and traditionally underserved in general, including transgender people and many others, possibly.

So I know what it's like for patients, and

family members, and caregivers living with a rare disease like Alport's, but I think we owe a duty to all healthcare consumers to do our best to make sure that therapies are safe and effective as possible for everyone. This is what evidence-based medicine and healthcare is all about, as we all know, and this is what we all count on the FDA to do.

Really, I was very hopeful today about the potential for bardoxolone to help healthcare consumers dealing with kidney disease and Alport's, but after hearing from all the medical experts here today and reviewing the clinical trials' outcomes myself, I'm just very discouraged by the bardoxolone clinical trial outcomes.

It's apparent that there are a lot of serious discrepancies with the research data. There's missing data, excluded data, negative side effects, adverse event issues like heart failure, high blood pressure, long-term kidney function problems, and other negative outcomes that we've all discussed today.

These issues were discussed throughout the research process with the FDA, and I just wish that the sponsor had more diligently worked with the FDA to meet the safety and efficacy requirements that meet the evidence-based standards for health care. We have to do that. As bad as we want to help patients who are having disparities in care and quality-of-life issues living with bad diseases and rare diseases, we still have to meet evidence-based standards put in place to protect all healthcare consumers.

So I wish I could have more positive things to say about bardoxolone, but I don't. So I'm very disappointed about it. Thank you.

DR. LEWIS: Thank you very much.

Dr. Merz?

(No response.)

DR. LEWIS: Dr. Merz, if you're on mute.

DR. BAIREY MERZ: Yes. Noel Bairey Merz. It just always takes a second.

I have another question. To help us understand the increased urinary microalbumin,

which is very well validated and informed me during the prior discussion, how well validated or accepted is the megalin expression hypothesis that at least I heard about first time today? It's a question to nephrologists again. Sorry.

DR. LEWIS: Do one of the nephrologists want to take that question on?

DR. PALEVSKY: Paul Palevsky. I can jump in. I'm not sure that we really have a megalin hypothesis. The company has indicated that the drug interferes with megalin expression. We are constantly having protein crossing the glomerular basement membrane, even albumin, and it is reabsorbed in the proximal tubule.

Most of the proteinuria that we worry about is due to increased glomerular permeability and leak of albumin. The question that I was posing when I brought this up was what data did the company actually have as to whether the change in albuminuria was due to change in glomerular function or change in tubular function? And as I understand, we don't know what the mechanisms of

the proteinuria here is.

I would suspect that there is at least a portion that is due to increased glomerular albumin loss given the increase in GFR, and we know from other circumstances that albuminuria correlates with risk of progression.

DR. BAIREY MERZ: Thank you.

DR. LEWIS: Thank you.

Dr. Butler?

Dr. Nachman, do you want to comment on Dr. Merz's question?

DR. NACHMAN: Patrick Nachman here. I was going to add, as you alluded to earlier, Dr. Lewis, that albuminuria and proteinuria is a marker of bad outcome, and not just for the kidney. And we don't fully understand what in proteinuria is a marker of poor outcome; at least I don't know whether it makes a difference whether the albumin comes from the glomerulus or from decreased reabsorption. We know that in different diseases, different degrees of proteinuria have different impacts, and as Dr. Lewis said, it affects cardiovascular health as

well, and we don't understand why.

So the fact that this could be from megalin or not from megalin, at least for me, doesn't help me that much in feeling more reassured or less reassured. That's my comment. Thank you.

DR. LEWIS: Thank you.

I think we'll move on to Dr. Butler.

DR. BUTLER: Thank you, Dr. Lewis. Javed Butler here.

I just want to highlight quickly that for a trial that had relatively younger patients and eGFR less than 30 was excluded, and so was clinical significant cardiovascular disease and elevated BNP, the elevation of BNP signal is of concern for future development of heart failure or cardiovascular outcomes.

This is particularly noticeable to me as the GFR goes up, and if anything, with a higher GFR, you would expect the values to go even further down and not up. Thank you.

DR. LEWIS: Thank you.

Dr. O'Connor?

DR. O'CONNOR: Thank you, Dr. Lewis.

I just would reiterate what Dr. Butler said, and given the modest side of CARDINAL, we have to lean in on BEACON. And the safety signals of heart failure and cardio issue events is worrisome. They surrogate marker of natriuretic peptide, UACR, going in the wrong direction, and then blood pressure in the trial is worrisome for [indiscernible].

I guess one of the questions would be, part of the mitigation strategy for this drug is the GFR across 30, and if an Alport syndrome patient developed diabetes, the drug would then have to be abandoned.

DR. LEWIS: Dr. Mendley.

DR. MENDLEY: Thank you. This is Susan Mendley. I'm going to talk to you about question 3b, which is the implication -- so if you're still discussing 3a, I'm happy to wait my turn.

DR. LEWIS: No, no. Go right ahead.

DR. MENDLEY: Okay. I think that what

you're seeing is the suggestion of a safety signal in the adolescent patients with the flattening of age-expected weight gain and the potential that this will over time affect statural growth. And the idea that you would begin this at the age of 12 would really move through the ages of maximum final growth and development.

So I would think that children would need to be treated within the context of a clinical trial in order to get complete longitudinal data collection. I don't think, based on this, it would be sufficient to say that pediatric nephrologists will pay attention to it. I'm sure they will, but I don't think we'll learn enough from that. Thank you.

DR. LEWIS: Thank you.

Mr. Conway?

MR. CONWAY: Thanks, Doctor.

I just want to give my comments real quickly to reinforce what Dr. Mendley just said and also what Dr. O'Connor has raised, and that is as somebody who's managed kidney disease since I was

15, looking at this information and understanding the interactions with other organs, I would absolutely be concerned about it as a patient consumer and as a parent, and it gives me serious pause. Thank you.

DR. LEWIS: Thank you very much.

Dr. Palevsky?

DR. PALEVSKY: With my prior comments about the albuminuria, I'm still concerned about the potential long-term implications. In terms of blood pressure, I think those effects could probably be mitigated, although eventually requiring more aggressive antihypertensive therapies. I share the concerns that have been raised about the increase in BNP, especially since GFR went up, and we normally expect BNP to be lower with higher GFRs rather than higher.

DR. LEWIS: Thank you.

I would remind people to put their hands down.

Dr. Rossert or Dr. Kasper, do you guys have any comments?

DR. ROSSERT: Thank you, Dr. Lewis. This is Dr. Rossert, industry representative. I don't really have a comment, except to remind the committee, and it was mentioned before, that there's no such thing as a perfect study, and we always need to be careful when looking at the design of the study in retrospect; otherwise, I don't have any comment. Thank you for asking.

DR. LEWIS: Thank you.

Dr. Kasper?

DR. KASPER: From my standpoint, the risk-benefit ratio here looks to be weighed towards risk, and that's acknowledging the fact that the poignancy of the public comments were highly influential, and certainly I have great empathy for all of them going through all this.

DR. LEWIS: Thank you very much.

I don't see any hands up, so I'm going to go ahead and summarize.

We began and [inaudible] speak to us today. However, our charge is to make sure that we provide them with a drug that is effective and is safe. I

think the committee on this last question had questions about safety. The increase in albuminuria, generally, I think many people on the community felt a negative prognostic factor, which I think does reflect the nephrology community feeling about it, and for that matter, the cardiology community since it is a risk factor for cardiovascular disease as well.

I think there was some concern about the megalin interpretation by the sponsor and whether that interpretation was adequate to alleviate the concern of an increase in albuminuria. In addition, I think our cardiology colleagues had a concern about the elevation of BNP and made the very good point that that was despite the fact that this was a relatively high GFR population and that the BNP went up despite the fact that the GFR went up; and then combined with the BEACON data showing increased heart failure and BNP being a surrogate, that seemed going in the wrong direction in the CARDINAL, that was a concern.

How would you [inaudible] the BEACON data,

the fact that if you have a GFR less than 30 and/or a diabetic, the drug might need to be abandoned; diseases do co-exist.

The adolescent concern for flattening of the growth curve was expressed and that children would have to be studied again [inaudible] to assuage that concern in terms of its impact on growth. At least one person felt that the blood pressure effects seen in BEACON and potentially present, although not actually statistically significant I guess in CARDINAL, could be mitigated, but the albuminuria effects could not be.

Myself often thinking of how to design trials, there is no perfect study. I agree completely, and it's always easy to look back at studies critically. However, I think the majority of the committee felt that this study did have places where the design could have better informed us, and also not suggested, harm instead of good.

I think we will now go to the next question, which is a voting question. Dr. Moon Hee Choi will provide the instructions for the voting now.

DR. CHOI: Question 4 is a voting question. 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 the 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 which is the round circular button in the window that corresponds to your vote, yes, no, or abstain. You should not leave the "no vote" choice selected.

Please note 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. Thereafter, 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 as you did, if you want to, however, you should also address any subpart of the voting question, if any.

Are there any questions about the voting process before we begin?

(No response.)

DR. LEWIS: I don't see any hands up. I will read the voting question.

Does the provided evidence demonstrate that bardoxolone methyl is effective in slowing the progression of chronic kidney disease in Alport syndrome and that its benefits outweigh its risks?

If you voted yes, provide your rationale. If you voted no, provide your rationale and provide recommendations for additional data and/or analyses that are needed to support approval.

Are there any issues or questions about the wording of this question?

(No response.)

DR. LEWIS: I don't see any hands up. If there are no questions or comments concerning the wording of the question, we will now begin the voting on question 4.

DR. CHOI: 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.)

DR. CHOI: The vote results are displayed. I will read the vote totals into the record. 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 want to. However, you should also address any subparts of the voting question, if any.

For the record, we have zero yes, 13 no, and zero abstentions.

(Pause.)

DR. CHOI: Dr. Lewis, are you able to see my message?

DR. LEWIS: Sorry. I think you muted me, and I didn't realize it.

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. Palevsky.

DR. PALEVSKY: Paul Palevsky. I voted no. I think that we've already covered the reasons. I would want to see at least one other marker of kidney function besides creatinine to know whether the changes in eGFR were due to the effects on generation given the associated weight loss that was seen, and we need to have data with a larger time off of treatment to be able to see the sustained effect of the medication after the acute pharmacodynamic effect has worn off.

DR. LEWIS: Thank you.

Dr. Nachman?

DR. NACHMAN: Patrick Nachman. I voted no.

I want to say, first of all, thank you to the patients and caregivers for your testimonials. They really matter tremendously is what I want to say.

In addition to the comments of Dr. Palevsky, I worry about the generalizability of the data presented, especially for patients who genetically are at greater risk of progression. Not only does data not show benefits, but what little data there is suggest that there is no benefit.

Having said that, I am sensitive to the idea that there might be a group of patients with some form of Alport syndrome that could benefit from this, and I think that parsing this out, with caveats about study design and outcome measures, I think would be worth looking into in the future. Thank you.

DR. LEWIS: Thank you.

Dr. Merz? And please say your name and how you voted.

DR. BAIREY MERZ: Noel Bairey Merz, and I did vote no. I want to commend not only the

patient volunteers who participated in the trial, but I commend the sponsor for taking on an orphan disease with a novel technology. It is very hard. We all recognize how hard it is to do not only small trials, but then small trials in a pandemic, and then small trials in patients scattered around the globe.

Nevertheless, I voted no not because of lack of efficacy. They met the primary outcomes as it was designed -- it's not a perfect trial -- but I am very concerned about the elevation in the UACR. Hearing that it is a potent predictor, and understanding that the target audience is relatively young, I think that's an unacceptable safety signal. I would encourage the company to explore where there may be more benefit than risk. Thank you.

DR. LEWIS: Thank you.

Dr. Mendley?

DR. MENDLEY: Susan Mendley, and I voted no. I want to say that I'm very sensitive to the patients' and parents' perception that any

improvement in estimated GFR represents hope, and I recognize the emotional challenge of kidney disease in young patients who have so much life ahead of them, so I think we have more work to do.

I agree with the comments that were made by others and would only ask that in a subsequent study there be a larger number of adolescent patients because I am concerned about the effects on weight gain and statural growth, and would want to, of course, see a benefit in GFR as well. Thank you.

DR. LEWIS: Ms. Alikhaani?

MS. ALIKHAANI: Yes. This is Jacqueline Alikhaani. I voted no, and I agree with the feedback from all of the medical experts on the call, from all of the doctors and scientists. My primary concerns are excluded data, excluded patients, missing data, trial design, very limited to no benefit, and the adverse events.

DR. LEWIS: Thank you.

Dr. Cook?

DR. COOK: Thomas Cook, and I voted no, and

I think it's already all been said. Thank you.

DR. LEWIS: Julia Lewis. I voted no. I think that the totality of data, including the preclinical, the data from diabetics, and the data within the CARDINAL study, is not sufficient to be assured that we would be providing patients with an effective therapy that would not actually cause harm.

Dr. O'Connor?

DR. O'CONNOR: Dr. Chris O'Connor. I voted no. Based on the totality of information, I think there was unclear efficacy on progression of disease with this drug, and I was concerned about the safety profile using the totality of data from BEACON and CARDINAL, particularly cardiovascular safety and the BNP and AUC elevations.

I want to commend the sponsor for taking this on, and I think there is a path forward, so I'd encourage them to keep going. And I want to especially thank the patients who participated in the clinical research. Thank you.

DR. LEWIS: Thank you.

Dr. Gorman?

CAPT GORMAN: Dr. Greg Gorman. My vote was no. My statement, it's unfortunate that this potentially helpful medication had a pharmacodynamic effect in the primary outcome and the GFR measure used, however, that GFR estimate isn't perfect. The length of the washout period was of uncertain sufficiency, and despite heroic statistical methods to discern the true effect on GFR from among the noise of that pharmacodynamic effect and measurement error, I wasn't convinced that bardoxolone methyl slowed progression of chronic kidney disease.

I might have given it the benefit of the doubt, given the orphan drug status and the lack of any Alport specific therapies, as poignantly detailed by our public commenters, but that's nullified by the unintended effect of the proteinuria and increased blood pressure, two conditions that have overwhelming evidence that linked them to progression of kidney disease. And even if the applicant could demonstrate

statistically significant but clinically tiny renal protective effects, it might be nullified by the concurrent proteinuric and hypertensive effects over the long term. Even a two-year study would not discern.

I agree that the weight loss in a few adolescents is a signal that would argue against approval in the adolescent range, as been specified. Future studies require more numbers of young and adolescent patients, and future studies should also capture quality-of-life and patient-reported outcome measures better. That's my statement.

DR. LEWIS: Thank you, Dr. Gorman.

Dr. Butler?

DR. BUTLER: This is Javed Butler, and I voted no for the reasons that have already been discussed. I would like to thank both the patients that participated in the trial and the sponsor for taking this trial on.

A very important question, there are signals that are really encouraging, but the net is not

currently explainable in terms of the risk. However, if you look at the epidemiology of the disease, an incredibly distinct minority in single digits participated in this trial, and with no other options, I truly hope that the sponsor plans to do a second trial. And if you get the same signal, especially enriching adolescent patients and those with a lower GFR, then the risk-benefit may tilt in an opposite direction if we have all of these issues related to the benefit being questioned, if they are answered both mechanistically and with better data collection. Thank you.

DR. LEWIS: Thank you.

David?

DR. MOLITERNO: Thanks, Dr. Lewis.

David Moliterno. I voted no, and I really appreciate the excellent comments from all of you. I think you did a great job. I, too, felt this was an emotionally charged meeting and I, like Dr. Gorman, wanted to give them a pass but just couldn't, with the totality of information, the

number of missing patients, and some of the negative signals that bothered me, that we might be trading one benefit for two problems.

So I do applaud the patients and the sponsor, and I hope that there is a pathway forward in the future for these patients.

DR. LEWIS: Thank you.

Dr. Kasper?

DR. KASPER: Ed Kasper. I voted no. I think that the FDA's charge is to choose for us safe and efficacious drugs, and it's not clear to me that this drug falls into either of those categories. However, I recognize the large amount of work that has been done, the patient volunteers, the public who made comments tonight, and the sponsor for taking on an orphan drug. This is a desperate disease, and it just points to how much more needs to be done going forward. Thank you.

DR. LEWIS: Thank you.

Mr. Conway?

MR. CONWAY: Thank you. Paul Conway. I voted no based on efficacy and safety, safety

first. It was disappointing to do so. I understand the courage that's been demonstrated both by the patients, the public speakers, and the company -- the applicant -- for going into the field of rare disease. It's not easy.

I think that patients have demonstrated a much higher risk tolerance than many people can understand, but what comes with risk tolerance and our leaning forward as a patient community is the need for data to make good decisions on, and I was not convinced based on that.

To the patients in particular I would say, I know what it's like to see a parent look at a diagnosis. I've been there, and it's tough. But I hope that the patients and the applicant keep going because I think there is some optimism here and a path forward. Thank you.

DR. LEWIS: Thank you.

I think that I will now try to summarize. I think the overwhelming thing to say in the summary is that all of us on this committee are emotionally empathetic to the tragedy of this disease as a rare

disease, particularly since its attacks are young people with so much life in front of them. And it's not because of anything they've done; it's a genetic disease.

We commend the volunteers [inaudible]. Without them, we would never advance medicine. We commend the sponsor who took on a rare disease, a very challenging study to do, or design, given the rarity of the disease and also some of the characteristics of the drug that made the study hard to design.

I think many of the speakers who voted no, the panelists who voted no, are hoping that the sponsor will not give up hope but will focus perhaps on a younger population with a more rapid decline in GFR, where maybe other kinds of more convincing outcomes could be utilized.

Overall, the questionable efficacy was troubling due to things like excluded data, differential discontinuation, the question of whether there was a long enough off-drug period to actually demonstrate a benefit of the drug. Also,

that might have been outweighed if there weren't also troubling safety signals with increased albuminuria, so increased blood pressure and the potential for increased cardiovascular events with the BNP signal, which translated into events in the BEACON trial. It's unfortunate that the drug, which has a lot of theoretical benefits for sure, that its hemodynamic effect makes it more difficult to study and demonstrate.

I'll stop there, and before we adjourn, are there any last comments from the FDA?

DR. THOMPSON: Hi. This is Aliza Thompson. I just want to express our extreme gratitude to the AC members for helping us with this very challenging issue. I also want to thank the sponsor for their important work in this area.

First and foremost, I want to thank the patients for coming forward to speak and for working with us in the past, and hopefully working with us in the future to find a path forward for safe and effective treatments for this truly horrible disease.

Adjournment

DR. LEWIS: I will add, again, thanks to all the patients who took time to speak to us today and the volunteers for the study. I also want to thank the FDA and their staff. I think they clearly put in a lot of thought, a lot of work, and probably a lot of heart and angst into their comments in preparation. They were extremely helpful to the panel.

I want to thank the sponsor for taking this on. Again, I think you had a very, very challenging task at hand, and I hope that you will take into consideration the comments of the panel about going forward with perhaps a different patient population and a different study design.

We will now adjourn the meeting. Thank you all.

(Whereupon, at 5:13 p.m., the meeting was adjourned.)