FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ARTHRITIS ADVISORY COMMITTEE (AAC)

Friday, October 23, 2015

8:00 a.m. to 3:19 p.m.

FDA White Oak Campus

Building 31, The Great Room

White Oak Conference Center

Silver Spring, Maryland

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

8:00 a.m.

Call to Order

Introduction of Committee

DR. NEOGI: Good morning. I'd first like to remind everyone to please silence your cell phones, smartphones, and any other devices if you have not already done so. I would also like to identify the FDA press contact, Eric Pahon. If you are present, please stand.

My name is Dr. Tuhina Neogi. I'm the acting chairperson for today's Arthritis Advisory Committee meeting. I will now call this meeting of the Arthritis Advisory Committee to order. We'll start by going around the table and introducing ourselves. I'll ask that everyone state their name, their institution or affiliation and specialty or area of expertise. We'll start down on the right.

DR. LEFF: I'm Richard Leff. I'm a rheumatologist and an independent consultant in the pharmaceutical industry.

DR. BERNEY: I'm Seth Berney. I'm chief of

rheumatology at the University of Arkansas for Medical Sciences.

DR. OLIVER: Alyce Oliver, Medical College of Georgia. I'm program director for the rheumatology fellowship and ambulatory medical director.

DR. GUALTIERI: I'm Lisa Gualtieri. I'm in the Department of Public Health and Community Medicine at Tufts University School of Medicine.

MS. CHAUHAN: Cynthia Chauhan, patient representative.

DR. BECKER: I'm Mara Becker. I'm a pediatric rheumatologist from Children's Mercy in Kansas City. My subspecialties are obviously pediatric rheumatology and clinical pharmacology.

DR. REIMOLD: I'm Andreas Reimold, a rheumatologist at the Dallas VA Medical Center and the University of Texas Southwestern Medical Center.

DR. JONAS: I'm Beth Jonas from the University of North Carolina in Chapel Hill. I'm a rheumatologist. I'm the director of rheumatology training there.

DR. CAPLAN: My name is Liron Caplan. I'm an

associate professor at the University of Colorado and the Denver VA. And my interests are in axial spondyloarthritis and pharmacoepidemiology.

DR. BAUTISTA: My name is Philip Bautista. I'm the acting designated federal officer for this committee.

DR. NEOGI: I'm Tuhina Neogi. I'm from Boston University School of Medicine, and I'm a rheumatologist and epidemiologist.

DR. MILLER: Donald Miller, professor of pharmacy practice at North Dakota State University.

DR. TCHETGEN TCHETGEN: Eric Tchetgen Tchetgen, professor of biostatistics and epidemiologic methods, Harvard University.

DR. DELOST: Kort Delost, community pharmacist, Prescriptions Plus Pharmacy, Bountiful, Utah.

DR. KABOLI: I'm Peter Kaboli. I'm the chief of medicine at the Iowa City VA Medical Center and a general internist and expertise in pharmacoepi and drug safety.

DR. SMITH: I'm Bob Smith. I'm a podiatrist

and pharmacist. And currently I'm working for DOS in Iraq.

DR. LEVIN: Greg Levin, acting statistics team lead, FDA.

DR. NEUNER: Rosemarie Neuner, rheumatologist, Division of Pulmonary, Allergy, and Rheumatology Products, FDA.

DR. YIM: Sarah Yim, Associate Director for Rheumatology in the Division of Pulmonary, Allergy, and Rheumatology Products of FDA. And I'm an adult rheumatologist.

DR. CHOWDHURY: I'm Badrul Chowdhury. I'm the division director, Division of Pulmonary, Allergy, and Rheumatology Products.

DR. PARKS: Mary Parks, deputy director, Office of Drug Evaluation II.

DR. NEOGI: Thank you.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's 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, the 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.

Now, I'll now pass it on to Phil Bautista, who will read the Conflict of Interest Statement.

Conflict of Interest Statement

DR. BAUTISTA: The FDA is convening today's meeting of the Arthritis Advisory Committee under the authority of FACA of 1972. With the exception of

industry representative, all members and temporary voting members of this committee are special government employees or regular fed 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 USC 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 Section 208, Congress has authorized FDA to grant waivers to special government employees and federal regular employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussion 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 USC 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 NDA 207988 for lesinurad oral tablets, submitted by Ardea Biosciences, Incorporated, for the treatment of hyperuricemia associated with gout, in combination with a xanthine oxidase inhibitor. This is a particular matters meeting during which specific matters related to Ardea Biosciences' NDA will be discussed.

Based on the agenda for today's meeting and all financial interests reported by 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 may have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Richard Leff is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Leff's role at this meeting is to represent industry in general and not any particular company. Dr. Leff is an independent pharmaceutical consultant.

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. NEOGI: We will now proceed with the FDA's introductory remarks from Dr. Sarah Yim.

FDA Introductory Remarks - Sarah Yim

DR. YIM: So I can't see a bunch of you. I'm

assuming you can't see me either.

(Laughter.)

DR. YIM: Thank you. I should have brought a stool.

Good morning. I'd like to welcome you to the Arthritis Advisory Committee meeting for the new drug application 207988 for lesinurad. As I mentioned before, my name is Sarah Yim, and I'm associate director for rheumatology in the division.

So all the rheumatologists know this. Many of you may know this also, that hyperuricemia is a disorder of the normal balance between uric acid production, which is largely from purine metabolism and uric acid excretion, which occurs via renal excretion, and to a lesser extent gastrointestinal excretion.

As an organic anion, uric acid needs transporters to cross the plasma membrane. In fact, 90 percent of the uric acid filtered through the kidneys is reabsorbed in the proximal renal tubule via membrane transporters, especially urate transporter 1 or URAT1.

Uricosurics such as probenecid increase

urinary uric acid excretion by inhibiting membrane transporters, and lesinurad also uses this mechanism. Xanthine oxidase inhibitors such as allopurinol and febuxostat work by reducing uric acid production. Uricase enzymes such as pegloticase work directly to break down uric acid stores.

As additional context, the currently approved urate-lowering therapies for gout are summarized in this table. The American College of Rheumatology treatment guidelines indicate xanthine oxidase inhibitors, which currently include allopurinol and febuxostat, are first-line therapy.

Allopurinol is approved at doses ranging from 100 to 800 milligrams per day. Doses greater than 300 milligrams should be divided into twice-daily administration. At the most commonly used dose of 300 milligrams daily, the mean serum uric acid decrease of 2 to 3 and a half milligrams per deciliter has been observed. Safety concerns with allopurinol include hypersensitivity reactions, severe cutaneous reactions, and gastrointestinal symptoms.

Febuxostat is approved at 40 to 80 milligrams

daily. At the 80-milligram dose, a mean serum uric acid decrease of 4 and a half milligrams per deciliter has been observed. Safety concerns with febuxostat include liver enzyme elevations, rash, and a possible cardiovascular safety risk.

Combination therapy with xanthine oxidase inhibitor and a uricosuric agent is considered appropriate when the serum urate target has not been met by appropriate dosing of a xanthine oxidase inhibitor. Currently, probenecid is the only uricosuric approved in the U.S. Probenecid inhibits a number of organic anion transporters, including URAT1.

The approved dose range is 500 to 1,000 milligrams twice daily and in light of its half-life of 3 to 8 hours. Although probenecid is an old drug and there's not a lot of modern data for it, in one recent study by Pui et al., at a mean dose of 1.3 grams per day, the mean serum uric acid decrease for probenecid was 0.17 millimoles per liter or approximately 2.9 milligrams per deciliter. Safety concerns with probenecid include nephrolithiasis and also drug-drug interactions.

Finally, pegloticase is the only uricase product approved for the treatment of hyperuricemia of gout. It is an infusion of 8 milligrams intravenously given every 2 weeks. Because uricases are derived from foreign proteins, pegloticase is highly immunogenic and is associated with anaphylaxis, infusion reactions, and loss of efficacy over time.

It is also associated with worsening of congestive heart failure. However, before immunogenicity results in a loss of efficacy, it is highly effective, dropping serum urate by almost 7 milligrams per deciliter on average.

Like probenecid, lesinurad's mechanism of action is via inhibition of URAT1. In vitro, lesinurad also inhibits OAT1, OAT3, and OAT4, although in vivo, this is limited to OAT4.

The proposed dose of lesinurad is 200 milligrams once daily in combination with a xanthine oxidase inhibitor. The maximum concentration of lesinurad is reached at 1 and a half to 2 hours, and its half-life is approximately 5 hours. With once-daily dosing, urinary uric acid excretion is

increased for about 12 hours with a maximum excretion occurring during the first 6 hours. Maximum lowering of serum uric acid is at 6 to 8 hours post-dose with a daily variation in serum uric acid of about 0.4 milligrams per deciliter.

Despite a half-life and mechanism similar to probenecid, only once-daily dosing was studied in the entire clinical development program. Doses below 200 milligrams were not evaluated in phase 2 or phase 3 studies because they did not result in sustained serum uric acid reduction over 24 hours.

As you will hear later, the efficacy and adverse effects associated with lesinurad appear to be dose dependent. This suggests that optimization of the dose and dosing interval could be important in optimizing the risk-benefit profile of this product.

A design of phase 3 trials in the lesinurad clinical development program was consistent with a typical trial for URAT-lowering therapies; that is, the patient population has hyperuricemia associated with gout but does not necessarily have an active gout flare or may or may not have a flare during this study.

The primary endpoint is the proportion of patients achieving target serum uric acid usually below 6 or 5 milligrams per deciliter. This is a surrogate endpoint for direct measures of patient benefit, which would be expected with long-term control of hyperuricemia.

Direct measures of patient benefit are often included as secondary endpoints in these studies and include things like reduction in flare rate, resolution of tophi and their incumbent complications, and in patients with active arthritis, outcomes such as reduction of pain or improvement in function.

As you listen to the presentations today, we ask that you keep in mind three considerations. First, the average treatment effect for the proposed dose of 200 milligrams on a background of xanthine oxidase inhibitor was an average decrease in serum uric acid of approximately 1 milligram per deciliter at month 6. Efficacy for clinical outcomes such as flare, tophus reduction, and physical function were not demonstrated during the controlled period of the studies.

Second, there are dose-dependent safety

concerns. With lesinurad 400 milligrams, there was an increase in adverse events, serious adverse events, serious an non-serious renal adverse events, and major adverse cardiovascular events. With lesinurad 200 milligrams, there was a smaller increase in adverse events, renal adverse events, and serum creatinine elevations.

Because of the dose-dependent safety concerns, appropriate dose and dosing interval selection is potentially more important. The 200-milligram dose proposed for marketing is close to the 400-milligram dose, not proposed for marketing due to safety concerns.

The plasma exposure of the 200-milligram and 400-milligram doses are overlapping. While this is not unusual, our concern is that differences in the relative safety profile between the two doses seen in the trials may not be as distinct if the product is approved and used in a broader population of gout patients. Also, given the PK and PD of the product, a more frequent dosing interval may have allowed for more efficacy at a lower nominal dose.

Later this afternoon, we'll be asking for the Arthritis Advisory Committee's thoughts on the efficacy of the 200-milligram dose and whether it's clinically meaningful; the safety of lesinurad, especially with respect to renal and cardiovascular risk; the dose-dependent safety concerns and whether the dose and dosing interval selections are adequate; then the voting questions on the adequacy of the efficacy, the adequacy of the safety, and the overall approval recommendation.

As per the Code of Federal Regulations, this advisory committee meeting is being utilized to conduct a public hearing on matters of importance that come before FDA to review the issues involved and to provide advice and recommendations to the commissioner. The commissioner has sole discretion concerning the action to be taken and policy to be expressed.

Thank you for your attention, and I'll turn the podium back to you, Dr. Neogi.

DR. NEOGI: Both the Food and Drug Administration, or FDA, 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 sponsor's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue, such as consulting fees, travel expenses, honoraria, and interest in the sponsor, 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 Ardea Biosciences' presentations.

Sponsor Presentation - Kimberly Manhard

MS. MANHARD: Good morning, Madam Chair,

members of the today's advisory committee, and members of the FDA. My name is Kimberly Manhard. I'm a senior vice president for regulatory affairs and development operations at Ardea Biosciences, a member of the AstraZeneca group. We are pleased to be here today to present our candidate, lesinurad, for the treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor.

Hyperuricemia is the underlying cause of gout. Most patients with gout are uncontrolled on currently available oral urate-lowering therapies. They do not achieve or sustain serum uric acid treatment goals and continue to suffer from recurrent gout flares and tophi. There is a need for new treatment options for hyperuricemia in patients with uncontrolled gout.

The addition of lesinurad 200 milligrams to a xanthine oxidase inhibitor, also referred to as an XOI, resulted in more patients with symptomatic gout achieving target treatment goals and was shown to be generally well tolerated with a manageable safety profile.

So what is lesinurad? Lesinurad is a novel,

oral, small molecule that provides urate-lowering therapy for uncontrolled gout. If approved, lesinurad would be the only new uric acid transporter 1 inhibitor, or URAT1, available for the treatment of patients with gout since probenecid came to the market more than 60 years ago.

By inhibiting URAT1, lesinurad increases uric acid excretion, thereby lowering serum uric acid levels in the body. In addition, lesinurad would be the first selective uric acid resorption inhibitor in the U.S. It inhibits both URAT1, responsible for the primary pharmacologic effect, and the organic anion transporter OAT4 involved in diuretic induced hyperuricemia. It does not inhibit other important drug transporters in the kidney such as OAT1 and OAT3, which are inhibited by probenecid.

Lesinurad has predictable pharmacokinetics characterized by a rapid absorption following oral dose with 100 percent bioavailability; plasmic exposure to dose proportional up to 1200 milligrams with clear separation of the 200- and 400-milligram doses studied in phase 3.

The population PK data from our phase 3 program confirmed dose proportionality with limited overlap in plasma C average values for these doses. Consistent with an elimination half-life of about 5 hours, there is no accumulation with once-daily dosing. And despite this relatively short half-life, lesinurad provides sustained serum uric acid lowering over 24 hours. This PK/PD relationship supports the rationale for once-daily dosing.

Renal excretion of parent drug and metabolites accounts for about 60 percent of the dose. Lesinurad exposure is higher in patients with mild and moderate renal impairment. However, no dose adjustment is needed based on the safety and efficacy data in this important subgroup of patients with gout.

In addition, lesinurad has a low potential for drug-drug interactions. Lesinurad exposure can be moderately affected by co-administration of CYP2C9 inhibitors. This is because approximately half of the oral dose is cleared by CYP2C9 metabolism. It is a weak inducer of CYP3A, and as stated before, it does not inhibit OAT1 and OAT3 in humans. Of importance,

lesinurad had no relevant interactions with commonly administered drugs in gout, including naproxen, indomethacin, colchicine, metformin, atorvastatin, and warfarin.

The current treatment guidelines for hyperuricemia associated with gout recommend an agent that increases uric acid excretion as a second-line treatment option for patients with gout, either added to an XOI in patients with uncontrolled gout or given alone in patients who cannot take XOIs.

Our global phase 3 clinical development program investigated lesinurad in this second-line setting. This program included four studies in three different patient populations with hyperuricemia: patients with an inadequate response to allopurinol, patients with tophaceous gout, and patients who are unable to take an XOI due to intolerance or contraindication.

The CLEAR 1 and CLEAR 2 studies, also referred to as studies 301 and 302, evaluated both lesinurad 200 and 400 milligrams added to allopurinol, compared to allopurinol alone. CRYSTAL, also known as study 304,

evaluated both lesinurad 200 and 400 milligrams in combination with febuxostat versus febuxostat alone. And lastly, in study 303, we looked at lesinurad 400 milligrams as a monotherapy versus placebo.

Because of serious renal-related adverse events with a 400-milligram monotherapy dose, we are not pursuing a monotherapy indication. Therefore, the remainder of our presentation is primarily focused on the phase 3 pivotal studies, CLEAR 1, CLEAR 2, and CRYSTAL, of lesinurad in combination with an XOI.

Combination therapy with lesinurad and XOI targets both excretion and production of uric acid. XOIs block production of uric acid. In the U.S., these include allopurinol and febuxostat, and as I mentioned, URAT1 inhibitors such as lesinurad increased excretion of uric acid.

This provides a dual mechanism approach to more effectively lower sUA and enables significantly more patients to achieve and maintain target treatment goals, which is necessary to control their gout. Combination therapy of lesinurad and an XOI is also associated with a more favorable renal safety profile

compared to monotherapy use. Based on the total

Based on the totality of the data, we are seeking approval for the use of lesinurad 200 milligrams once daily for the treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor. Similar to other approved urate-lowering therapies, lesinurad is not recommended for the treatment of asymptomatic hyperuricemia. Also, lesinurad should not be used as monotherapy.

I will now take you through the agenda for the rest of our presentation. Dr. Kenneth Saag from the University of Alabama at Birmingham will provide an overview of the current treatment landscape for gout and discuss the need for additional therapies. We will review efficacy, general cardiovascular and renal safety, the benefit-risk of lesinurad, and our proposed risk management plan.

Lastly, Dr. Michael Becker from the University of Chicago and a recognized expert in the treatment of gout will provide his perspective on the benefit-risk of lesinurad 200 milligrams in combination with an XOI.

In addition, we have other external experts with us today, Dr. Glenn Chertow, Dr. David Warnock, and Dr. William White, to help answer questions. All of our invited experts are being compensated for their time.

I would now like to welcome Dr. Saag to the lectern.

Sponsor Presentation – Kenneth Saag

DR. SAAG: Good morning. I'm Ken Saag, and I'm a professor of medicine and epidemiology at the University of Alabama at Birmingham. I'm a practicing rheumatologist with a special interest in gout and hyperuricemia. And I've been seeing patients and doing research in the gout area for the past 25 years.

I'm here today because there are limited options for the many patients with gout who don't achieve and sustain target serum urate levels with our current therapies. This leaves them at risk for continued gout symptoms and for disease progression. As a result, those of us caring for these patients with uncontrolled gout feel very strongly that there is a clear medical need for new therapeutic options for the

treatment of this serious and disabling disease.

Let me first review the etiology and the health burden of gout and add to the excellent initial review of the topic by Dr. Yim. As many on the panel well know, gout is a urate crystal deposition disease that affects an estimated 8.3 million people in the U.S. alone.

Uric acid deposition results from elevated levels of urate in the blood or hyperuricemia. There are two main pathways that contribute to hyperuricemia, either overproduction of urate or underexcretion of uric acid. The vast majority of our patient with gout are underexcreters.

Hyperuricemia is defined as a serum urate greater than 6.8 milligrams per deciliter. This defines the solubility threshold of urate. And hyperuricemia may ultimately lead to the formation and the deposition of urate crystals in body tissues, including the joints.

So it's this threshold that's critical to the goal of therapy. And it's important to remember that in the absence of hyperuricemia and the deposition of

these urate crystals, gout does not exist.

Here's an example of acute gout in the toe, with the blow-up image showing the toe exuding what's often referred to as "milk of urate." From this picture, you can easily appreciate why gout causes such severe pain and ability to work and a reduction in the activities of daily living.

This graphic demonstrates how gout develops and progresses over time as the uric acid load increases. Gout usually only develops after years of asymptomatic hyperuricemia. By the time a patient experiences an acute gout flare, serious crystal deposition has already occurred.

Shown here in the green lines are the episodic acute flares, which are separated by the asymptomatic periods. Over time, these flares develop and become more frequent and more severe. Eventually, this leads to a chronic arthritis into urate crystal nodules, or tophi, if the gout is untreated.

Now, this figure demonstrates the relationship between the serum urate concentration and the incidence of acute gout flares. In this retrospective study of

more than 260 patients with gout who were followed over a 3-year period, patients with an average serum urate level exceeding the target range of less than 6 had a substantially higher likelihood of recurrent gout flares than did the patients who maintained the target range.

Gout patients with poorly controlled hyperuricemia are at risk for the development of tophi, which are often accompanied by progressive and disabling arthritis. Tophi in and around joints and joint erosion, seen by the arrow on the right panel, are usually not detectable by regular X-ray until several years into the disease course. With newer technologies, we're now able to detect the acute urate deposits, as shown in this colorful, dual-energy, computerized, tomographic image or DECT scan.

Hospitalizations due to gout have also increased in recent decades as you can see in this abstract, which will be presented in a couple weeks at the ACR meeting. And they now exceed those for rheumatoid arthritis. This isn't surprising considering the rising incidence of gout in the U.S.

and worldwide.

In addition to the burden and the health consequences of gout, there are also a number of comorbidities that are commonly associated with gout. As we can see here, serious comorbidities are more frequently observed in individuals with gout than in the non-gout populations. These include hypertension, chronic kidney disease, nephrolithiasis, and cardiovascular disease.

Although growing evidence suggests that hyperuricemia may be implicated in the pathogenesis of these comorbidities, causality has not been proven.

Several studies have found that gout is associated with an increased risk of cardiovascular death. This is a 12-year observational study of more than 50,000 men, which showed an increased risk of all-cause mortality, all cardiovascular death, and fatal coronary heart disease in gout patients who had no prior history of coronary heart disease.

Let me next review the current treatment approaches for gout. To eliminate the signs and symptoms, we need to treat the underlying cause, which

is hyperuricemia. This is done by decreasing the production of urate, or by increasing the excretion of uric acid, or by both. Treatment guidelines for gout, including those published recently by the American College of Rheumatology, recommend reduction of serum urate to a target range below 6, as we heard from the FDA; and below 5 in patients with persistent symptoms and/or tophi.

Just as it takes many years for gout to develop, it can take many years to reduce the urate accumulations enough to affect the gout symptoms. There are currently only four urate-lowering therapies available in the U.S. for the treatment of gout, and I want to go through each of these.

The American College of Rheumatology guidelines recommend using xanthine oxidase inhibitors, which decrease the uric acid production, as the first line of treatment for most patients. Currently available, xanthine oxidase inhibitors include allopurinol and febuxostat.

While adequate for some patients, many others don't achieve serum urate goals with these drugs alone.

This leaves these patients inadequately controlled and at risk for recurrent gout flares and for tophus development.

Three randomized controlled studies comparing allopurinol 300 milligrams, the most commonly prescribed dose, and febuxostat 890 milligrams, the highest dose approved, showed that even in these clinical trials, only about 40 to 70 percent of patients -- or rather, 40 to 70 percent of patients did not achieve initial serum urates of less than 6. And approximately 50 to 80 percent of patients did not sustain these target goals.

Since allopurinol is the most commonly used medicine for gout and approved for up to 800 milligrams, a common question I often get is why don't we just prescribe a higher dose of allopurinol, but regrettably, this just isn't happening in the real world.

As you can see, doses of allopurinol higher than 300 milligrams are very rarely prescribed. This is largely due to concerns about safety with higher doses, especially in those who are renally impaired

where lower doses have been recommended. Additionally, there are limited data available on the safety and efficacy of allopurinol at daily doses greater than 300 milligrams.

Although up-titration to target has been recommended in the allopurinol label since 1966 and again in the recent ACR treatment guidelines, data show us that allopurinol is often not titrated at all.

We collaborated with colleagues at Kaiser, and we conducted a review of electronic medications of over 13,000 patients who were receiving allopurinol over a 2-and-a-half year period. We found that over 70 percent of patients were never titrated to a higher dose. Of those that did dose escalate, the escalation to 300 milligrams or more was very infrequent, even for rheumatologists, and was even less frequent for non-rheumatologists.

Regardless of the dose of allopurinol used, a serum urate of less than 6 was only achieved in less than a third of patients at the end of the study. So as a result, a substantial number of patients remain uncontrolled and in need of additional therapy.

So if our target goals are not reached with xanthine oxidase inhibitors, then the gout guidelines advise adding a drug that increases uric acid excretion. This would provide a dual mechanism of lowering serum urate.

Probenecid is the only approved urate-lowering therapy in the U.S. that increases uric acid excretion, and it's been on the market since 1951. Yet, probenecid is very rarely prescribed. Less than 2 percent of patients on urate-lowering therapy in the U.S. are receiving probenecid.

So as I showed earlier, despite the fact that approximately 60 percent of patients are not achieving a target on a xanthine oxidase inhibitor, very few are actually receiving the recommended second-line therapy. This is likely due to the necessary frequency of probenecid dosing, which is 2 to 4 times a day.

There are also a number of drug-drug interactions of probenecid with medications commonly used in the gout population. This includes some NSAIDs such as Naprosyn and Indocin, the RAS inhibitors like captopril and enalapril in loop diuretics. In

addition, data regarding the efficacy and safety of probenecid as a urate-lowering therapy in gout patients is extremely limited, particularly from randomized trials.

Lastly, our treatment guidelines suggest pegloticase, which is a biological uricase therapy as a third line of treatment. It's demonstrated efficacy in treating refractory gout patients with the dramatic lowering of urate to levels less than 1, and it also leads to significant tophus resolution.

This effect on these clinical endpoints further confirms serum urate as an appropriate surrogate marker for clinical benefit in gout. Despite its benefits, pegloticase is also associated with the development of anti-pegloticase antibodies, which in about 40 percent of patients results in a loss of its urate-lowering efficacy, and it's really been associated with anaphylaxis. So as a result, pegloticase is seldom used.

In summary, fortunately, and different from other forms of arthritis, we know what causes gout. We can accurate diagnose it. And if adequately treated,

we can completely eliminate gout manifestations. Yet, we still have a large treatment gap in the management of gout.

In order to improve the signs and symptoms of gout, we need to treat the hyperuricemia. We do this by lowering serum urate to levels below the saturation threshold. But unfortunately, between 40 and 70 percent of patients don't achieve or maintain the necessary urate levels with the first-line treatment, which is xanthine oxidase inhibitors alone.

Once patients have failed xanthine oxidase inhibitors, they have very limited therapeutic options to lower their serum urate levels, and, unfortunately, this leaves many patients uncontrolled and at risk for gout complications.

In conclusion, there's a considerable need for additional treatment options for patients with persistent gout who don't achieve serum urate targets on our available therapies. New gout treatment options are needed that are easy to use that have proven efficacy and adequate safety as determined from large, randomized, controlled clinical trials.

Thank you, and I'd know like to turn the lectern over to the sponsor.

Sponsor Presentation - Chris Storgard

DR. STORGARD: Good morning. My name is Chris Storgard. I'm a rheumatologist and the vice president of clinical research and develop at Ardea Biosciences. Today, I will present the efficacy results from our three double-blind, placebo-controlled, 12-month pivotal studies, CLEAR 1, CLEAR 2, and CRYSTAL. These results are the first critical assessment of the effective combination treatment for hyperuricemia and gout in a randomized controlled clinical trial setting.

Overall, these studies confirm that when used in combination with either allopurinol or febuxostat, lesinurad enables more patients, substantially more patients, to achieve and maintain the recommended serum uric acid treatment goals.

While we studied both the 200- and 400-milligram doses of lesinurad, I will focus on the results of the lesinurad 200 milligrams since this is the dose that we recommend. I will first review the study design and results from CLEAR 1 and 2. Because

these were replicate studies with identical design and endpoints, I will show these together.

The CLEAR studies evaluated lesinurad in combination with allopurinol and enrolled patients with uncontrolled gout. All patients had a history of at least 2 gout flares in the prior year, and all had confirmed serum uric acid levels above the recommended target despite allopurinol treatment.

The patients entered screening on their stable, prescriber-determined dose of allopurinol, and that dose remained unchanged during the study. As we heard from Dr. Saag, 300 milligrams of allopurinol is the highest dose of allopurinol used by 95 percent of patients.

In our trials, 300 milligrams of allopurinol was the minimum dose allowed. The maximum dose was either 800 or 900 milligrams depending on the local label. Two hundred milligrams was permitted only for patients with moderate renal impairment. Patients with severe renal impairment, those with a creatinine clearance of less than 30 mLs per minute, were excluded.

Eligible patients with serum uric acid above target were then randomized to receive lesinurad 200 milligrams, 400 milligrams, or placebo in combination with their allopurinol. Gout flare prophylaxis was initiated during screening and continued through month 5.

In CLEAR 1 and 2, the demographics were reflective of the gout population and were generally similar and well balanced across the treatment groups. The majority of patients were male and white, the mean age was approximately 52 years, and the mean body mass index was over 33.

Patients entered the studies with a variety of comorbid conditions. The majority of patients, approximately 60 percent, had some degree of renal impairment and 14 to 22 percent had moderate renal impairment. Nine to 19 percent reported a history of kidney stones. Other comorbidities were generally balanced across the treatment groups and were consistent with the gout population.

The baseline gout disease characteristics were also similar between the treatment groups in both

studies. Patients had longstanding disease of approximately 12 years. They were highly symptomatic, reporting on average 5 to 6 gout flares in the prior 12 months. Note that the number of patients with target tophi in both studies was low. The serum uric acid levels at screening were high with a mean of approximately 8 milligrams per deciliter. This is despite being on allopurinol. Consistent with the current prescribing practices, the majority of patients were on 300 milligrams of allopurinol per day.

Now, let's turn to patient disposition. Over 80 percent of patients in both CLEAR studies completed treatment through month 6, the time of the primary endpoint. Between 70 and 79 percent of patients completed treatment through month 12. The most common reasons for study treatment discontinuation across the studies were noncompliance, patients lost to follow-up, and adverse events. Very few patients discontinued treatment due to a gout flare.

Now, I will discuss the primary endpoint results and the results from additional prespecified serum uric acid analyses. In both CLEAR studies, the

primary endpoint was the proportion of patients with a serum uric acid level less than 6 by month 6. Less than 6 is a target recommended by the ACR treatment guidelines for the treatment of hyperuricemia associated with gout.

The primary statistical analysis was an intent-to-treat analysis using a non-responder imputation, which means that patients who have either dropped out or are missing their month 6 data are considered non-responders. The primary endpoint in both CLEAR studies was achieved.

In CLEAR 1, 54 percent of patients in the lesinurad 200 milligrams plus allopurinol group, the green bar, achieved target serum uric acid compared with 28 percent on allopurinol alone at month 6. These results are replicated in the CLEAR 2 study. These results are statistically significant and clinically meaningful. As twice as many patients achieved the serum uric acid target goal with lesinurad 200 milligrams plus allopurinol across both studies.

The sensitivity analysis using the last observation carried forward imputation method

demonstrates similar results, and in the clinically important subgroup of patients with renal impairment, those with a creatinine clearance of less than 90 mLs per minute, and specifically those with moderate renal impairment with a creatinine clearance of less than 60 mLs per minute.

Lesinurad 200 milligrams plus allopurinol demonstrated response rates that were consistent with the overall population. These results demonstrate that lesinurad 200 milligrams is efficacious when used in combination with allopurinol, including in patients with mild or moderate renal impairment.

The change in serum uric acid from baseline in both studies was rapid by month 1 and was sustained throughout the 12-month trial. Here we have the serum uric acid level on the Y-axis and the monthly visits on the X-axis.

At each visit, patients receiving lesinurad 200 milligrams and allopurinol, as shown in the green line, had a statistically significant greater decrease in serum uric acid from baseline compared with allopurinol alone in gray. And the mean serum uric

acid was maintained below the treatment goal of less than 6 at all post-line visits.

This magnitude of serum uric acid lowering achieved with the addition of lesinurad 200 milligrams is clinically relevant because not only does it double the proportion of patients reaching the target goal of less than 6, but when we look at the number of patients able to achieve the more stringent serum uric acid target of less than 5 -- this is recommended for patients with more severe disease -- the addition of lesinurad 200 milligrams results in nearly 3 times as many patients in CLEAR 1 and nearly 7 times as many patients in CLEAR 2 able to achieve this target.

Now, let me turn to CRYSTAL beginning first with the study design. The CRYSTAL study evaluated combination treatment with lesinurad and febuxostat in patients with tophaceous gout. All patients were required to have at least one measurable tophus, and all patients were required to have serum uric acid levels above target at the time of screening. As with the CLEAR studies, patients with severe renal impairment were excluded.

Three weeks prior to randomization, all patients were started on febuxostat 80 milligrams. After 3 weeks of febuxostat treatment, all patients, regardless of their serum uric acid level, were randomized to receive lesinurad 200 milligrams, 400 milligrams, or placebo in combination with febuxostat. As in the CLEAR studies, gout flare prophylaxis was initiated during screening and continued through month 5.

The demographics were representative of the gout population and generally balanced between treatment groups. With the majority of patients being male and white, the average age was 54 and mean body mass index was 32.

Similar to CLEAR, patients in CRYSTAL reported a variety of comorbid conditions that were generally balanced across the treatment arms. Sixty-one to 71 percent had a creatinine clearance of less than 90, 20 to 26 percent had a creatinine clearance of less than 60, and 20 to 15 percent had a history of kidney stones.

All patients had tophaceous gout with at least

one measurable target tophus and all patients had longstanding disease averaging 14 years in duration. They were highly symptomatic, reporting an average of 6 to 7 flares in the prior 12 months.

The mean serum uric acid levels were high at screening, higher than 8.5 milligrams per deciliter. Similar to the CLEAR studies, over 80 percent of patients completed treatment through month 6, the time of the primary endpoint, and more than 70 percent of patients completed treatment through month 12. The most common reasons for study treatment discontinuation across all treatment groups were noncompliance and adverse events.

Now, let's look at the efficacy results, including the primary endpoint and additional serum uric acid analyses. The primary endpoint in CRYSTAL was the proportion of patients with a serum uric acid level that is left than 5 by month 6. Less than 5 is a serum uric acid target recommended by ACR guidelines for patients with greater disease severity such as those with tophi.

As with CLEAR, the primary analysis was an

intent-to-treat analysis using a non-responder imputation method, meaning patients who have either dropped out or missing month 6 data are considered non-responders.

Forty-seven percent of patients on febuxostat alone achieved target serum uric acid less than 5 by month 6. The addition of lesinurad 200 milligrams increased the response rate to 57 percent, but the result was not statistically significant. The sensitivity analysis using the last observation carried forward imputation showed similar results.

The result was unexpected, however, when we looked at treatment effects across the entire duration, it became evident that the month 6 result with lesinurad 200 milligrams was not consistent with the results at other time points. At all other visits, a higher proportion of patients treated with lesinurad 200 milligrams and febuxostat achieved the target serum uric acid of less than 5 compared to treatment with febuxostat alone.

Given the inconsistent result at month 6, an extensive evaluation of potential causes was conducted.

No clear explanation was identified. But perhaps even more relevant than achieving target at one time point is the ability to sustain it.

Additional analyses demonstrated the lesinurad 200 milligrams with febuxostat increased the proportion of patients with serum uric acid less than 5 over extended durations. This included 3 or 6 consecutive visits, even when including the month 6 interval. More than twice the proportion of patients on lesinurad 200 milligrams and febuxostat achieved serum uric acid target at all 12 months compared to febuxostat alone.

Now, of particular interest are the results of the prespecified subgroup of patients with a serum uric acid greater than 5 at baseline because these are the patients who did not achieve target on febuxostat alone. At every visit, including month 6, the addition of lesinurad 200 milligrams significantly increased the proportion of patients achieving target.

At month 6, lesinurad 200 milligrams plus febuxostat resulted in nearly twice as many patients achieving target serum uric acid less than 5 compared with febuxostat alone, and substantially more patients

were able to achieve even the lowest serum uric acid level of less than 4 with the combination as well.

Taken together, the totality of evidence demonstrates that lesinurad 200 milligrams when used in combination with febuxostat is efficacious, especially in those patients not able to achieve target on febuxostat alone. These results are clinically important because these are the patients in greatest need of additional treatment options, and these are the intended population for treatment with lesinurad.

In addition to serum uric acid response, the lesinurad program evaluated additional endpoints, including gout flare rates, tophus resolution, and patient-reported outcomes. Some of these were designated as key secondary analyses.

We employed a hierarchical testing algorithm to control for type 1 error of the primary and key secondary analyses. In CLEAR 1 and 2, the primary endpoint was achieved for both lesinurad doses and the mean rate of gout flares could be formally tested. The result was not significant for either dose group, and formal testing was stopped.

In CRYSTAL, as 200 milligrams did not achieve the primary endpoint, nor further formal testing could be performed for lesinurad 200 milligrams in CRYSTAL. Regardless of the formal testing algorithm, lesinurad 200 milligrams in combination with an XOI was not superior to an XOI alone in these key secondary endpoints.

I'll briefly show you the results of the gout flares in tophi. The mean rate of gout flares requiring treatment during this last 6 months of study was a key secondary endpoint in CLEAR 1 and 2. This interval was chosen because gout flare prophylaxis was to continue through month 5.

The mean flare rate was low, lower than expected, with comparable rates across all treatment groups. In CRYSTAL, the rates were generally higher likely because patients had tophi. Although we did not see a reduction with 200 milligrams compared to febuxostat alone, the rate with lesinurad 400 milligrams was lower.

The proportion of patients experiencing a complete resolution of at least 1 target tophus was a

key secondary endpoint across all studies. In the CLEAR studies, especially CLEAR 1, very few patients had target tophi at baseline. In either CLEAR study, the results did not favor lesinurad.

In CRYSTAL, all patients entered the study with measurable tophi, and in this study, there was a numeric trend in the proportion of patients experiencing a complete resolution, but the result was not statistically different compared with febuxostat alone.

Change in total tophus area was also assessed as a prespecified analysis, but it was not a key secondary endpoint. In CRYSTAL, the reduction in tophus area was greater in patients received lesinurad 200 milligrams with a 50 percent reduction in tophus area at month 12 versus 28 percent with febuxostat alone.

Although disappointing, the results of the key secondary endpoints were not completely unexpected. To date, no oral urate-lowering therapy has demonstrated an improvement in flares or tophi during the time frame of the randomized control trial, though with continued

treatment in extension studies, clinical benefit has been observed.

Let me review some of the data from our ongoing extension studies. All patients who completed the CLEAR or CRYSTAL studies were eligible to continue treatment. Approximately 60 percent of those patients who entered the pivotal studies enrolled into the extension studies. Patients receiving lesinurad in the pivotal studies continued the same dose of lesinurad in the extension, and those receiving placebo were randomized to lesinurad 200 milligrams or 400 milligrams. All patients continued on their same background XOI as in the pivotal study.

I'll focus on the results of the subgroup of patients that received lesinurad 200 milligrams in the pivotal studies and enrolled into the extension studies to illustrate the results of extended treatment.

In patients continuing treatment with lesinurad 200 milligrams plus allopurinol, there was a steady decline in the proportion of patients with a gout flare requiring treatment throughout the 24-month period. A similar decline in gout flares requiring

treatment was also observed in patients continuing treatment with lesinurad and febuxostat.

Tophi improved as well. The proportion of patients who experienced a complete resolution of at least one target tophus continued to increase over time with both lesinurad plus allopurinol and lesinurad plus febuxostat.

Given the limitations inherent in optional, uncontrolled extension studies, these results are not evidence of superior treatment effects, but they do support the clinical experience where continued maintenance of serum uric acid targets results in fewer flares and greater tophus resolution over time.

In summary, three pivotal studies demonstrate the efficacy of lesinurad 200 milligrams with an XOI. Two replicate CLEAR studies confirmed that lesinurad 200 milligrams added to allopurinol results in a statistically significant and clinically relevant sUA lowering, with a doubling in the proportion of patients able to achieve and maintain the serum uric acid target treatment goal of less than 6, and more than a tripling in the proportion of patients achieving serum uric acid

target of less than 5.

In CRYSTAL, although the month 6 primary endpoint was not achieved, substantially more patients did achieve and maintain recommended treatment goals at all other time points during this study. What is clinically relevant is that the addition of lesinurad 200 milligrams nearly doubled the response rate at every visit, including month 6 in the subset of patients not at target on febuxostat alone. Importantly, this is the intended treatment population, patients who have not achieved target on an XOI alone.

Taken together, the data confirmed that by targeting both uric acid excretion and production, lesinurad 200 milligrams, when combined with an XOI, gets more patients to goal and supports the use of lesinurad 200 milligrams for the treatment of hyperuricemia associated with gout.

Now, I would like to invite Dr. Nihar Bhakta to the lectern to discuss the safety results.

Sponsor Presentation – Nihar Bhakta

DR. BHAKTA: Thank you, Dr. Storgard.

Good morning. My name is Nihar Bhakta. I'm a

nephrologist and executive medical director at Ardea Biosciences. Today, I will present the general and cardiovascular safety data from our clinical development program. These demonstrate that lesinurad 200 milligrams in combination with a xanthine oxidase inhibitor is generally well tolerated with a comparable overall safety profile to that observed with a xanthine oxidase inhibitor alone, with the exception of mechanism-based serum creatinine elevations.

The focus of this presentation will be the 12-month, phase 3, randomized placebo-controlled pivotal studies and the data from our two ongoing extension studies. I will review data for both lesinurad doses studies with a focus on the 200-milligram dose for which Ardea is seeking approval.

In the clinical development program, more than 2500 individuals have been exposed to lesinurad. Nearly 1800 unique patients with gout have been exposed to lesinurad for over 1900 person-years in the phase 2 and 3 studies. Almost 1,000 patients were exposed to lesinurad at any dose for at least 12 months. With the long-term extension study still ongoing, nearly 300

patients have received lesinurad for at least 24 months, with some patients getting it for up to 3 years.

Overall, lesinurad 200 milligrams per day in combination with a xanthine oxidase inhibitor had a similar adverse event rate to a xanthine oxidase inhibitor alone. Most adverse events were mild or moderate in intensity.

The rate of adverse events leading to treatment discontinuation and of those classified as serious adverse events was also similar between lesinurad 200 milligrams and placebo, with a higher rate observed for lesinurad 400 milligrams. Additional evaluation of the extension studies did not identify any new safety signals in patients with extended exposures to lesinurad.

Adverse events with an incidence rate greater than 2 percent in either lesinurad group and at least 1 percent greater than the placebo group are presented here. Hypertension, headache, influenza, blood creatinine increased, and gastroesophageal reflux disease occurred more frequently on lesinurad 200

milligrams than placebo.

Analyses of patients who continued into the extension studies demonstrated exposure-adjusted incidence rates that were consistent with those observed in the pivotal studies. To further examine the hypertension adverse events, we also evaluated the hypertension standardized MedDRA query for a broader set of hypertension related terms, including blood pressure increased.

This SMQ analysis demonstrated no difference between the treatment groups with respect to the development of hypertension as an adverse event. 6.2 percent in the placebo plus xanthine oxidase inhibitor group and 6.5 percent in the lesinurad 200 milligrams plus xanthine oxidase inhibitor reported any hypertension related term. Therefore, hypertension is not considered an average drug reaction of lesinurad.

Moving now to serious adverse events. As previously shown, a similar proportion of patients on lesinurad 200 milligrams and placebo experienced serious adverse events, with a higher incidence in the

lesinurad 400-milligram group. The pattern and character of the types of serious adverse events were comparable between groups, with the most common serious adverse events being cardiac or renal related, both of which will be addressed in more detail shortly.

We also looked at the exposure-adjusted incidence rate of these same serious adverse events terms in the extension studies and saw similar findings. Overall, increased exposure did not change the serious adverse event profile of lesinurad 200 milligrams.

Next, I will review fatalities in the lesinurad clinical development program. We analyzed fatalities carefully and in great detail. Overall, in the lesinurad development program, there have been 20 deaths. There was 1 death in phase 1 and 1 death in the extension of phase 2. Additionally, 3 deaths occurred during the screening period of the phase 2 and 3 studies when patients were on xanthine oxidase inhibitor alone.

Specifically, with regards to the phase 3 studies, there were 6 deaths that occurred

post-screening in the control part of the phase 3 studies. These included one patient with gastric cancer and 5 patients with adjudicated cardiovascular death. There were 9 deaths that occurred in the uncontrolled extension period of the phase 3 studies, where patients had over 1100 years of exposure to lesinurad. These included 1 suicide and 8 adjudicated cardiovascular deaths. The cardiovascular causes were heterogeneous and included a variety of causes such as hemorrhagic and non-hemorrhagic stroke, pulmonary edema, and arrhythmia.

Deaths occurred between 38 and 655 days after study drug initiation. Three of these deaths occurred when the patient was off lesinurad for over 30 days.

Now moving to our laboratory data. In addition to a complete evaluation of adverse and serious adverse events, the studies routinely collected laboratory data for an overall evaluation of safety. A comprehensive evaluation of chemistry and hematology parameters demonstrated that there were no clinically relevant changes from baseline in mean or media values. Evaluation of individual patient shifts from baseline

to last value were also comparable between the treatment groups.

Given the hepatic toxicity associated with xanthine oxidase inhibitors, liver function testing was of particular interest in the lesinurad clinical development program. Overall, there was no evidence of drug-induced liver injury with the addition of lesinurad. Notably, there were no cases of Hy's law noted in the entire development program with lesinurad.

Now, we will review the two topics of special interest. I will first review the cardiovascular safety of lesinurad followed by Dr. Scott Adler, who will discuss renal safety. Cardiovascular safety was a topic of special interest because of the generally high level of cardiovascular risk associated with gout patients. As such, during the development of lesinurad, we evaluated date related to cardiovascular safety on an ongoing basis.

Evaluation of cardiovascular safety started in the preclinical setting. Based upon the mechanism of action, there was no expectation that URAT1 inhibition would demonstrate a direct impact on cardiac or

vascular physiology. Our preclinical safety pharmacology studies did not suggest that lesinurad would have an impact on cardiovascular safety. Additionally, there was not an impact observed on in vitro platelet aggregation by ADP and thromboxane studies.

Finally, a thorough QT study with a positive control conducted in humans demonstrated no impact of lesinurad therapy on the QT interval or any other ECG parameters. This information was all coupled with the lack of a cardiovascular signal in phase 1 and 2.

Many patients enrolled in the phase 3 studies had hypertension, hyperlipidemia, diabetes, and moderate renal impairment. Over 75 percent of the patients had at least one known cardiovascular risk factor or comorbid condition, while 1 in 5 had at least three. Given the at-risk population being evaluated, Ardea chose to implement additional measures beyond standard adverse event reporting and pharmacovigilance to monitor for cardiovascular events.

A cardiovascular endpoints adjudication committee was utilized to prospectively and in a

blinded matter adjudicate all potential cardiovascular events. Dr. William White is the chair of the committee of three independent and blinded physicians who review events set for adjudication.

The committee reviewed cardiovascular events from four potential pools. They evaluated all deaths, serious adverse events that met specific predefined cardiovascular criteria, investigated reported cardiovascular adverse events, and the CEAC chair performed scheduled reviews of all serious and selected non-serious adverse events in a prespecified list to help ensure that all potential cardiovascular events were referred to adjudication. The majority of the events sent for adjudication were investigator flagged or were serious adverse events.

There were a total of 88 patients who had information sent for adjudication, and some patients had multiple events. The groups were well balanced with respect to the number of patients who had events sent for adjudication across the three treatment groups.

The adjudication committee would then

determine the appropriate category for each event. An event could be deemed cardiovascular event, a non-cardiovascular event, or insufficient information to adjudicate. As noted, some of the 88 patients had multiple events that fell into more than one category. There were a total of 48 patients with cardiovascular events. There were 39 patients with events determined to be non-cardiovascular events, and there were 15 patients with an event that had insufficient information to adjudicate.

Regarding events with insufficient information, many of these events were obtained from the additional listing review by the CEAC chair. None of these events were serious or fatal. There was a high degree of variability in the type of adverse event terms with the most frequent terms being chest pain and syncope related. Every event on lesinurad was noted to have resolved by the end of the study period.

Now, let's review the findings with respect to cardiovascular events. Of the patients who experienced events sent for adjudication, about half experienced an event that was determined by the CEAC to be a

cardiovascular event, which included those events in the composite endpoint of major adverse cardiovascular events or MACE.

Overall, cardiovascular events were comparable between treatment groups. Across the three groups, there was a total of 15 patients who experienced an event categorized as a MACE, which included cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke; 3 patients on placebo, 4 patients on lesinurad 200 milligrams, and 8 patients on lesinurad 400 milligrams.

Non-MACE cardiovascular events included congestive heart failure, arrhythmia not associated with ischemia, and venous and peripheral arterial thromboembolic events.

Four of the 5 fatalities that were previously described as having occurred in the pivotal combination therapy program were adjudicated as cardiovascular deaths, 2 on lesinurad 200 milligrams and 2 on lesinurad 400 milligrams. There was a higher number of patients who experienced a non-fatal myocardial infarction in the lesinurad 400-milligram group

compared to the lesinurad 200-milligrams or placebo groups. And finally, there were 3 strokes on placebo and none on either dose of lesinurad.

Additionally, with respect to the MACE observed, we evaluated the PK model of the lesinurad plasma exposure for patients with evaluable data with and without MACE across doses. Each dot represents the population PK model median concentration for an individual patient.

A valuation of the exposure in patients with and without MACE on lesinurad 400 milligrams demonstrated no relationship. For lesinurad 200 milligrams, there was a similar finding with no relationship of exposure to MACE. Overall, the incidence of MACE events was low across all three treatment groups in the pivotal studies, and we saw a similar low incidence of MACE in the uncontrolled extension studies.

These rates are similar to the MACE rates observed in the Ardea sponsored LASSO trial with similar inclusion and exclusion criteria and the same cardiovascular events adjudication committee, which

enrolled over 1700 patients on allopurinol alone.

In summary, lesinurad 200 milligrams in combination with xanthine oxidase inhibitor provides patients with a well characterized and consistent general and cardiovascular safety profile. We saw similar incidence of adverse events and serious adverse events between treatment groups, and no clinically relevant changes from baseline to last value in laboratory parameters.

Analysis of cardiovascular safety demonstrated that while there was a numerical imbalance in MACE with lesinurad 400 milligrams, the incidence rates were low and comparable between lesinurad 200 milligrams with an xanthine oxidase inhibitor and an xanthine oxidase inhibitor alone. Additionally, no new safety signals were observed in the extension studies supporting chronic administration of lesinurad 200 milligrams with an xanthine oxidase inhibitor.

I will now turn the lectern to Dr. Adler to discuss renal safety.

Sponsor Presentation - Scott Adler

DR. ADLER: Good morning. My name is Scott

Adler, and I'm a nephrologist and a senior medical director with AstraZeneca. In this presentation, I will discuss the renal safety findings from our phase 3 pivotal studies, including its mechanism of action and the pharmacodynamic effect of lesinurad, which we believe is directly related to these findings. Let me begin by describing how the kidney normally handles uric acid.

Shown here is a schematic of a nephron. On the left side is the blood supply that delivers uric acid to the kidney. The blue dots represent uric acid and the pink ovals represent the uric acid transporter URAT1. Uric acid is freely filtered at the glomerulus and enters the proximal tubule where more than 90 percent is reabsorbed back into the bloodstream through URAT1.

Any uric acid that's not reabsorbed is excreted in the urine. Patients with gout, however, reabsorb relatively more of the filtered uric acid than people without gout. This inefficient excretion of uric acid contributes to hyperuricemia.

Looking now at how lesinurad works, lesinurad

shown here as green triangles is a selective uric acid reabsorption inhibitor. It binds to URAT1 in the proximal tubule and decreases the amount of uric acid returned to the bloodstream. The pharmacodynamic effects are twofold, an increase in urinary uric acid excretion and a decrease in the serum uric acid concentration. An increase in urinary uric acid excretion can lead to intratubular microcrystallization or precipitation of uric acid within the urinary tract.

There are two major factors that influence the solubility of uric acid in the urine and are important in the context of the renal safety findings. The first factor is the uric acid concentration. The amount of uric acid excreted in the urine is decreased during treatment with an xanthine oxidase inhibitor and underpins the safety rationale for combination therapy. Uric acid concentration can also be decreased through the intake of adequate fluid and the recommendation to drink 2 liters per day during lesinurad treatment.

The second factor is the urine pH, with a low urine pH decreasing the solubility of uric acid. The urine pH is lowest at night and increases throughout

the morning hours. Lesinurad is dosed once daily in the morning in combination with an xanthine oxidase inhibitor to reduce the potential for uric acid precipitation.

I will next describe the uric acid excretion following lesinurad administration. This bar graph demonstrates that the maximal effect on urinary uric acid excretion is observed within the first 6 hours. The orange bar depicts uric acid excretion in untreated gout patients and the lighter blue bar in patients treated with lesinurad 400 milligrams as monotherapy.

Lesinurad 400 milligrams in combination with allopurinol is shown in the darker blue bar and clearly shows a relative decrease in uric acid excretion. During the 6- to 12-hour time period, after combination dosing, the amount of uric acid excreted falls back to or below untreated levels.

Overall, these data show that combining arthritis with an XOI has less uric acid excretion than monotherapy. This is important, as the uric acid excretion correlates with the rates of renal events observed in our phase 3 trials with higher rates

observed in the monotherapy setting. Let me share these data with you.

In the monotherapy study, we observed a higher incidence of adverse events and serious adverse events on lesinurad 400 milligrams than on placebo. This difference was primarily due to non-serious and serious renal related events. As stated previously, based on these renal safety findings, lesinurad should not be used as monotherapy.

Given the uric acid excretion data, we expected that combination with an XOI would demonstrate an improved renal safety profile compared to monotherapy, and our data demonstrate that. Let me review these data, including analysis of the serum creatinine and renal related adverse events.

We started our evaluation of the phase 3 pivotal program with assessment of the most objective parameter of renal function within our laboratory database, the serum creatinine. Analyses of serum creatinine were proposed and agreed upon with the FDA. They included assessment of patients who experienced an elevation of at least 1.52 and 3 times their baseline

value at any time.

The baseline serum creatinine was defined as the highest value within 14 days prior to randomization. This was based on an analysis of the intrasubject variability of serum creatinine values prior to randomization. In addition, a resolution was defined as a return within 20 percent of baseline.

Moving on to the results of these assessments, in this graph, we see the proportion of patients who experienced a serum creatinine elevation at least 1.5 times baseline at any time. These elevations were identified by the evaluation of the routine laboratory assessments within the clinical laboratory database.

There was a higher proportion of patients with a serum creatinine elevation on lesinurad 200 milligrams in combination with an XOI compared to XOI alone, and the rate was higher for lesinurad 400 milligrams combination therapy.

A similar pattern was observed for patients with an elevation of at least 2 times baseline as demonstrated by the dotted portion of the graph, and at least 3 times baseline in the hash portion of the

graph. Additionally, exposure adjusted incidence rates of serum creatinine elevations in the extension studies are consistent with those seen in the pivotal studies.

To further understand these elevations, we evaluated the proportion that resolved by the last study assessment. This graph shows that in the lesinurad 200 milligrams plus XOI group, the green bar, approximately 90 percent of all serum creatinine elevations resolved, including elevations greater than 2 times baseline and 3 times baseline. Of these elevations, the majority resolved while the patients continued to take lesinurad as shown by the solid portion of the bars.

Importantly, most of the serum creatinine elevations resolved by the next study visit. There were 3 patients on xanthine oxidase inhibitor alone and 3 patients on lesinurad 200 plus xanthine oxidase inhibitor with unresolved serum creatinine elevations at the end of the pivotal trial.

Two of the three lesinurad 200-milligram patients entered an extension study, and the serum creatinine elevations resolved while continuing

therapy. These data indicate that the majority of serum creatinine elevations observed on the lesinurad 200 plus XOI group are reversible.

We were interested in understanding if factors present at baseline increased the risk for serum creatinine elevations. The patients with serum creatinine elevations were similar to the overall safety population with respect to demographic characteristics, baseline disease, treatment characteristics, and comorbidities.

Subgroup analyses demonstrated that there was no apparent association between the instance of serum creatinine elevations and baseline renal function, gout flare prophylaxis medication, concomitant use of non-steroidal anti-inflammatory drugs, diuretics, or agents acting on the renin angiotensin system.

We also conducted a multivariate analysis of 300 parameters, including baseline lab values in blood pressure, adverse events, physical examination results, and the presence or absence of tophi among others. None of the associations were strong enough to be of practical importance in either predicting serum

creatinine elevations or in identifying a subgroup of patients with increased risk.

In addition, we looked closely at two patients who had been treated with lesinurad 400 milligrams who underwent a renal biopsy to better understand the etiology for the serum creatinine elevations. The histologic findings did not provide information on the specific underlying cause. In both cases, there was no evidence of allergic interstitial nephritis or glomerulonephritis.

In addition to these analyses, we also evaluated our population PK data. Despite a clear dose response, evaluation of the modeled average lesinurad concentrations only demonstrated a weak relationship between exposure and serum creatinine elevations. This is likely due to multiple dynamic factors in addition to the amount of uric acid excretion such as urine pH and urine volume, both of which impact the risk for uric acid precipitation.

As part of our evaluation of renal safety, we also wanted to understand the renal function in all patients. In fact, evaluation of the mean estimated

creatinine clearance in all patients during the pivotal studies demonstrated almost no differences between the lesinurad 200 plus XOI and XOI-alone treatment groups, with no decline observed over the 12-month study period.

We also evaluated the absolute change in estimated creatinine clearance from baseline to last value for lesinurad treated patients. There is no clinically relevant change observed in the lesinurad 200 plus XOI treatment group. Additional evaluation of the approximate 20 percent of patients in each group who are off therapy for at least 7 days, whether at the end of 12 months or study discontinuation, demonstrated no notable difference in the estimated creatinine clearance when compared to their baseline across the treatment groups.

In addition to renal function, we also evaluated investigator reported non-serious and serious adverse events. We evaluated a broad customized list of renal related adverse event terms. In the pivotal studies, the lesinurad 200 milligram plus XOI treatment group had a renal related adverse event profile that

was comparable to the XOI-alone group.

The only notable difference between the two groups was with the preferred term of blood creatinine increase consistent with the serum creatinine elevations already reviewed. There was a higher incidence of renal related adverse events in the lesinurad 400 milligram plus XOI group.

The subset of renal related serious adverse events was also comparable between the lesinurad 200-milligram plus XOI and XOI-alone treatment groups. There were not patients in the lesinurad 200 plus XOI group and 2 patients on XOI alone with renal related serious adverse events. However, in the uncontrolled extension studies, serious adverse events of acute renal failure were reported for both doses of lesinurad.

Of these, there were two patients who developed acute and chronic kidney disease with non-recovery. Both patients had a past history of chronic kidney disease with moderate renal impairment and proteinuria at baseline. They were both randomized to lesinurad 200 milligrams plus XOI in the pivotal

trial, completed the pivotal trial, and then entered into an extension study continuing on lesinurad 200 plus and XOI.

The first patient was hospitalized with heart failure, bilateral lower extremity cellulitis, and acute renal failure 567 days after initiating lesinurad therapy. Following admission to the hospital, lesinurad was discontinued, and the patient's renal function continued to decline, requiring chronic renal replacement therapy approximately 10 days later.

The second patient had a serum creatinine elevation greater than 1.5 times baseline approximately 400 days after initiation of lesinurad therapy. Lesinurad was discontinued, and there was mild improvement in renal function. Over the next year, renal function progressively declined, and the patient required chronic hemodialysis approximately 16 months after lesinurad was discontinued. Both patients had complicated medical conditions, which contributed to the progression of the underlying chronic kidney disease.

One additional patient required acute

hemodialysis following a cardiac arrest that occurred approximately 10 days after lesinurad was discontinued. Dialysis was required for approximately 3 weeks and renal function recovered by the time of hospital discharge.

Given that patients with moderate renal impairment are at greater risk for declining renal function over time, we performed additional analyses to evaluate the safety of lesinurad in this subgroup. The most important factor that impacts uric acid excretion in patients with moderate renal impairment is the glomerular filtration rate. The decrease in GFR lowers the amount of uric acid filtered and the amount of uric acid excreted.

In addition, there is a reduction in the renal clearance of lesinurad. With a reduction in the renal clearance of lesinurad, we observe an increase in the systemic exposure as shown in this lesinurad concentration time curve. Despite this increase, the exposure profile is different from the 400-milligram profile particular during the zero to 6-hour time frame.

As expected with a reduction in renal clearance, the concentration of lesinurad in the urine is decreased in patients with moderate renal impairment compared to patients with normal renal function as shown in this graph. Despite this decreased urine lesinurad concentration, pharmacodynamic activity is still observed in patients with moderate renal impairment.

In this graph, we demonstrate the total uric acid excretion in the first 6 hours following administration of lesinurad in patients with normal and moderate renal impairment. With decreasing renal function, there is less uric acid excreted. With the addition of lesinurad, there is an increase in uric acid excretion. But in those with moderate renal impairment, there's less uric acid excreted than those with normal renal function without treatment.

These data suggest that patients with moderate renal impairment may not be at additional risk with the 200-milligram dose of lesinurad in combination with an XOI. This is supported by the renal safety profile of this subgroup in our pivotal trial data.

When compared to the overall population, evaluation of serum creatinine elevations to at least 1.5 times baseline in this subgroup with moderate renal impairment demonstrated a similar incidence within each treatment group. This was also true for elevations to at least 2 times baseline as seen in the dotted portion of the graphs.

When looking at the renal function over time in the patients with moderate renal impairment, the estimated creatinine clearance over time was unchanged from baseline in the lesinurad 200 plus XOI treatment group.

When we evaluated the investigator reported adverse event data, patients with moderate renal impairment on XOI alone were more likely to experience a renal related adverse event compared to the overall population. Compared to XOI alone, the incidence of renal related adverse events was not increased in those patients with moderate renal impairment on lesinurad 200 plus XOI. A similar finding was observed for renal related serious adverse events.

As probenecid is associated with an increase

in kidney stones, we investigated the incidence of kidney stones in our phase 3 pivotal studies. The incidence of non-serious and serious kidney stones adverse events was low across the treatment groups in our phase 3 pivotal trials despite enrollment of approximately 15 percent of patients with a history of kidney stones.

In summary, lesinurad 200 milligrams in combination with an XOI demonstrates a renal safety profile that is consistent across all renal function categories. The primary finding was an increase in serum creatinine elevations, most of which resolved during continued treatment with lesinurad 200 milligrams, and most resolved by the next study assessment.

As such, we believe that the renal events are the result of transient obstruction due to intratubular uric acid precipitation. The renal related adverse event profile was comparable between the lesinurad 200-milligram plus XOI and XOI-alone treatment groups.

Additionally, the renal safety profile between pivotal and extension studies was generally consistent,

supporting chronic administration of lesinurad 200 milligrams with an XOI. Evaluation of patients with moderate renal impairment demonstrated a consistent safety profile between lesinurad 200 milligrams in combination with an XOI when compared to that observed in the overall population.

I will now turn the lectern over to Dr. Chris Storgard for the benefit-risk assessment.

Sponsor Presentation - Chris Storgard

DR. STORGARD: Thank you, Dr. Adler.

Let me summarize the data presented today and present our risk management proposal. As we first heard from Dr. Saag, gout is directly related to the presence of uric acid crystals. To improve the clinical manifestations of gout in the long term, we must first effectively lower and maintain serum uric acid levels below saturation levels to prevent new urate crystals for forming and allow existing crystals to resolve.

As we also heard, many patients do not achieve the recommended serum uric acid target with the current use of XOIs as first-line therapy, leaving them at risk

for continued urate crystal deposition and its consequences.

Unfortunately, there are few options available for these patients and all have limitations. Thus, there is a clear unmet need for new second-line treatment options that effectively lower serum uric acid and get patients to goal. Lesinurad can fill this need.

Let me briefly summarize the efficacy results from our phase 3 pivotal studies. The replicate CLEAR study showed that the addition of lesinurad 200 milligrams to allopurinol achieved sUA lowering that was both statistically significant and clinically meaningful. The combination doubled the proportion of patients achieving and maintaining the target sUA levels, lesson 6, and tripled the proportion of achieving less than 5.

In crystal, when the lesinurad 200 milligrams was combined with the highest approved dose of febuxostat, the proportion of patients achieving the target sUA lesson 5 was significantly greater at all visits except month 6. And in the subgroup of patients

not at goal on febuxostat alone, the added benefit of lesinurad 200 milligrams was significant all visits, including month 6, nearly doubling the proportion of patients achieving an sUA lesson 5. These results are clinically important, as patients not at goal on an XOI alone are in greatest need of additional treatment options.

Overall, the safety profile of lesinurad 200 milligrams in combination with an XOI is manageable and generally similar to that of an XOI alone. The incidence of adverse events in patients taking lesinurad 200 milligrams with an XOI was comparable to those taking an XOI alone, and most adverse events were mild or moderate in severity. The only notable difference is an increase in reversible serum creatinine elevations most of which resolved without treatment interruption.

We have experience with lesinurad in our extension studies for up to 3 years, and importantly, the safety profile was unchanged with extended dosing. Notably, the safety profile between 200 and 400 milligrams remains distinct with extended

treatment.

We've also looked at the potential impact of the PK exposure overlap between these two doses. Shown here is the average lesinurad exposure for patients in the phase 3 studies as derived from population PK analyses. Exposures are dose proportional and as expected.

When we look at the interquartile ranges of the two doses, there is no overlap, and only 10 percent of the exposures with 200 milligrams were above, and 90 percent were below the median exposure of 400 milligrams. We believe that this overlap does not impact the safety profile of lesinurad 200 milligrams. Let me explain why.

First, as we heard from Dr. Bhakta, the population PK analysis did not show an exposure MACE relationship. And as we heard from Dr. Adler, only a weak exposure of serum creatinine elevation relationship was seen. This is likely because there are multiple dynamic factors such as urine pH and urine volume that can influence the risk of uric acid precipitation.

Lastly, this overlap has been incorporated and accounted for in the results of the large randomized studies with 1900 patient-years of lesinurad exposure, which demonstrates a consistent and distinct safety profile for lesinurad 200 milligrams compared to 400 milligrams.

Let me now turn to our risk management proposal, which is being designed to inform patients, prescribers, and pharmacists about the importance of co-administration of lesinurad with an XOI through appropriate labeling, communications, and enhanced pharmacovigilance activities.

The identified and potential risk for lesinurad are highlighted throughout the proposed label. A boxed warning is proposed that describes the increased risk of acute renal failure when lesinurad is used without an XOI and in the case that lesinurad should be used in combination with an XOI.

The warnings and precautions present the importance of monitoring a renal function and for symptoms of acute renal failure, as well as guidance on when to interrupt lesinurad treatment. A

contraindication is included regarding use in patients with severe renal impairment, end-stage renal disease, or on dialysis, as these patients were excluded from the phase 3 studies.

Lesinurad demonstrated consistent efficacy and safety in patients with moderate renal impairment, but because of limited data in patients with a creatinine clearance of less than 45, we are recommending use with caution in this group. Although a causal relationship has not been established, the label will also highlight the occurrence of MACE observed in the phase 3 program.

The label will be reinforced with proposed communications materials, including a patient medication guide. Letters will be sent to all prescribers and pharmacists who are likely to prescribe or dispense lesinurad and also to professional organizations.

Additional measures will be taken with electronic medical records and pharmacy systems to alert prescribers and pharmacists of the need to prescribe or dispense lesinurad only to those patients currently taking an XOI and not to prescribe or

dispense as monotherapy.

We propose to evaluate the effectiveness of this comprehensive communication plan via surveys that will assess the understanding of patients, prescribers, and pharmacists of the importance of co-administration of lesinurad 200 milligrams with an XOI.

We will also be conducting a number of post-approval, enhanced pharmacovigilance activities. In addition to standard pharmacovigilance, including the collection and analysis of individual adverse events, the review of identified risks, and identification of new signals, we are proposing enhanced activities. This includes a targeted questionnaire, which will be sent to all healthcare professionals who report a renal related event.

In addition, the extension studies will continue to assess the renal and cardiovascular safety as well as monitor for any unidentified potential risks.

Due to the low incidence of MACE, the uncontrolled extension studies and standard pharmacovigilance activities may not be sufficient to

fully assess CV safety, so we have proposed a post-approval safety study for consideration by the FDA. This prospective observational cohort study will compare new users of lesinurad in combination with an XOI to those who are continuing users of an XOI alone.

The primary endpoint is MACE-plus, which is MACE and hospitalizations for unstable angina. The study will include data from electronic research databases and medical records. Propensity scoring will be used to match 1 new lesinurad plus XOI user with 4 continuing users of an XOI alone. The study has been designed to rule out a hazard ratio of 1.8 for MACE plus with 90 percent power, and to accomplish this, we will intend to evaluate approximately 20,000 patients. Results are expected within approximately two years post-approval.

If approved, lesinurad will be the first agent in 60 years that addresses the inefficient excretion associated with gout. Lesinurad will fill an important treatment need by providing physicians an effective therapeutic option for patients not responding to XOIs.

Lesinurad is the first and only agent to

provide proven efficacy and safety in combination treatment with an XOI in large randomized, placebo-controlled clinical trials. Overall, the combination is generally well tolerated, and the identified risks are manageable with the proposed comprehensive risk mitigation program.

I would like to emphasize lesinurad was developed for patients with uncontrolled gout in need of additional therapy. It was not developed nor intended to be used as a first-line treatment option. In the second-line setting with appropriate risk management, the benefit-risk profile for lesinurad is positive.

I will now ask Dr. Becker to provide his clinical perspective.

Sponsor Presentation - Michael Becker

DR. BECKER: Good morning. I am Michael Becker, and I am a professor emeritus of medicine at the University of Chicago. I'm a practicing rheumatologist and have had clinical investigative interest in gout and hyperuricemia since the 1960s. In this clinical perspective, I'd like to address three

questions in regard to long-term gout therapy. First, does sustained urate lowering to a subsaturating goal level result in clinical benefit? Second, what are the impediments to achievement of the goal? And third, what role can lesinurad play in expediting goal attainment.

Observational and clinical studies confirm that maintaining serum urate levels below saturation resolves crystals in tissues, including joints and tophi. The key phrase here is maintaining subsaturating urate levels because in contrast to the treatment of other diseases, successful urate-lowering treatment depends on urate reduction to below a discrete threshold value. We would not expect that reducing urate to values above saturation would produce benefit.

That resolving urate crystals ultimately results in clinical benefit was established in a randomized, placebo-controlled trials of the intravenously administered urate-lowering biologic agent pegloticase, where serum urate levels less than 1 milligram per deciliter were observed.

In the case of oral agents, where the serum urate levels achieved are not nearly as low, the clinical benefits of goal-range urate lowering are expected to take longer to achieve. In fact, with all urate-lowering agents, clinical endpoints such as tophus resolution or reduction in gout flares has not been achieved during the periods of randomized control trials, including the qualifying trials for the last oral urate-lowering therapy approved in the U.S., febuxostat.

So despite the clear efficacy demonstrated by lesinurad xanthine oxidase inhibitor combination therapy, in terms of rapid sustained serum urate lowering, it does not surprise me that clinical benefits, in terms of reduction in flares and tophi, were not observed in the 12 months of the clinical trials. If serum urate goals are consistently maintained over a longer period of time, I would expect that the clinical benefits will be observed as we are seeing in the ongoing lesinurad extension studies.

What are the impediments to achieving serum urate goal levels in gout patients? First, the XOIs

allopurinol and febuxostat have high rates of failure to reach or maintain goal urate concentrations at the doses commonly prescribed. This situation is compounded by the lack of dose titration of allopurinol in practice, something that we've not been able to address successfully over the past 50 years.

Second, there are very few good options available for the large number of patients who fail on current XOIs and need additional serum urate lowering. ACR treatment guidelines for gout and indeed the allopurinol label since 1966 recommend the use of combination therapy of an XOI and an agent increasing renal uric acid excretion when additional urate lowering is required.

However, the only approved uricosuric agent available for gout is probenecid, which the practicing community rarely prescribes. Probenecid has many limitations, including dosing frequency, drug-drug interactions, and perhaps most important, minimal clinical trial data regarding the safety and efficacy of probenecid when used in combination with an XOI.

Although intravenous pegloticase has

demonstrated impressive results, its use is reserved only for the most severely affected and otherwise treatment-resistant patients. There is a clear need for new effective, second-line treatment options to manage the hyperuricemia associated with gout. If approved, lesinurad 200 milligrams, when added to an XOI, can address this need and bridge the treatment gap between XOIs and intravenous pegloticase.

The lesinurad clinical development program represents the first time that combination therapy with an XOI has been studied in randomized controlled clinical trials. Getting patients to the urate target range is the only established means to control gout.

The lesinurad clinical data clearly demonstrate that lesinurad 200 milligrams, when used in combination with either allopurinol or febuxostat, resulted in clinically meaningful serum urate lowering. In addition, the large randomized trials also provide a well characterized safety profile that in my opinion is acceptable and manageable for these patients with limited options.

Overall, I believe the positive benefit-risk

profile of lesinurad 200 milligrams, in combination with an XOI, supports its approval and will contribute importantly to a successful gout treatment paradigm. Thank you, and now the sponsor will return to the lectern to answer your questions.

Clarifying Questions

DR. NEOGI: Thank you.

We will move on to the clarifying questions. Are there any clarifying questions for Ardea Biosciences? Please remember that all participants from the panel, FDA, and Ardea should state their name for the record before you speak. If you can, please direct questions to a specific presenter.

Dr. Miller?

DR. MILLER: Don Miller. This is for Dr. Adler. You had some data on the incidence of kidney stones overall. We also had about 10 or 15 percent of patients with prior kidney stones. Do you have data on renal events in that subgroup?

DR. STORGARD: Yes, we do. We have information on the rate of kidney stones that occurred in the patients who had prior history of kidney stones.

Dr. Adler, could you please show that data?

DR. ADLER: In patients that had kidney stones and had a history of kidney stones, we had 8 patients with a prior history of stones that developed stones on the placebo, 2 out of 3 patients on lesinurad 200, while only 3 of 13 on lesinurad 400 had a history of stones.

DR. NEOGI: I'll go ahead with the next question, then. I was curious as to whether or not flare gout attack history evaluated in relation to renal AEs and MACE.

DR. STORGARD: So we did attempt to look at that relationship, and we did not see any correlation that was meaningful.

DR. NEOGI: Dr. Reimold?

DR. REIMOLD: Andreas Reimold. Also for Dr. Adler I believe, I was interested -- even though the patient number gets small -- in those taking higher doses of allopurinol or -- yes, allopurinol, certainly higher than 300. Was there any difference in the renal adverse events?

DR. STORGARD: We looked at the subgroup of

patients taking higher doses of allopurinol greater than 300, and we saw consistent efficacy. And also, importantly, as you're asking regarding safety, we did not see an alteration in the safety profile in those patients taking high-dose allopurinol.

I know you asked about renal. We also specifically looked at the hepatic profile in those patients given the concern with higher-dose allopurinol, and we did not see any evidence of any impairment in renal function or hepatic impairment in those patients.

DR. NEOGI: Dr. Caplan?

DR. CAPLAN: Thank you. Regarding the slide CO-79, which reports the mortality, a number of the fields are reported as not applicable rather than zero, and I just wanted an explanation for that.

DR. STORGARD: That is because in the uncontrolled extension studies, we did not have a comparator. And in the phase 3 monotherapy study, only lesinurad 400 milligrams was studied. So non-applicable means that that dose or comparator was not available in that portion of the studies.

DR. NEOGI: Dr. Berney?

DR. BERNEY: Seth Berney. Have you tested this compound or drug in alcoholics, both safety and efficacy? And how effective is it in patients who take aspirin and diuretics?

DR. STORGARD: So regarding the first question, we did not specifically test this in alcoholics, but we did have a very liberal alcoholic intake exclusion criteria in that we were allowed up to 14 drinks per week, was the exclusion criteria.

DR. BERNEY: That's only two drinks a day. And at least in my experience, that's not very alcoholic-ish.

(Laughter.)

DR. STORGARD: Appreciate that. But we did not specifically enroll a cohort of alcoholics to the studies.

DR. BERNEY: And the reason why I ask is, in clinical practice, we see a lot of patients with gout who drink a fair amount. And the alcohol seems to contribute to the development of their hyperuricemia. So I was curious about the use of this drug in those

patients in regards to efficacy but also liver safety since, as I was perusing the information that we had received, there's some question about hepatotoxicity.

DR. STORGARD: If I can just better understand your question on hepatotoxicity, I'd be happy to address that. In our clinical trials, we did not see any evidence of increased proportion of greater than threefold elevations. There were no Hy's laws. And if we could see the LFT changes over time, please?

When we looked at just the LFT changes over time -- the line graph, please -- we actually are seeing that patients receiving lesinurad 200 milligrams and 400 milligrams of -- the line graph of LFT changes over time, please. First, I'll show you what we're seeing here, as mentioned earlier -- there we go. Thank you.

So what was reported in the main presentation with those were the higher categories of cutoff. But here now, looking just at the ALT and AST and bilirubin changes, over time, you're seeing in gray the XOI-alone group and in green the 200 milligrams plus XOI. So we are not seeing even any slight increases with

200 milligrams in the xanthine oxidase inhibitor as a population.

I believe you also had a question regarding efficacy in some of the subgroups, and primarily those with aspirin use. Lesinurad has demonstrated consistent efficacy in all patient subgroups tested. That includes those taking baseline aspirin. As you can see here, consistent response rate compared to the overpopulation, as well as in those taking diuretics.

DR. NEOGI: Dr. Tchetgen Tchetgen.

DR. TCHETGEN TCHETGEN: Eric Tchetgen Tchetgen. Concerning slides CO-45, could you please clarify -- I have two clarifications, one, how you accounted for missing data here, and the second one is how exactly that significance level was computed.

DR. STORGARD: This is an observed case analysis, so the data points you're seeing here represent data that's actually present in this analysis. Regarding how the statistics were performed, it was based upon the change from baseline to each monthly visit. It was not comparing the placebo group versus 200, but for instance the 200 at month 1 versus

their baseline visit. That was the change.

DR. TCHETGEN TCHETGEN: So there are multiple changes here. I'm assuming the correlation was accounted for --

DR. STORGARD: Dr. Bushnell, could you please address the question?

DR. TCHETGEN TCHETGEN: -- in multiplicity?

DR. BUSHNELL: Will Bushnell, AstraZeneca. These were visit-wise analyses and ANCOVAs that were done. There was no control for multiplicity here.

DR. NEOGI: Tuhina Neogi. I'll ask another question. A lot has been said about the purported mechanism of the renal AEs being of the urate precipitation. I understand that's the hypothesized mechanism, but are there any other potential etiologies that could help physicians monitoring think about what other possibilities there could arise.

I don't think you showed actual data that there was uric precipitation. And I think when I read the background material, in the animal models, there was no evidence of the urate precipitation.

DR. STORGARD: So if I first may address the

data that supports our hypothesis. As we see here, when we take a look at 400 milligrams of lesinurad -- and I think this is the best example because we have data.

In 400 milligrams as given as a monotherapy, you see that increase in urinary uric acid excreted. Used in combination with an XOI, it is decreased. And this amount of urinary uric acid excreted correlates with the incidence rates of serum creatinine elevations, so lower in combination than monotherapy.

Now, if we could also now see the resolutions of serum creatinine elevations, please. Importantly, as Dr. Adler presented, the serum creatinine elevations, the majority of these all resolved and the majority well on treatment. So this would not support a nephrotoxic type picture with this resolution with continued treatment. So we believe that the most likely hypothesis is the intratubular acute obstruction due to uric acid precipitation.

DR. NEOGI: Dr. Kaboli?

DR. KABOLI: Peter Kaboli. My question has to do with outcomes that are important to patients, which

are flares, tophi, and health-related quality of life. And I completely understand that in a 12-month study that's really hard to show.

Do you have any data in the extension studies that suggest that there is patient-level clinical benefit as opposed to just blood level improvements?

DR. STORGARD: Dr. Fung, could you please address the question regarding PROs and any suggestion of benefit in the extension studies, please?

DR. FUNG: Maple Fung from Ardea Biosciences. Similar to what Dr. Storgard had already showed regarding the extension studies, over time, we continued to show -- initially, on the left-hand side of this figure is the CRYSTAL study, study 304, showing that there was a decline in their pain VAS scores. And that improvement continues to progress throughout the extension studies in the two years that patients have been on study. This is just one example representative of PRO benefits we saw in our extension studies.

DR. KABOLI: But anything with flares?

DR. STORGARD: So regarding the flares, yes. If we could have the original core study in the

extension, please? Sorry. The figure of the extension flare rate from the core presentation. Thank you very much.

So what we're seeing here, again, this is the cohort of patients who received lesinurad 200 milligrams in the pivotal studies and then continued treatment into the extension study, in the CRYSTAL study. So this is 200 milligrams plus febuxostat. And you're seeing -- with continued treatment, we are seeing a reduction in the number of flares that are observed in this extension study.

But also, regarding the tophi resolution, again, this is showing only those patients receiving 200 milligrams in the core and continuing treatment into the extension; on the left in combination with allopurinol, and on the right in combination with febuxostat.

As mentioned earlier, we're not making any statements regarding superior treatment as we do not have a placebo control arm in this study, but we do see that continued improvement with a reduction in flares and an increase in the number of tophi resolution that

would be expected and has been observed in clinical practice.

DR. NEOGI: Dr. Berney?

DR. BERNEY: Seth Berney. To clarify that, in your extension study where you showed the febuxostat and the compound of decreased flares, you do not have a comparator with the febuxostat and placebo. Is that correct?

DR. STORGARD: That's correct. In the extension studies, all patients were on lesinurad, so we do not have that comparator in the extension studies.

DR. BERNEY: So there's no data on whether that's statistically significantly better than what conventional therapy would provide.

DR. STORGARD: That's correct. We do not have data on that.

DR. NEOGI: Ms. Chauhan.

MS. CHAUHAN: Regarding the demographics, how do your demographics reflect the actual incidence of gout in the populations that you studies? And when you break down the adverse events by demographics, is there

anything that stands out regarding race or sex?

DR. STORGARD: So the demographics of our population we believe are representative of the gout population in general. We looked at various demographics to look for any changes in the AE profile or the safety profile, and we did not see any. So lesinurad demonstrated consistent efficacy across all the demographics that we were looking at and included females and race and ethnicity and age.

DR. NEOGI: Dr. Reimold?

DR. REIMOLD: Thank you. Andreas Reimold. I'm returning one more time to the renal issues. It's been mentioned today, and also in the meeting materials, that increasing volume intake, also alkalinization of urine, might be desirable to minimize side effects. Was that actually addressed and quantified? And if so, are there hard data as to improved outcomes with that?

DR. STORGARD: Regarding the use of alkalinization, that was included in the protocols. We did try and look to see whether or not that had any impact. Unfortunately, few patients actually used

alkalinization. There were only 16 patients in the pivotal studies on lesinurad who took an alkalizing agent, so we were unable to make any conclusions to the impact of alkalinization.

DR. REIMOLD: Volume?

DR. STORGARD: Regarding volume, we did actually put in an amendment where we further encouraged and specified the amount of hydration to be taken, 2 liters of fluid per day. And we performed an assessment pre-amendment and post-amendment, and we were not able to see any impact there on the renal function.

DR. NEOGI: Dr. Delost?

DR. DELOST: For Dr. Storgard, I just have a question regarding the design and the draws of the serum urate. Was it randomized on the draw time during the day? Because of its relative short half-life, I was wondering if there was a randomization of when those serum urate levels were drawn or it was all drawn at the same time.

DR. STORGARD: It was random. We did not specify the time of the serum uric acid draws. It was

specified that it should be done after their morning dose and whenever they came into the clinic.

DR. DELOST: Like 6:00 at night, there probably wasn't any --

DR. STORGARD: No, that's correct. But I think if you're wondering did that have any impact on our assessment, we looked at that. We looked carefully at that. And I can show you some of that analysis here. We looked at the distribution of sample times in the clinic based upon the data we have in our population PK data.

You're seeing here that the majority of patients came in at around 3 and a half hours. The maximal impact of -- the maximal lowerings observed within 4 to 6 hours, we had less than 20 percent of patients actually having their blood draws at that maximal impact.

So what we're seeing here is that the random sampling that we had we believe is not overestimating or underestimating the effectiveness of lesinurad.

DR. DELOST: So you don't foresee a clinical impact on that because of --

DR. STORGARD: No, we do not. And as was mentioned by the FDA, that small change during the day with lesinurad 200 milligrams is not significant. So we believe that the efficacy is consistent throughout the 24-hour period.

DR. DELOST: Thank you.

DR. NEOGI: Dr. Leff?

DR. LEFF: Yes. Hi. This is a question about just risk factors I guess for the -- MACE events were rare, renal events, and not actually prospective. But at the time of the event or just beforehand, were the serum uric acids, in terms of the lower ones, potentially associated with those events or not?

DR. STORGARD: We looked closely at that. We looked at serum uric acid levels at baseline, maximum serum uric acid change at any time of the study, and the serum uric acid prior to the MACE event. There was no association. Fifty percent of the patients who had a MACE event had an sUA greater than 5 and 50 percent had an sUA less than 5. So we were not seeing a relationship with sUA lowering in MACE events.

DR. NEOGI: Dr. Caplan?

DR. CAPLAN: Thank you. Liron Caplan. Regarding slide CO-37, you report a number of comorbidities. CHF is not mentioned as one of those. And I'm wondering, particularly given the recommendation for 2 liters of fluid intake, whether you had any data indicating how this drug would perform in folks with CHF.

DR. STORGARD: The protocols excluded patients who had New York heart failure class 3 or 4 from participating, so we do not have specific data in that subset of patients.

DR. CAPLAN: But there was no -- in your communication or your plan, there was no indication that folks with CHF shouldn't be administered this, if I'm remembering correctly.

DR. STORGARD: So we did perform our analysis on the hydration recommendation before and after the amendment, and we did not see any impact regarding adverse events that were related to fluid overload. So we're not concerned that the fluid recommendations will propose a risk to those patients.

DR. CAPLAN: But you excluded them, and then

you said you didn't see any rates of fluid overload, which you wouldn't expect to see if you had excluded folks with CHF.

UNIDENTIFIED MALE SPEAKER: Class 3 and 4.

DR. CAPLAN: Three and 4, but still.

DR. STORGARD: Three and 4, yes. We cannot comment on that population with class 3 and 4, as they were not in our studies.

DR. NEOGI: Tuhina Neogi. I'll ask the next question. I wanted to see if you could comment upon Dr. Yim's introductory slide. One of the points raised was a question about bid dosing. And I understand the rationale for doing the once-daily dosing. That was well laid out in your presentation. But perhaps you could address that particular point about whether or not there might be a similar efficacy and perhaps a gain of improved safety with bid dosing.

DR. STORGARD: So we've considered bid dosing from the beginning of the program, and in the interest of patient safety, we did not pursue that. So we have not done any studies with twice-daily dosing. And the reason for that, as Dr. Adler presented, if we're

increasing the uric acid excretion within 6 hours after dosing, and if that were to be done at night when the urine pH is lowest and the urine volume is lowest, we feel that that would be an environment with the highest probability of uric acid precipitation.

So going into this, with the history of kidney stones as reported with probenecid, that was one of the things we were concerned about. And we did not see that, the rate of increase of kidney stones in our studies despite allowing patients with history of kidney stones to enroll, and it may be related to the fact that we're giving this in the morning rather than in the evening. So from the interest of patient safety, we feel it was not appropriate to dose it twice daily.

DR. NEOGI: Dr. Becker?

DR. BECKER: Hi. Mara Becker. I was hoping you might be able to comment a little bit more on the drug-drug interactions since this drug is a CYP2C9 and CYP3A4 effector and how that might affect your drug labeling recommendations.

DR. STORGARD: Dr. Kerr, could you please

address the question?

DR. KERR: Brad Kerr, Ardea Biosciences. The interactions via the CYP3A4 induction would be expected to affect drugs that are considered sensitive substrates of CYP3A. And the effect is not large or beyond the order of 25 to 50 percent for change in exposure for those drugs that are the most sensitive substrates of CYP3A. And that's in contrast to the interactions with probenecid, which are inhibitory interactions where you see large increases in exposure due to the 01-03 inhibition, which lesinurad does not do clinically.

Regarding the 2C9, clinical inhibitors of CYP2C9 are uncommon. In our phase 3 study, there's only one patient who was a moderate inhibitor of CYP2C9 at the time a blood concentration was drawn, so we couldn't assess the impact in the phase 3 studies. But in the phase 1 study, we know fluconazole, which is a moderate inhibitor of CYP2C9, caused an approximately 50 percent increased exposure of lesinurad. So that would be less than a step-wise increase in dose from 200 to 400 milligrams.

DR. NEOGI: Dr. Berney?

DR. BERNEY: How does this drug compare with probenecid in terms of efficacy of urate lowering?

DR. STORGARD: We cannot find a lot of studies on probenecid. In combination with an XOI, there are no randomized trials, so I can't comment on that. We considered doing a head-to-head trial early on because I think that's the question many of us would have wanted to see.

When we looked at our phase 3 studies, 40 percent of the patients were on concomitant medications that were listed as a significant or important drug-drug interaction, so that was a challenge in order to do that head-to-head trial. Also, because probenecid is given multiple times daily, there were significant challenges with the feasibility of blinding. But regarding specific direct comparisons of the magnitude of sUA lowering, I cannot comment on probenecid in combination with an XOI, as there were not randomized trials.

DR. CAPLAN: One other question. Do you have data on what adverse effects are expected if patients

do not drink the extra fluid or water that you've recommended?

DR. STORGARD: We do not have specific data on that.

DR. CAPLAN: Because one of the concerns that I've always had, and one of the issues that have prevented me from prescribing uricosurics, is that patients aren't going to drink the extra volume through the day. So that might limit this drug's usefulness, so I was really curious whether there was data on that topic.

DR. STORGARD: What I can tell you is when we did our assessment pre the amendment of the hydration requirements versus post the amendment, the renal related adverse events were similar, approximately 9 percent in both.

DR. NEOGI: Dr. Caplan?

DR. CAPLAN: You had mentioned earlier that, I believe, there were 18 patients in which they were receiving some kind of therapy for alkalinization. Is that correct?

DR. STORGARD: I believe it was 16, but I'm

not sure -- yes, 16.

DR. CAPLAN: And was that part of the protocol? Did they come in on that or did they initiate that in the context of the trial because of what you saw in the urine pH?

DR. STORGARD: I believe the majority of those were added. Some of them were on the drug at the beginning, but I don't have that specific breakdown for you right now.

DR. CAPLAN: And do you know how many had a urine pH of over 6.5?

DR. STORGARD: Of those patients?

DR. CAPLAN: Of anyone. In other words -- if I understood this correctly in the background material, there was mandatory testing of urine pH. I guess my question was whether you're anticipating that being part of the monitoring for this medication.

DR. STORGARD: So we did collect urine, and we did try and do pH on those urines. However, because of the collection method, there was up to 72 hours by the time of collection to the time of urinary pH measurement. And because of the impact of sitting at

room temperature on urine pH, we did not feel that those measurements were reliable. The median urine pH on that was still around 5.5 across all treatment groups.

DR. CAPLAN: So was the decision -- what was the basis of the decision whether to alkalinize the urine or not? Was that just left to the clinician?

DR. STORGARD: Sure. The protocols indicated that if a patient had more than one serum creatinine elevation, that the -- well, the physician was informed of the option of alkalinizing the urine. If it had more than one, to consider it. If the patient had more than 2 elevations, that it was mandatory to use alkalinization to try and raise the pH.

DR. CAPLAN: So is that going to be part of the description of how to -- you know, that sort of monitoring and than alkalinization protocol, is that going to be part of the description of how to use the drug appropriately?

DR. STORGARD: That is not part of our current proposal, and the reason being is that we really did not have an opportunity to test its effectiveness. So

without being able to test the effectiveness of an intervention, if you will, we do not feel it's appropriate to put it in as part of the proposed monitoring or activities to do.

DR. NEOGI: Dr. Berney?

DR. BERNEY: Sure. Other than severe renal failure and CHF, what other conditions do you anticipate would exclude the use of this drug?

DR. STORGARD: So lesinurad is being recommended for use for patients who have not achieved goal on a xanthine oxidase inhibitor. Right now, the only contraindications that we have in place are those with severe renal insufficiency with a creatinine clearance of less than 30 and those on renal dialysis or renal replacement -- sorry, on end-stage renal disease.

We did include in our warnings precaution, a warning for use in patients with a creatinine clearance of less than 45 because of limited numbers. The efficacy and safety in that population was consistent with the overall population. We do not have any other contraindications in place at the present time.

DR. BERNEY: I'm sorry. What other conditions have you looked at to ensure safety?

DR. STORGARD: The phase 3 population we believe is a broad representative population. A subpopulation you're concerned about?

DR. BERNEY: Well, liver disease patients, actually.

DR. STORGARD: The liver disease patients, there's no dosing adjustments recommended for mild or moderate hepatic impaired patients. It was not studied -- we did a phase 1 study that evaluated lesinurad in patient with hepatic impairment with mild and moderate, and the impact on PK was not altered. So no dose adjustments for patients with mild or moderate hepatic impairment.

DR. NEOGI: Dr. Oliver?

DR. OLIVER: Alyce Oliver. You showed that between the study drug and the control, in terms of looking at high blood pressure, that there was no difference. It appears that amlodipine -- or excuse me, the study drug can decrease the efficacy of amlodipine. Were you able to do a subgroup analysis

seeing if it did -- in that population, taking amlodipine, were there differences in hypertension?

DR. STORGARD: Dr. Bhakta, could you please address the question?

DR. BHAKTA: Nihar Bhakta, Ardea Biosciences. With respect to your question, we evaluated specifically patients who were taking a CYP3A4 antihypertensive medication, including amlodipine at baseline. We involved all CYP3A4 medications in that analysis. We did see a small increase in the number of patients who experienced a hypertension adverse event in that subgroup of patients.

There are 9 patients on placebo who experienced a hypertension adverse event; 13 patients on lesinurad 200 milligrams who experienced a hypertension adverse event. Therefore, we're recommending that patients who are utilizing a CYP3A4 medication, for hypertensive purposes, with lesinurad be monitored for loss of efficacy.

DR. OLIVER: Alyce Oliver. Along a similar note, what are your recommendations for sildenafil?

DR. STORGARD: Dr. Kerr, could you please

comment on our sildenafil interactions, please?

DR. KERR: Brad Kerr, Ardea Biosciences. The sildenafil DDI study, sildenafil is a sensitive substrate of CYP3A, and the 200-milligram dose resulted in approximately a 35 percent decrease in sildenafil exposure. And the recommendation in the draft label is to monitor for activity.

DR. NEOGI: If there are no further questions, we'll take a 15-minute break. Actually, I'm going to make that 13 minutes.

(Laughter.)

DR. NEOGI: So panel members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. We'll resume at 10:25.

(Whereupon, at 10:12 a.m., a recess was taken.)

DR. NEOGI: If I could ask everyone to please take your seats, we'll get started with the next portion.

We will now proceed with the FDA presentations.

FDA Presentation – Rosemarie Neuner

DR. NEUNER: Hello. My name is Rosemarie Neuner. I'm a rheumatologist in the Division of Pulmonary, Allergy, and Rheumatology Products at the FDA. Today, Dr. Chen from the Office of Clinical Pharmacology and Dr. Wang from the Office of Biostatistics and I will be presenting the FDA's review findings on lesinurad for the treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor.

My presentation today will include a brief background and review of the issues associated with this application, followed by an overview of the phase 3 trials for lesinurad. I will then hand over the podium to my colleague, Dr. Chen, who will discuss the clinical pharmacology considerations for lesinurad.

She will be followed by Dr. Wang, who will discuss the statistical considerations of lesinurad's efficacy before I return to present a summary of safety issues that were identified over the course of the FDA's review of this drug.

As Dr. Yim and Dr. Saag have mentioned, there

are currently four therapeutic agents approved for the treatment of gout. These include the xanthine oxidase inhibitors, allopurinol and febuxostat, the uricosuric agent probenecid, and the uricase pegloticase, which are associated with variable degrees of urate lowering and various toxicities. If approved, lesinurad would be included with the other second-line agent probenecid by virtue of its uricosuric mechanism of action.

There are three issues that we ask you to keep in mind as you listen to the FDA presentations today. The first two, which will be discussed in detail later in our talks, are lesinurad's efficacy and various dose-dependent safety issues. As you have heard Dr. Yim state earlier, the average treatment effect for the proposed dose of 200 milligrams of lesinurad on background xanthine oxidase inhibitor was a decrease of approximately 1 milligram per deciliter of serum uric acid at the month 6 time point.

In terms of dose-dependent safety issues, the 400-milligram dose of lesinurad was associated with an increase in overall adverse events, serious adverse events, serious and non-serious renal adverse events,

and major adverse cardiovascular events, or MACE, while the 200-milligram dose was associated with an increase in adverse events, renal adverse events, and serum creatinine elevations.

The third issue for your consideration is the adequacy of dose and dosing interval selection. As you have heard during the applicant's presentation, the 400-milligram dose of lesinurad is not proposed for marketing due to safety concerns. However, the 200- and 400-milligram doses have overlapping plasma exposures, which will be discussed by Dr. Chen during her talk. In view of lesinurad PK/PD profile use of a more frequent dosing interval may have provided for similar or better efficacy at a lower dose.

The applicant's phase 3 clinical development of lesinurad is comprised of four trials, three 12-month randomized controlled studies, 301, 302, and 304, that evaluated 200-milligram and 400-milligram doses of lesinurad in gout subjects on background xanthine oxidase inhibitor therapy, and one 6-month randomized controlled monotherapy study, 304, that evaluated 400 milligrams of lesinurad.

Although stage 301 and 302 were replicate trials with similar design features, studies 304 and 303 differed from them and each other in some important ways. These include differences in the entry requirement for baseline serum uric acid. Study candidates for 304 who had not received prior urate-lowering therapy had to have a serum uric acid greater or equal to 8 milligrams per deciliter, while subjects already on urate-lowering therapy had to have a lower serum uric acid of greater than or equal to 6 milligrams per deciliter.

Differences in clinical manifestations of hyperuricemia. Subjects enrolled in study 304 were also required to have one or more tophi of a specified test, while the common protocol for studies 301 and 302 mandated that patients had to have 2 or more gout flares in the past 12 months. Although the protocols for the 3 xanthine oxidase studies enrolled patients with a history of renal stones, the protocol for the monotherapy study, 303, excluded subjects with a history of renal stones.

Another important difference in the design of

these phase 3 studies was a choice of primary endpoints. Studies 301, 302, and 303 evaluated the same primary endpoint, which was the proportion of subjects who achieved the target serum uric acid level of 6 milligrams per deciliter or lower at month 6. However, study 304 evaluated a lower serum uric acid target threshold of 5 milligrams per deciliter or lower at month 6. Of note, none of these protocols prespecified the timing of the serum sampling for the serum uric acid levels for the primary endpoint.

Overall, the treatment groups within the phase 3 trials were generally balanced. However, I would like to highlight some additional differences between these studies. Study 301 was conducted primarily in the U.S., while the other three trials were multiregional studies.

Comparable baseline serum uric acids were observed in studies 301 and 302. However, study 303 had the highest baseline mean serum uric acid at 9.3 milligrams per deciliter, while study 304 had the lowest baseline mean serum uric acid of approximately 5.3 milligrams per deciliter. Additionally, 50 percent

of the subjects in the study had already reached a threshold serum uric acid level or a primary endpoint of 5 milligrams per deciliter.

The majority of the subjects in studies 301 and 302 were also taking 300 milligrams of concomitant allopurinol at baseline, while very few subjects in either of these trials were taking doses higher or lower than 300 milligrams per day of allopurinol. Additionally, very few subjects who participated in these four trials had creatinine clearances before 45 or 60 mLs per minute.

Now, Dr. Chen will present the FDA's clinical pharmacology review findings.

FDA Presentation - Jianmeng Chen

DR. CHEN: Thank you, Dr. Neuner.

Good morning, everyone. My name is Jianmeng Chen. I am the clinical pharm reviewer for this NDA. In my presentation, I will cover the basic pharmacokinetic characteristics of lesinurad, briefly go through the dose selection for phase 3 studies, the exposure response analysis for the efficacy and the safety for the phase 3 studies, and will discuss the

risk-benefit profile in the context of renal impairment.

As the sponsor just mentioned, lesinurad is 100 percent available with maximum concentration reached within 4 hours. It is recommended to be taken with food due to the increase uricosuric acid lowering effect with food. Lesinurad is highly protein bound, and it is metabolized by CYP2C9. The terminal half-life is 5 hours, similar to that of probenecid.

Lesinurad exposure is higher in patients with renal impairment with about 73 percent increase in exposure --

(Pause.)

DR. NEOGI: So we will be going out these back doors to the right, and then out into the courtyard outside, and then we will resume as soon as we can.

(Whereupon, at 11:34 a.m., a recess was taken.)

DR. NEOGI: If everyone could please quickly get to your seats, we'd like to get going again, to try to keep on time as much as we can. I think we were in the midst of Dr. Chen's presentation. Is Dr. Chen

back?

(Pause.)

DR. CHEN: Hello again, everybody. Just as you heard before the nice walk outside, lesinurad is 100 percent bioavailable with maximum concentration reached within 4 hours. It is recommended to be taken with food because of the increased uric acid lowering effect with food.

Lesinurad is highly protein bound and is metabolized by CYP2C9. The terminal half-life is 5 hours, similar to that of probenecid. Lesinurad exposure is higher in patients with renal impairment with a 73 percent increase in exposure in moderate renal impairment.

As it is a CYP2C9 substrate, the exposure is higher in CYP2C9 per metabolizers, which will account for about 1 to 5 percent of the general U.S. population. The extent of exposure in this subgroup of patients will be similar to that of patients with moderate renal impairment.

The doses selected for phase 3 were based on phase 1 and phase 2 dose-ranging studies. Before

phase 3, various doses were evaluated in both healthy volunteers and gout patients. The rest daily dosing regimen was used in all clinical studies.

Study 110 demonstrated the daily serum urate variation with the once-daily dosing regimen, and doses lower than 200 milligrams or higher than 600 milligrams were only assessed in healthy volunteers. The dose response on background of allopurinol was confirmed in the phase 2 study 203.

The once-daily dosing regimen was used in all phase 1, 2, and 3 clinical studies. As you heard from the sponsor, the PD effect is supposed to last longer than the PK half-life, and uric acid lowering effect did not return to baseline at 24-hour post-dose. The sponsor also stated the theoretical safety concern with twice-daily dosing. However, the once-daily dosing regiment does lead to some uric acid variations throughout the day.

This figure is taken from study 110, which was a study in gout patients. The figure shows the mean serum uric acid change from baseline over a 24-hour post-dose for lesinurad monotherapy, allopurinol

monotherapy, and the combination therapy. The daily variation of serum uric acid, relative to lesinurad dose, is demonstrated by both the lesinurad monotherapy, as shown in the green curve, and the contribution of lesinurad in the combination therapy, as shown in the blue numbers in this table.

You may appreciate that the most uric acid lowering effect was observed around 6 to 12-hour post-dose, and highest serum uric acid level was at pre-dose or 24-hour post-dose. The phase 3 studies, the sampling time points for serum uric acid is not prespecified. For primary endpoint assessment, most samples were collected between 1- to 4-hour post-dose in phase 3.

With the daily variation in serum uric acid, the dose response for lesinurad is assessed for 6-hour post-dose, which would represent the maximum effect of lesinurad, as shown in the left panel. The dose response is also assessed for 24-hour post-dose, which would represent the trough effect of lesinurad, as shown in the right panel. These are single-dose studies in healthy volunteers.

The figure show the mean percentage serum uric change from baseline adjusted by placebo, which is the Y-axis over different doses, which is the X-axis. As you can see in the plot, there is a nice dose response between 5 to 1600 milligrams with 200 milligrams and 400 milligrams on the steep part of the dose-response curve. Therefore, at once-daily dosing regimen, doses lower than 200 milligrams would lose efficacy significantly.

On the other hand, with the short half-life and daily variation of serum uric acid relative to lesinurad dose, potentially a lower dose given more frequently may also be effective. However, a more frequent dosing regimen was never tested in the whole development program.

Several dose-ranging studies were done in gout patients, assessing doses 200 to 600 milligrams as monotherapy or in combination with allopurinol or febuxostat. What's presented here is the dose-ranging study in combination with allopurinol. The figure shows the mean percentage serum urate change from baseline measured at pre-dose on day 27.

As you can see in the plot, there's a nice dose response between 200 to 600 milligrams once daily with 600 milligrams being the most efficacious. With consideration of safety, the two doses of 200 and 400 were carried on to phase 3 studies.

Now, we'll talk about the exposure response or dose-response analysis for the combined phase 3 study 301 and 302. The sponsor just shared with you the phase 3 data of lesinurad, which showed a dose response in efficacy for both the responder analysis and absolute serum uric acid decrease.

Consistent with the dose response, the exposure-response analysis demonstrated an increase of proportion of responders with increased exposure. There is overlapping exposure for 200 milligrams and 400 milligrams, and the exposure for post-200 milligrams and 400 milligrams are on the steep part of the exposure response curve.

For safety, you already heard the dose-dependent renal toxicity from the sponsor. The graph summarizes the mean creatinine clearance change from baseline from the two different doses around

6 months of study in the combined studies 301 and 302. The Y-axis represents the actual change in creatinine clearance, and the X-axis shows the months into the trial. You can see a clear dose-dependent decrease in creatinine clearance in the lesinurad treatment group.

Average exposure in the 400 milligrams is about twofold higher than the 200-milligram group. As shown in the box plot here, at the individual patient level, there is some overlap in exposure between the two doses, which is expected.

Also in the graph, the exposure of patients who experienced MACE event or a major renal adverse event during the 12-month placebo-controlled study, also the patients who experienced fatal MACE events, dialysis, or a renal biopsy in the extension study. The MACE events were shown in the red diamond, and the renal events were shown in the open black circle. Note that the PK information is not available for all patients with safety events.

We can see that the MACE events and renal events were observed for both doses, and there is a trend of higher incidence of MACE events with higher

exposure of lesinurad. The MACE events happened in the same range of exposure for both doses. For specific numbers, the average concentration for the 200-milligram arm is about 1700 nanograms per mL. For MACE event patients who are on 200-milligram arm, the average exposure is about 3,000 nanograms per mL.

Now, I will focus on efficacy and the safety in patients with renal impairment. The sponsor just talked about the dose-dependent adverse events. As you will hear from Dr. Neuner, both the FDA and the sponsor agreed that the 400-milligram dose is not safe for gout patients despite a slightly better efficacy.

For moderate renal impairment patients, it is defined as the population of patients with estimated creatinine clearance between 30 to 60 mL per minute. The exposure is about 50 to 73 percent higher. That means in this subgroup of patients, they're exposed to lesinurad exposure comparable to 300 to 350-milligram dose in general population. This will lead to a safety concern in a subgroup of patients.

For efficacy, the sponsor just shared with you the mechanism of lesinurad. As with other uricosuric

drugs, the efficacy of lesinurad depends on the adequate glomerular filtration in kidney. A decrease in GFR will lead to decreased uric acid in the urine, and you would expect less efficacy in this subgroup.

To come to a recommendation for patients with renal impairment, we looked into the impact of renal impairment efficacy and safety in phase 3 studies. Please note that the phase 3 studies enrolled patients with baseline creatinine clearance above 30 mL per minute, and there are no dose adjustments for patients with renal impairment in phase 3.

Consistent with the mechanism of the drug, the subgroup analysis in studies 301 and 302 showed a trend of decreasing efficacy with decreasing renal function as shown in the responder analysis for the combined studies compared to allopurinol alone and treatment with lesinurad 200 milligrams and background of allopurinol as another 30 percent responder in patients with creatinine clearance at least 60 mL per minute.

Although not statistically significant, a numerical trend in the declined efficacy, decreased creatinine clearance was observed with only 10 percent

responder benefit with lesinurad 200 milligrams in patients with creatinine clearance less than 45 mL per minute. Similarly, when we look at the absolute change in serum uric acid, you can see the same trend of decline in efficacy.

For patients with creatinine clearance less than 45 mL per minute, lesinurad lowered the serum uric acid by about 0.3 milligrams per deciliter compared to the 1 milligram per deciliter effect size in the general population. Based on this analysis, we concluded that the efficacy decreased with decreased baseline renal function and the efficacy in patients with creatinine clearance less than 45 mL per minute is minimal.

We also looked into renal impairment's impact on safety. With the subgroup analysis as shown here, it seems that the dose-dependent creatinine clearance decrease happens to patients with all categories of baseline renal functions. However, the impact of creatinine clearance decline is most severe with patients with worst baseline renal function.

This table summarized the shift of renal

function category from baseline to the last observed value during the core study, which includes studies 301, 302, and 304. As shown in this table, 5 percent of patients with baseline moderate renal impairment deteriorated to severe renal impairment with the one-year treatment of lesinurad 200 milligrams as opposed to 1 percent in the placebo group. While a similar trend was observed for patients with baseline normal or mild renal function, the consequence is more severe for patients with worst baseline renal function.

Finally, for safety events, Dr. Neuner will have a more comprehensive review of safety events. Here we mainly focused on the most severe adverse events: deaths, non-fatal MACE events, and severe renal adverse events during the regular core study; all patients who need dialysis or renal biopsy during the extension study. These adverse events were summarized for placebo and lesinurad 200 milligrams on background of XOIs based on different categories of baseline renal impairment.

While the numbers are small, we see a higher incidence of these severe adverse events in patients

with worst baseline renal function for both the placebo group and the lesinurad group. Also, we noted that for the lesinurad 200-milligram arm, the most severe adverse events all happened in patients with baseline creatinine clearance less than 60 mL per minute.

To summarize the FDA's clinical pharmacology findings, the pharmacokinetic half-life of lesinurad is similar to that of probenecid. The 200 and 400 once-daily doses are at the steep part of the dose-response curve with a short half-life and a daily variation of serum uric acid relative to lesinurad dose. Potentially, a lower dose given more frequently may also be effective.

The average exposure of 400-milligram dose is about twofold higher than that of the 200-milligram dose. However, there is overlapping exposure at individual level. In patients with higher exposure with lesinurad, there are higher risks of adverse events.

In terms of renal impairment, we observed a decreased efficacy with deteriorating renal function in the phase 3 studies, and lesinurad was associated with

a decrease in renal function as measured by creatinine clearance. More adverse events were seen in patients with lower baseline creatinine clearance.

Now, Dr. Wang will present FDA's statistical findings of efficacy.

FDA Presentation - Yu Wang

DR. WANG: Hello. Good morning. My name is Yu Wang. I'm a reviewer in the Division of Biometrics II. I will present the statistical evaluation of efficacy for the key phase 3 clinical studies. The applicant is seeking approval for the use of lesinurad 200 milligrams once daily in combination with a xanthine oxidase inhibitor for the chronic treatment of hyperuricemia associated with gout.

My presentation will first briefly go over the design of the phase 3 clinical program and the analysis plan for the key efficacy endpoints. I will then discuss the key efficacy results, including the primary endpoint analysis and supportive analysis results and a summary of the secondary endpoint results. I will also briefly cover demographic subgroup analysis results and the potential impact of missing data. At the end, I

will summarize the key findings of the review of the efficacy data.

I will begin with the design and analysis methods of the phase 3 studies. But before discussing the details of the phase 3 clinical trials that evaluated lesinurad, I want to again remind you of the important patient outcomes in gout and the typical approach to efficacy endpoint selection in phase 3 clinical trials to evaluate chronic gout treatments.

The important patient outcomes in gout -- in other words, the direct measures of patient benefit -- include reduction in the rate of gout flares, resolution of symptoms from tophi, and improvement in pain and physical functioning.

In phase 3 clinical trials, reduction in serum uric acid, typically using a binary response variable defined by achieving levels below the threshold of 6 milligrams per deciliter, has been used as the primary efficacy endpoint. Reduction in serum uric acid levels is used as a surrogate endpoint for long-term improvement in the direct measures of patient benefit listed here; in other words, long-term

reduction in symptoms and improvement in functioning and quality of life.

It is common to include some direct measures of benefit, for example, gout flares and tophi resolution and patient reported outcomes as secondary endpoints in clinical trials, in order to provide important supportive efficacy information; although, trials of 6- to 12-month duration may not be long enough to identify some benefits expected to be mediated through persistent lowering of serum urate.

As you have heard from Dr. Neuner, the phase 3 clinical program included four randomized, double-blind, multicenter, placebo-controlled studies. Among them, studies 301 and 302 were replicate studies to assess the efficacy and the safety of lesinurad compared to placebo when used in combination with allopurinol in patients with an inadequate response to allopurinol alone.

Study 304 assessed the efficacy and the safety of lesinurad compared to placebo when used in combination with febuxostat in subjects with tophaceous gout who may or may not have been receiving

urate-lowering therapy at study entry. All the above three combination therapy studies were of 12 months duration and similar in design, comparing two doses of lesinurad with placebo in patients receiving a background xanthine oxidase inhibitor. In contrast, study 303 was a 6-month study to assess the efficacy and safety of lesinurad 400 monotherapy compared with placebo in subjects with gout who were intolerant of or had a contraindication to an XOI.

As discussed previously, the proportion of patients achieving target serum urate levels is a surrogate endpoint for direct measures of patient benefit in chronic gout studies. In study 301, 302, and 303, the primary efficacy endpoint was the proportion of patients with a serum uric acid level below 6 milligrams per deciliter at month 6.

In study 304 in tophaceous gout patients, a lower response threshold of 5 milligrams per deciliter was used for the primary endpoint. In the primary analysis, subjects who were missing month 6 serum uric acid data were considered non-responders. Therefore, the primary endpoint was a composite measure of both

achievement of the serum uric acid target and adherence to the study medications through month 6.

Comparisons of response rates between the lesinurad dose groups and the placebo group were conducted using Cochran-Mantel Haenszel tests. To account for the comparison of two doses of lesinurad to placebo in studies 301, 302, and 304, a Bonferroni correction was applied to control the overall type 1 error rate.

Several patient outcomes were evaluated as secondary endpoints with different subsets of endpoints prespecified as key secondaries across the four phase 3 studies. In this presentation, I will discuss the results of the three outcomes listed here. They are direct measures of patient benefit that were evaluated as key secondary endpoints in at least one of the three phase 3 studies.

The first endpoint is gout flares. The mean rate of flares requiring treatment from the end of month 6 to the end of month 12 was analyzed using a negative binomial regression model to calculate incidence rate ratios comparing treatment groups.

The second endpoint is tophi resolution. In the subset of subjects with at least one target tophus at baseline, a Cochran-Mantel Haenszel test was used to compare treatment groups with respect to the proportion of subjects who experienced complete resolution of at least one target tophus by month 12.

The third endpoint is the Health Assessment Questionnaire Disability Index or HAQ-DI. Treatment groups were compared with respect to the proportion of patients who experienced an improvement in HAQ-DI of at least 0.25 from baseline.

I will now present the primary efficacy results of the main phase 3 studies. Rates and the reasons of discontinuation of study treatment prior to month 6, which was the time point of the primary endpoint assessment are summarized in this table. Nearly all subjects who discontinued the study treatment prior to month 6 also withdrew from the study. I derived this overall disposition table based on integrated data from the three combination therapy studies 301, 302, and 304. Trends were similar within the individual studies.

The overall discontinuation rate was 16 percent and the lesinurad arms tended to have slightly higher overall discontinuation rates than the placebo arm. Of note, there was greater discontinuation due to adverse events in the lesinurad arms with rates of 5 percent and 6 percent in the 200- and 400-milligram arms as compared to 3 percent on placebo.

This table presents the subject disposition at month 6 in study 303. The discontinuation rate was considerably higher in the lesinurad arm at 33 percent than in the placebo group at 16 percent. Greater dropout due to adverse events and withdrawal of consent, in particular, contributed to the noticeably higher dropout rate in the lesinurad 400-milligram arm.

Here, I present the primary efficacy endpoint results in the allopurinol background therapy studies 301 and 302. Statistical significance was reached at both doses in both studies. At month 6, 54 to 55 percent of subjects on lesinurad 200 milligrams had concentrations of serum uric acid lower than 6 milligrams per deciliter as compared to 28 and 23 on

placebo; thus, around 30 percent more patients on lesinurad 200 milligrams achieved as the serum uric acid goal than those on placebo. The estimated effect of lesinurad 400 milligrams was slightly larger than that for the lower 200-milligrams dose in these two studies.

In a supportive analysis, treatment groups were compared with respect to the mean reduction in serum uric acid from baseline to month 6 using an ANCOVA model adjusted for baseline value and the stratification factors. Greater mean reductions of approximately 1 to 1.1 milligram per deciliter were observed in the lesinurad 200-milligram arms than in the placebo arms in studies 301 and 302. Greater improvements of about 1.2 to 1.4 milligrams per deciliter were observed in the lesinurad 400-milligram arms.

The primary analyses were based on the responder rate responding to a threshold of serum uric acid level less than 6 milligrams per deciliter at month 6. This is a supportive cumulative responder plot for study 301. In this plot, the X-axis displaced

different thresholds to classify a patient as successfully treated. The Y-axis represents the proportion of ITT patients who achieved the corresponding threshold, with patients with missing data classified as non-responders for all thresholds. The red-colored curve corresponds to the lesinurad 200-milligram arm, the green-colored curve corresponds to the lesinurad 400-milligram arm, and the blue curve represents the placebo arm.

Generally, across arms, there is separation between the treatment groups in the proportion of subjects successfully treated across a range of potential thresholds used to define success. These plots provide descriptive evidence that the effect of lesinurad over placebo on the proportion of patients who are sUA responders is not dependent on the specific threshold of 6 milligrams per deciliter. There were similar results for study 302.

This table presents the primary efficacy results for study 304. A statistically significant treatment effect was observed for lesinurad 400-milligram arm versus placebo. However, the effect

of lesinurad 200 milligrams was not statistically significant, with an estimated difference between lesinurad 200 milligrams and placebo in the proportion of responders of only 10 percent.

While the lesinurad 200-milligram arm failed the primary endpoint in study 304, there was an estimated mean reduction from baseline of 0.8 milligrams per deciliter in serum uric acid level for the 200-milligram dose as compared to placebo.

This table presents the primary efficacy results for study 303, the monotherapy study. A significant treatment defect was observed for lesinurad 400 milligrams versus placebo with an estimated effect of 28 percent.

Consistent with the treatment effect observed in the proportion of responders, a benefit for lesinurad 400 milligrams was observed with respect to the mean change from baseline. The effect size over placebo of 1.6 milligrams per deciliter might be considered to be an estimate of the maximal serum uric acid effect possible with the studied doses of lesinurad given that study 303 evaluated the higher

dose of lesinurad and that the study was carried out in the absence of other concomitant urate-lowering therapies.

I will now move to the presentation of selected secondary efficacy endpoints. These and the next two slides present the analysis results for selected secondary efficacy endpoints. No statistically significant benefit for either dose of lesinurad over placebo was demonstrated for any of these secondary endpoints in studies 301 and 302 in patients with background allopurinol therapy. In addition, there was little to no trend toward benefit for the rate of gout flares as shown here by incidence rate ratios close to 1.

For endpoints of tophi resolution and HAQ-DI, there were trends in the wrong direction for both doses of lesinurad in both studies. For example, with the proposed 200-milligram dose, an estimated 5 and 10 percent fewer patients had at least a 0.25 improvement in HAQ-DI in the two studies on lesinurad 200 as compared to placebo, although these differences were not statistically significant. Results were

similar with slight trends in the wrong direction for several other patient reported outcomes such as SF-36, Patient Global, and patient pain score.

Similar to studies 301 and 302, in study 304, there was no statistical evidence of benefit or any consistent trends toward benefit for these three secondary endpoints for the proposed 200-milligram dose. There were trends toward benefit for the higher 400-milligram dose for gout flares and tophi resolution. But again, both doses trended in the wrong direction for HAQ-DI response.

Primarily due to the shorter duration of 6 months, the time points of assessment and endpoints ascertained, the analysis methods in the monotherapy study 303 were different from the combination therapy studies. This table presents the differences between the lesinurad 400-milligram and placebo groups in the proportion of patients with a gout flare between months 5 and 6 and in the proportion who had a HAQ-DI response at month 6. Again, no statistically significant results or consistent trends toward benefit were observed.

As described earlier, there was considerable dropout in the three xanthine oxidase inhibitors add-on phase 3 studies with dropout rates of approximately 15 to 25 percent depending on the study, treatment arm, and time point. The primary efficacy analysis considered patients who dropped out to be non-responders. Importantly, tipping point sensitivity analyses indicated that the treatment effect of lesinurad on serum uric acid in studies 301 and 302 was convincing notwithstanding the missing data. However, the potential effect of missing data might be more problematic with respect to the evaluation of safety.

There was slightly greater dropout rates in the lesinurad arms than placebo with greater dropout on lesinurad due to adverse events, suggesting that those patients remaining on treatment in the lesinurad arms may have represented a healthier subset of subjects than the subset of patients remaining on treatment in the placebo arm.

This potential lack of comparability between patients remaining on treatment, on the lesinurad and placebo arms, could induce bias in favor of lesinurad

in key safety analyses; the unknown but potential effect of missing data on the reliability of key safety analyses adds to the uncertainty about potential safety signals, which will be discussed in greater detail by Dr. Neuner.

Here, I will present results of selected subgroup analyses. The data from studies 301 and 302 were pooled to give more precise estimates, as these two studies were similar in design. For the primary endpoint of serum uric acid responder rate, no statistically significant interactions were present and estimated effects were relatively consistent across the demographic subgroups. Results were similar in study 304.

I will now summarize the efficacy findings based on the key phase 3 studies. In both allopurinol add-on studies 301 and 302 and for both the 200- and 400-milligram lesinurad doses, there was statistically significantly greater proportions of patients on lesinurad than placebo achieving the primary responder endpoint defined by a serum uric acid less than 6 at month 6.

The effect of lesinurad 200 milligrams was relatively modest with estimated 26 percent and 32 percent greater probabilities of achieving levels less than 6 milligrams per deciliter as compared to placebo or greater mean reduction of around the 1 milligram per deciliter in these two studies. There was no statistical evidence of an effect of lesinurad 200 milligrams on serum uric acid reduction in the febuxostat add-on studies, study 304.

In addition, there was no statistical evidence or any clear trends toward benefit with respect to a number of secondary endpoints such as gout flares between month 6 and month 12, tophi resolution at month 12, and patient reported outcome measures such as HAQ-DI. For some patient reported outcomes such as HAQ-DI, there were actually slight but consistent trends toward worst outcomes on lesinurad than placebo.

As mentioned previously, reduction in serum uric acid is a commonly used surrogate endpoint for long-term direct measures of patient benefit such as reduction in flare rate and improvement in quality of life, and there was replicate and convincing

statistical evidence that lesinurad reduces serum uric acid levels in patients who received background treatment with allopurinol.

Nevertheless, the relatively modest effect of lesinurad on serum uric acid levels, combined with the lack of any supportive trends for important secondary endpoints, leads to considerable uncertainty about the magnitude of long-term patient benefit provided by lesinurad. Thank you.

Presentation – Rosemarie Neuner

DR. NEUNER: Thank you, Dr. Chen and Dr. Wang. I would now like to discuss various safety concerns associated with the administration of lesinurad. The safety database submitted in support of lesinurad contained 12 months of double-blind safety data from three xanthine oxidase background studies 301, 302, and 304, which comprised the primary safety population upon which the safety analysis for this drug are based. Additional double-blind safety data from the phase 3, 6-month, monotherapy study and from ongoing phase 2 and 3 open-label extension studies were also submitted in support of lesinurad's safety profile in gout.

As of the 120-day safety follow-up, over 1800 gout patients had been exposed to lesinurad out of which 949 subjects were treated with the to-be-marketed dose of 200 milligrams for a total exposure of 855.8 person-years. The numbers of patients exposed to lesinurad for 6 and 12 months exceed the ICH-E1A guidelines for the assessment of a safety profile of a drug or a biological product intended for treatment of a common disease.

Review of the safety database for the pooled populations of the 12-month studies 301, 302 and 304 and the population from the 6-month monotherapy study 303 revealed that the majority of the patients in these studies experienced at least one adverse event while participating in these trials.

Additional inspection of these data showed that there were a higher number of subjects in the lesinurad treatment groups who experienced serious adverse events, serious renal adverse events, and major adverse cardiac events also known as MACE. Also, more lesinurad treated patients discontinued treatment as a result of adverse events. The number of deaths were

also high in the lesinurad treatment groups as compared to the corresponding placebo groups, which I will discuss next.

As shown in this table, there were a total of 6 deaths that occurred in patients taking lesinurad reported in the controlled phase 3 trials as follows. Four patients died due to cardiovascular events, one patient died due to gastric cancer, and one patient died of unknown causes. Overall, the types of deaths were consistent with the risks related to the underlying and concomitant medical conditions, which included hypercholesterolemia, hypertension, diabetes, chronic kidney disease, and cardiovascular disease reported by these subjects.

Based on the 6 deaths observed during the controlled phase 3 lesinurad studies, the incidence rates for deaths in lesinurad groups were low overall, but they were higher in a dose-dependent manner as compared to the corresponding placebo groups. This finding is disconcerting in view of the modest treatment effect observed in these studies as discussed earlier in my presentation.

As I mentioned earlier in my presentation, more patients in the 400-milligram lesinurad treatment groups experienced serious adverse events as compared to the 200-milligram treatment group or the corresponding placebo groups. The highest exposure adjusted incidence rate for serious adverse events was observed in the lesinurad 400-milligram monotherapy treatment group. Similarly, a higher exposure adjusted incidence rate for serious adverse events was observed in the lesinurad 400-milligram group as compared to the 200-milligram and placebo-treatment groups in the pooled xanthine oxidase add-on studies.

The system organ classes that contributed to the higher overall rate of serious adverse events in lesinurad treatment groups were cardiac disorders, renal and urinary disorders, and metabolism and nutrition disorders. The higher rate of serious adverse events and the metabolism and nutrition disorders was mainly due to gout flares, which are an expected adverse event associated with urate-lowering therapies. The higher rates of renal and urinary disorders in the lesinurad treatment groups shall be

discussed later in my review.

As I stated previously, a higher proportion of patients discontinued study treatment as a result of an adverse event in the lesinurad treatment groups in a dose-dependent manner as compared to the corresponding placebo groups in the pooled xanthine oxidase add-on studies and the monotherapy study. The highest rate of discontinuation due to adverse events occurred in the 400-milligram lesinurad monotherapy group. Renal and urinary disorders, musculoskeletal connective tissue disorders, and investigations were the most common types of adverse events resulting in patients discontinuing study medication in these controlled studies.

The higher rates of discontinuation in the renal and urinary disorder system organ class were due to cases of renal failure and renal impairment in the lesinurad 400-milligram treatment groups as compared to placebo in these studies. More subjects in the 400-milligram lesinurad treatment groups also were due to myalgias, back pain, and pain in the extremity than in the corresponding placebo groups, which falls under

musculoskeletal and connective tissue disorders. The higher discontinuation rate for the investigation system organ class was primarily due to increased blood creatinine levels in the lesinurad 400-milligram treatment group and the xanthine oxidase add-on studies.

Now, I wish to turn my attention to the renal adverse events observed in the controlled phase 3 lesinurad studies. The population in these studies have multiple risk factors for renal adverse events, including chronic kidney disease, diabetic nephropathy, hypertension, and congestive heart failure, as well as the use of concomitant medications such as colchicine, NSAIDs, diuretics, and RAS agents.

The risk for lesinurad associated renal toxicity is best evidenced by safety data from the monotherapy study 302 in which treatment with the drug is clearly associated with a higher rate of renal adverse events as compared to placebo. The types of renal adverse events observed included reversible and non-reversible creatinine elevations, as well as acute and chronic renal failure. This risk appears to be

dose dependent as the higher rate of renal adverse events was also observed in patients treated with lesinurad 400 milligrams as compared to the 200-milligram dose and placebo in the safety database from the pooled xanthine oxidase add-on studies.

This table shows that all of the serious adverse renal events that occurred in subjects treated with lesinurad occurred in patients randomized to receive the 400-milligram dose in these phase 3 trials. The patterns of serious renal adverse events is similar for both 400-milligram treatment groups. The incidence rates for serious renal adverse events is numerically higher in the 400-milligram arm as compared to the placebo in the pooled xanthine oxidase inhibitor background studies.

There were a total of 4 subjects in the safety database submitted in support of lesinurad that went on to require hemodialysis or underwent renal biopsies as a result of developing acute or worsening renal failure while participating in the phase 3 lesinurad studies.

Although no patients randomized to treatment with the 200-milligram dose experienced serious renal

adverse events during the controlled studies, of these patients had continued taking 200 milligrams of lesinurad with background allopurinol in the extension studies when they developed serious worsening in their renal function requiring hemodialysis.

All four of these cases were confounded by concomitant use of medications that affect renal function while 2 out of the 4 also had underlying chronic kidney disease or other medical conditions that also affect renal function. The renal histopathology, as you have heard, from these subjects' biopsy did not clarify the etiology of their acute renal failure.

As another indicator of potential renal toxicity, increases in serum creatinine were also observed with lesinurad treatment in the four phase 3 studies. Higher proportions of lesinurad treated patients experienced elevations in serum creatinine equal to or greater than 1 and a half, 2 or 3 times baseline.

This occurred in a dose-dependent manner in the pooled studies with background xanthine oxidase inhibitors. All of the serum creatinine elevations in

the 6-month monotherapy study occurred in patients who received lesinurad. Of doubt, not all the serum creatinine elevations had resolved with or without discontinuation of study medication by the least study visit. Higher rates of persistent serum creatinine elevations greater than or equal to 1 and a half or 2 times baseline were noted in patients exposed to 400 milligrams of lesinurad.

Now, I wish to discuss the renal stone safety data. An increased risk for renal stones was observed in the lesinurad 400-milligram treatment groups compared to placebo. This is not unexpected given lesinurad's mechanism of action. However, the incidence of renal stone events did not appear to be increased with lesinurad 200 milligrams in the pooled studies with background xanthine oxidase inhibitors.

Now, I wish to turn my attention to MACE events. As shown in this table, a small number of MACE events occurred in all study arms of the pooled studies with background xanthine oxidase inhibitor as well as in the 400-milligram lesinurad monotherapy treatment group. The incidence of MACE in the lesinurad

200-milligram group did not appear to be increased compared to placebo. A higher number of subjects in the lesinurad 400-milligram treatment groups experienced MACE events compared to placebo.

This imbalance was mainly due to a higher number of nonfatal MIs associated with lesinurad 400-milligram group in the background xanthine oxidase inhibitor studies and the overall number of cardiovascular deaths seen in patients randomized to lesinurad.

As displayed in this table, in the pooled studies with background xanthine oxidase inhibitor, the number of subjects with MACE events, the incidence rates for MACE, and the number of MACE events were higher for the 400-milligram treatment group. Additionally, the confidence intervals for comparisons between lesinurad and placebo were very wide, indicative of considerable uncertainty in determining if a potential cardiovascular safety signal exists with the administration of lesinurad.

To summarize the FDA safety concerns, treatment with lesinurad appeared to be associated with

dose-dependent higher rates of deaths, serious adverse events, discontinuations due to adverse events, renal toxicity, particularly when administered as monotherapy that included elevated serum creatinines and acute and chronic renal failure resulting in hemodialysis, renal stones, and MACE events.

Consideration regarding the safety profile, including safety amendments to expand guidance on subject hydration and management of serum creatinine elevation, were implemented during the studies that may have reduced the risk. Although lesinurad 200 milligrams appears to be lower risk than 400 milligrams, the exposure of the two doses is overlapping, and distinctions between the two doses may be less evident if used in a broader population.

In terms of risk-benefit considerations, treatment with lesinurad 200 milligrams plus xanthine oxidase inhibitor once daily result in a statistically significant but modest decrease in serum uric acid. However, as Dr. Chen pointed out, its urate-lowering efficacy decreased with worsening renal function. As you heard from Dr. Wang, results from endpoints

assessing direct clinical benefit such as decreases in gout flare, tophi resolution, or improved physical function were neutral or trended worse in the lesinurad treatment groups.

In view of the documented dose-dependent adverse events, careful consideration of the benefits and risks is essential to determine whether lesinurad 200 milligrams once daily with the xanthine oxidase inhibitor should be approved.

On behalf of the FDA presenters, we wish to acknowledge our colleagues who put a lot of work and effort into the review of this application in preparation for today's meeting. We also wish to thank the advisory committee members for your attention and look forward to your discussion and comments. Our deepest thanks to you all.

Clarifying Questions

DR. NEOGI: Thank you. We'll now move on to clarifying questions for the FDA. Again, please remember to state your name for the record before you speak. And if you can, please direct questions to the specific presenter.

Dr. Reimold?

DR. REIMOLD: Andreas Reimold. I had a question for Dr. Chen on page 12, the second slide. This is the one about dose-dependent, creatinine clearance decline in patients with various baseline renal function.

Basically, if we're focusing on the 200-milligram dose of lesinurad, if you have totally normal renal function, you have a much more substantial decline than if your renal function is most significantly impaired where over time, there seems to be essentially no change in creatinine clearance. So I guess from that, there shouldn't be extra caution for the worst creatinine clearance patients, at least from this kind of measurement.

DR. CHEN: Thank you very much for your question. Jianmeng Chen from FDA. So we noted the same trend of apparently less creatinine clearance decline in patients with the worst baseline renal functions. We think the renal toxicity is due to the urate precipitation in urine as the sponsor stated. If there is less urate -- or uric acid in the urine in

this patient with worst baseline renal function, maybe they are less susceptible to this kind of toxicity.

Also, in our PK review, there's also less or lower concentration of lesinurad, the drug itself, in urine, in these patients. So this may all contribute. But I also want to specify that overall numbers are small, so the observed effect is what it is. Also, these patients, the sponsor in the protocol, they have procedures to intervention, if the serum creatinine clearance got really bad. That may also affect what you see here.

Does that answer --

DR. REIMOLD: There are some interventions that affect this? What was that exactly?

DR. CHEN: So if the creatinine clearance -- if the serum creatinine clearance -- if the serum creatinine goes really high, the sponsor in the protocol has intervention procedures.

Dr. Rosemarie may -- Dr. Neuner may --

DR. NEUNER: The protocol had been amended so that patients who had achieved a serum creatinine level 3 times at baseline were to have been discontinued.

There were also other guidelines to investigators, that patients whose serum creatinines had reached certain levels were supposed to have their renal or nephrotoxic concomitant medications stopped, and then there was supposed to be eventually a stop in the administration of the study medication before it was reinstituted.

DR. CHEN: Thank you, Dr. Neuner. So overall, we did see less creatinine clearance decline, but the same amount of creatinine decline may mean a lot more for patients with worst baseline renal functions.

DR. REIMOLD: Thank you.

DR. CHEN: Thank you.

DR. NEOGI: Dr. Berney?

DR. BERNEY: The lesinurad is 98 percent protein bound, primarily albumin. Is there any speculation as to what would happen with the adverse events in patients who are hypoalbuminemic?

DR. CHEN: The sponsor did not submit specific data, but they did look at the protein binding of lesinurad in patient with hepatic impairment, and there's not much alteration in protein binding in those patients.

DR. BERNEY: Were the albumins measured in those patients?

DR. CHEN: The hepatic impairment was classified as Child-Pugh category, and albumin is one of the standards, but I didn't look at albumin levels specifically.

DR. BERNEY: Okay.

DR. NEOGI: Dr. Oliver?

DR. OLIVER: Alyce Oliver. The first slide on page 13, Dr. Chen, the changes in renal status, were those permanent changes or changes during the study, where they went from normal to mild or mild to moderate renal function?

DR. CHEN: Thank you. May I have the backup slide number 16 up there? So your question is whether the renal function stabilized after first months.

This is sponsor's data about cumulative incidence of serum creatinine elevation mode, and twofold of the baseline. X-axis is the months into the trial, and Y-axis is the cumulative incidence. You can see that the deterioration of renal function kind of continues throughout the trial, and it did not

stabilize after first month.

DR. NEOGI: Dr. Caplan?

DR. CAPLAN: The sponsor submitted slide CO-107, and you provided us with an analysis, what at least to me looks like a similar analysis on -- this is page 9, slide 18, showing at least in the 200 group a 5 milliliter per minute decline in creatinine clearance. But that doesn't look exactly like the slide the sponsor submitted. So my question was whether there was some way of squaring that.

DR. CHEN: Thank you. If you look at the sponsor's slide, first of all, the scale of the Y-axis is different. And also, you can see that these curves are not all starting at zero, at baseline. So if you mentally move the curves, start at the same point, you would come to the similar conclusion as my slide.

DR. CAPLAN: Is the slide that you produced a comparison to the baseline or is the comparison between the --

DR. CHEN: I'm sorry. Yes, it's comparison to the baseline.

DR. CAPLAN: Because in slide 107, it looks

like the gray line representing the placebo, the creatinine clearance actually increases over the first 2 months. So there's a slope upward. Even if you move that to where the green line is, that's the 200, it looks to me, at least in the slide the sponsor is providing -- admittedly, I can tell obviously that the Y-axis is different, but just even in terms of the slope difference, the placebo, the gray line, goes up and the active agent at 200 milligrams seems flat. And that doesn't at all look like the slide --

DR. CHEN: Yes. I think the difference is from the definition of baseline creatinine clearance. What I used is the last creatinine clearance before the dose. And the sponsor -- also you can see the difference from here. Maybe that's from the screening baseline creatinine clearance, and what I presented is what the data says.

DR. NEOGI: Dr. Leff?

DR. LEFF: Thank you. I have two questions. One is about the slide just before that on page 9, where it looks like you looked at exposure response based upon meeting the primary endpoint. And it looks

like there are four different groups. I don't know if you could explain that. It looks like there's placebo, page 9, the first slide, that was just before the one we were looking at, just before this one. That one.

It looks like there are four groups. Could you explain this a little bit?

DR. CHEN: Yes. I'll get a little bit mathematically if you can know. I appreciate. On the plot, you can see 5 circles. First, the red circle represents the placebo, and the other 4 black circles represents the treatment group. The doses of 200 and 400, patients were combined together. And then they were put in 4 bins based on their exposure, which is on the X-axis.

So if you combine all patients on the lesinurad treatment group, if it's 400 -- and base on their exposure, you put them in 4 bins. That's the 4 black dots, you see? The first black dot represents patients with the lowest 25 percent of exposure.

DR. LEFF: Okay. Thank you. I had a separate question. A number of times, it's come up that you're concerned if the drug gets exposed in a wider

population, that there may be greater variability than observed in these clinical studies. Are there some particular underrepresented groups that you're concerned about?

DR. CHEN: I think they state that due to the narrow therapeutic index for this drug. As you can see, most of the uric acid lowering agents were approved over a large dose range, the allopurinol, probenecid, or allopurinol, febuxostat. But for this drug, 200 milligrams is the only dose that we find -- actually, I cannot state that. But it appeared to be the minimum effect dose and also the maximum safe dose.

So in that regard, in a larger population, what we've -- for example, CYP2C9 polymorphism, 1 to 5 percent of the general population, it may not become an issue in the trial, but may become an issue potentially in a larger population.

DR. YIM: Hi. This is Sarah Yim. That was a great response, but I think also our concern is patients in the trial were pretty representative, but they also were selected. So if you go into a broader

population, there might be people with worse renal function that might be taking the drug, or there might be polymorphisms, as Dr. Chen mentioned.

So it's a theoretical concern. We're not saying that the trials themselves were inadequately representative, but everyone knows that clinical trial patients are often a little better off than patients in general.

DR. LEFF: Okay. Thanks.

DR. NEOGI: Dr. Tchetgen Tchetgen?

DR. TCHETGEN TCHETGEN: Eric Tchetgen Tchetgen. This is a question for Dr. Wang. The responders analysis clearly demonstrate a significant effect. However -- and also, there's this imputation of the non-responders for the missing data. So hopefully that gives some protection of the type 1 error and lead to some conservative analysis. As you stated, we can feel fairly confident that that is in fact evidence of an effect.

Then there's the analysis of the change, analysis which did not at all address the missing data. I just did a complete case analysis as I understood it.

DR. WANG: The sponsor's prespecified analysis for change from baseline is LOCF, so it's last observation carried forward.

DR. TCHETGEN TCHETGEN: I see. I suppose my question is, in your opinion, what would be the impact of missing data in this second analysis of change, last observation carried forward. Could that explain the -- could that potentially explain the smaller magnitude of the effect when looking at the change?

DR. WANG: I don't think we can draw that conclusion. It really depends on the dropout, the trend and the treatment effect. Without careful exploration of the trend, we cannot say the effect is decreased.

DR. TCHETGEN TCHETGEN: Was there any attempt to look at whether baseline variables predicted -- correlated at all with the trend of dropout? Particularly, those baseline characteristics that showed heterogeneity for the imputation effects, I think that would be the concern.

DR. WANG: We conducted two types of subgroup analyses. The first type is the demographic factors.

We also conducted a subgroup analysis on baseline renal function and allopurinol dose. I think that was the main two factors of the baselines. So there was no interaction -- no statistically significant interaction found.

DR. TCHETGEN TCHETGEN: Was there any evidence that the rate of dropout or the missingness rate was associated with any of the baseline characteristics? I suppose that was my --

DR. WANG: We didn't take that approach to explore. Thank you.

DR. NEOGI: Tuhina Neogi. I'll ask the next question. I was hoping that we could get some clarification about the renal function and whether or not some of this decline in renal function actually resolved because I feel that we're getting a different set of data from the FDA presentation. I'm not sure which speaker would be best able to address that.

DR. YIM: Unfortunately, I'm not quite sure how to explain the sponsor's data. We had the data sets and did the analyses ourselves from the sponsor's submitted data sets. So I'm not quite sure how to

explain the difference. Maybe the sponsor can comment.

DR. NEOGI: Perhaps before we get to that, I just wanted to see if there were any additional questions for FDA presenters. And I did want to take a few minutes to see if there were any outstanding questions for the sponsor. So first, perhaps, we could just finish up with any remaining questions for the FDA presenters.

Dr. Delost?

DR. DELOST: I noticed that the safety portion, you took it out and extrapolated to the continuing study, the extended study. Did you analyze the trends on the efficacy for the continued study?

DR. YIM: This is Sarah Yim. We didn't analyze the efficacy data or the safety data, really, from the extension studies. We looked at it. But the problem with those studies are, of course, that you lose the control group. And there's also a bit of a survivor bias in the sense that patients who are remaining on the study at that point have done well. So we just aren't quite sure how to interpret those data.

DR. NEOGI: So I would like to now see if there are any additional -- remaining clarification questions for the sponsor, and perhaps we can first start with the question regarding the renal function and interpretation of whether or not these are actually resolving.

DR. STORGARD: Could I please have our slide using the 4-panel figure that has the creatinine clearance for 200 milligrams last value on treatment, last value off treatment?

So the analysis that we performed here, which is slightly different in that we are looking at the entire 12-month duration of the trial. I believe the FDA's figure went to 6 months. And what we're looking at here is the creatinine clearance by the same renal function categories. And you're seeing the change from baseline to last value on treatment and off treatment.

I think the question was is there reversibility. What we're seeing here with 200 milligrams, in each of the renal function categories, even on treatment, the change is not really clinically relevant, but you can see off treatment,

that change is even more positive than on treatment. So we do not see any evidence, based on this data, of any long-term negative impact on renal function.

There was also a question, if I may clarify, regarding the MACE exposures for 200 milligrams. Our analysis was slightly different. And that I think could be by the fact that we had required the time of dose to be accounted for. So we only have measures of 3 MACE subjects on 200 milligrams compared to the 4 that the FDA had provided. We only had time points of dose and the time points of the PK for three of those subjects.

What you're seeing here for those 3 subjects, their exposures were less than the median of the lesinurad 400 milligrams. Also, what we're looking at here is the average -- the median of the average lesinurad exposure for each dot represented here. The one subject on 200 milligrams that was higher, we do have exposures for that patient.

The mean exposure on 200 milligrams for patients with MACE was 1,720 nanograms per mL. The one subject who we don't have timing for had a value of

11,750 nanograms per mL. We assume that that was taken very shortly after drug administration, but we don't know. Because we didn't have, we did not put that in our analysis. But the other three patients, based upon the median of the average, had a C average exposure on 200 milligrams less than the median of 400 milligrams.

I believe there was also a comment regarding the magnitude of a serum uric acid change. If I could see the magnitude of change that we were seeing in some of our studies here. Again, I just wanted to emphasize that although what we're talking about is medians, we do have 30 percent of the patients having a greater than 2 milligram per deciliter change and 10 percent having a greater than 3 milligram per deciliter change.

Just a reminder that what that has translated into, a doubling in those achieving a target less than 6 and a tripling in a target less than 5. And this was observed even if we had high baseline serum uric acids greater than 7 and greater than 8. So we believe that the overall magnitude that we are seeing is important.

If I may make one last comment --

DR. NEOGI: I think we'll save that for our

afternoon conversation question period. And I'll have Dr. Jonas have the last question before our break.

DR. JONAS: Beth Jonas. With respect to the decrease in creatinine clearance that we're talking about here, are there any data on the use of concomitant medications and their role in the drop in creatinine clearance, specifically with respect to chronic use of NSAIDs?

DR. STORGARD: We looked at the concomitant medications, and we did not see any direct association. But we also did know that most of the patients who had elevations were on concomitant medications. NSAIDs were used in roughly 60 percent of the patients at any time. What I can show you here is that when we take a look at the use of NSAID use, in those with or without an elevation, you're seeing that we do have patients equally distributed amongst the group. So we're not seeing any direct association there, but most people were on an NSAID.

DR. NEOGI: Thank you.

We'll now break for lunch. We'll reconvene in this room again in 40 minutes, at 1 p.m. Please take

any personal belongings you may want at this time. Committee members, please remember that there should be no discussion of the meeting during lunch, amongst yourselves, with the press, or with any members of the audience. Thank you.

(Whereupon, at 12:19 p.m., a lunch recess was taken.)

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

(1:00 p.m.)

Open Public Hearing

DR. NEOGI: If everyone could take their seats, please.

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 or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at 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 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. Thank you for your cooperation.

We will start with speaker number 1. We'll have speaker number 1 step up to the podium and introduce yourself, please. Please state your name and any organization you are representing, for the record.

DR. CAROME: Good afternoon. I'm Dr. Mike Carome, director of Public Citizen Health Research

Group. Public Citizen and I have no financial conflict of interest. Before joining Public Citizen, I was a practicing, board certified nephrologist for nearly two decades and often evaluated patients with acute kidney injury.

Public Citizen strongly opposed FDA approval of lesinurad for treatment of hyperuricemia for the proposed indication because, one, the drug offers meager clinically meaningful benefits relative to placebo for gout patients with hyperuricemia; and the drug has serious risks, including definite significant renal toxicity and possible cardiovascular toxicity. And because of one and two, as a result, the risks of the drug far outweigh its benefits.

The pivotal trials 301, 302, and 304 demonstrated that lesinurad plus a xanthine oxidase inhibitor indeed are more effective in lowering serum uric acids in a statistically significant way versus placebo. However, the FDA reviewers emphasized that the magnitude of lesinurad's urate-lowering effects was only modest for all three trials.

For studies 301 and 302, the adjusted

difference in mean serum uric acid changed over baseline for the lesinurad 200-milligram treatment groups versus a placebo group ranged from roughly 1.1 at month 6 to 0.9 milligrams per deciliter at month 12. Likewise, in study 304, the adjusted difference in mean serum uric acid changed over baseline for lesinurad 200-milligram treatment group versus placebo ranged from roughly 0.8 milligrams per deciliter at month 6 to to 1.1 at month 12.

More importantly, the FDA reviewers noted that the changes in the surrogate endpoint were not associated with any statistically significant differences showing benefit for the 200-milligram lesinurad treated subjects on clinically meaningful secondary endpoints in any of the three pivotal clinical trials, including the rate of gout flares requiring treatment at month 6 to 12, resolution of tophi by month 12, and measurement of patient disability.

Those results are summarized here for two of the key endpoints for study 301, the gout flares, the top two rows, and the tophi resolution, the bottom two

rows, no benefit with the 200-milligram dose of lesinurad; same thing for study 302, no benefit on those same endpoints with lesinurad 200 milligrams; and same thing for study 304.

In summary, the efficacy data indicate that lesinurad offers little clinically meaningful benefit and does not represent a major therapeutic breakthrough in the management of hyperuricemia and gout. These limited benefits must be weighed carefully against the risk of the drug. Approval of drug could be justified only if the safety data revealed no serious safety signals.

However, safety data from the four phase 3 randomized clinical trials submitted in the sponsor's NDA -- 301, -2, -3 and -4 -- identified dangerous dose-dependent increases in renal adverse events, MACE events, serious adverse events, and deaths compared with placebo. While these safety signals were most prominent at the 400-milligram dose of lesinurad, evidence of unacceptable risk was also apparent at the 200-milligram dose.

In terms of renal toxicity, preclinical

toxicology studies demonstrated that lesinurad is nephrotoxic in rats. FDA reviewers noted in particular the following.

Chronic toxicology studies showed evidence of kidney toxicity in rats. In rats, the dose of 600 milligrams per kilogram per day was lethal due to kidney toxicity with tubular degeneration and single-cell necrosis and GI toxicity. At the dose of 300 milligrams per kilogram per day, kidney findings were limited to tubular dilatation and changes in clinical chemistry parameters.

These findings suggest lesinurad has the potential for kidney toxicity. The kidney toxicity observed in the rat was not likely due to uric acid crystalluria and nephrolithiasis, as rats, like most mammals, possess functional uricase and have lower serum uric acid levels. Thus, in rats, lesinurad is a direct nephrotoxin that can damage renal tubular cells.

Note that the FDA's expression of the animal dose exposure relative to the proposed human dose appears to lack appropriate adjustment for the differences in body surface area between humans and the

animals, resulting in a misleading inflation of the ratio of the animal dose to human dose.

The safety data from the phase 3 randomized clinical trials for lesinurad provide overwhelming evidence that the drug causes acute kidney injury in humans. The mechanism for this lesinurad induced renal injury likely includes uric acid induced nephropathy as well as direct toxicity to renal tubular cells.

Table 38 from the FDA review packet showed a marked lesinurad dose related increase in the rate of renal related adverse events for the 12-month studies 301, 302, and 304 and the 6-month monotherapy study, 303. A clear dose-response relationship can be seen for the most common renal related adverse events in all three pivotal phase 3 trials, the blood creatinine elevation, and the pooled safety data.

Particularly concerning is the imbalance in cases of acute renal failure, the most severe form of acute kidney injury, at the 400-milligram dose, but clearly, there is renal toxicity at the 200-milligram dose.

Table 44 from the FDA review, which provides

the incidence of various degrees of serum creatinine elevations for the phase 3 trials, provides compelling evidence of a dose-response toxicity relationship for lesinurad. Note that under the kidney disease, improving global outcome, clinical practice, or KDIGO guidelines for acute kidney injury, increases in serum creatinine of 1.5 to 1.9 times baseline, 2.0 to 2.9 times baseline, and 3 or more times baseline are defined as stage 1, stage 2, and stage 3 acute kidney injury, respectively.

An increased incidence of acute kidney injury for all three stages occurred in a dose-dependent manner and was evident, even at the 200-milligram lesinurad dose, in studies 301, 302, and 304, and that's shown here. The same dose-response relationship was seen when looking at the number of serum creatinine elevations greater than or equal to 1.5 and greater than or equal to 2.0 times baseline. This data was from tables 45 and 46, respectively, from the FDA reviewers' packet.

Particularly concerning is the number of serum creatinine elevations that were prolonged or had not

resolved by the time of last assessment, and there were cases that had not resolved by the time of the last assessment.

Two subjects who had normal baseline renal function and developed acute kidney failure while taking lesinurad underwent kidney biopsies. Both revealed changes as described in the briefing packet that are consistent with acute tubular necrosis. In both cases, lesinurad cannot be ruled out as the cause for the ATN.

FDA reviewers noted the following regarding the renal safety data. The risk of lesinurad-associated renal toxicity is best evidenced by safety data from the monotherapy study 303. In this study, treatment with the drug is clearly associated with a marked increase in the risk for renal adverse events, 18 percent, including reversible and non-reversible creatinine elevations, and serious renal related adverse events, 5 percent, including acute and chronic renal failure, as there were no cases of renal adverse events associated or seen in the placebo group.

But importantly, similar substantial evidence

of lesinurad-associated toxicity was apparent in studies 301 and 302. Importantly, after the protocols for the ongoing phase 3 studies, 301, -2, and -4, were amended in June 2013, with about a year to go in those studies, based on emerging renal safety data -- and that amendment instructed all subjects to drink 2 liters of fluid per day -- there was no change in exposure-adjusted incidence rates of renal-related adverse events pre- and post that amendment.

For example, there were 8.4 renal related adverse events per 100 patient-years versus 9.5 renal related adverse events per 100 patient-years, respectively, for the 200-milligram lesinurad groups. Similarly, there was no benefit from the fluid looking at the 400-milligram groups.

In addition, real-world use of lesinurad, outside the context of a carefully monitored clinical trial and inevitably for off-label uses, will undoubtedly lead to rates of renal adverse events that exceed those seen in phase 3 clinical trials. It is, thus, not unlikely that if approved, lesinurad will trigger an epidemic of drug-induced acute renal

failure. On the basis of the preclinical and clinical renal safety data alone, the FDA should not approve the NDA for lesinurad, but the serious safety concerns about lesinurad are not limited to its renal toxicity.

As shown in table 32 from the FDA review, there was a troubling increase in the number of serious cardiac adverse events between the placebo and lesinurad treated subjects in the pooled data from studies 301, 302, and 304, with an increase in frequency of these adverse events as the dose of lesinurad increased. Even at the 200-milligram dose, though, there were adverse events that exceeded the rate seen in the control subjects seen here.

There was also an increase in the number of MACE events between the placebo and lesinurad treated subjects for the phase 3 trials seen in this excerpt from table 35 from the FDA review packet, which you've seen before already.

Finally, the point estimates for the exposure-adjusted incidence of MACE, including the number of subjects with MACE and the number of MACE events, increased with lesinurad exposure, particularly

at the 400-milligram level, and that's shown here. Although the number of MACE events was small, the cardiovascular safety signal should be assumed to be real, particularly for a drug that offers meager benefits and is not a breakthrough treatment for this disease.

There is also other notable safety data that the FDA has covered shown in this table here. The FDA review reveals that any treatment emergent adverse events, or TEAs, any severe such adverse events, any serious such adverse events, and any such adverse events leading to study drug discontinuation and deaths occurred with higher frequency in the lesinurad treated subjects, particularly at the 400-milligram dose.

Gout is not a life-threatening disease, and importantly, there are multiple FDA approved drugs already on the market. Lesinurad does not offer any major, unique breakthrough benefits compared to the approved therapies. And in fact, the data from studies 301, 302, and 304 show, at best, meager clinical meaningful benefits.

In contrast to the limited benefits, the

clinical trials have documented very serious safety concerns, the most significant being compelling evidence of nephrotoxicity and a troubling cardiovascular safety signal. The currently available data thus demonstrate that the risk of the drug far exceed its benefits.

There is no evidence that instructing patients to drink at least 2 liters of fluid per day and always combining lesinurad with a xanthine oxidase inhibitor will prevent the type of renal injuries seen during the clinical trials of this drug. Indeed, adverse renal events occurred despite such measures during the phase 3 clinical trials.

Moreover, such proposed renal risk mitigation steps presume that the renal toxicity seen in the clinical trials is due only or primarily to uric acid nephropathy. However, given the preclinical animal data and clinical trial data, that assumption is likely false.

In addition, as previously stated, real-world use of this drug undoubtedly will lead to rates of renal and other adverse events that exceed those seen

in the phase 3 clinical trials.

In conclusion, the only reasonable course of action for the FDA, given this data, is to reject approval of the NDA for lesinurad. FDA approval with reliance on warnings in the product labeling, a risk evaluation and mitigation strategy that relies primarily on giving extra fluid, and post-market surveillance studies would be a reckless approach and would not be in the interest of public health because it would cause more harm than benefit. Therefore, we urge the committee to recommend that the FDA not approve lesinurad. Thank you.

DR. NEOGI: Will speaker number 2 step up to the podium and introduce yourself, please? Please state your name and any organization you're representing for the record.

MR. BELTON: Good afternoon, committee members. My name is David Belton. I'm a patient advocate and member of the Global Healthy Living Foundation's 50-state network. I want to thank you for allowing me to speak today.

I came here today from Sand Fork, West

Virginia where I live. I'm 64, had to take early retirement due to a few very painful medical conditions, one of which is gout. I was first diagnosed with gout in '95. I was experiencing pain in my left foot for a few months before going to the doctor. The pain tended to move around from my ankle, to my heel, and finally found a home in my big toe.

One night, an all-consuming pain centered in my big toe began, and a very long night ensued. Fortunately, I was able to get a ride to the doctor in the morning, where they were able to reduce the pain and diagnosed gout.

The first drug I was prescribed was indomethacin, and it was quite harsh. I was then switched over to various other NSAIDs along with colchicine. I continued to experience a few severe gout flares a year after that, as well as numerous small ones. Gout has been the primary reason that I have missed work over the years, and it was never successfully managed.

A few years ago, the cost of colchicine skyrocketed, which left me with few options and very

little quality of life. I became aware of a gout study through my PCP that used Uloric and a study drug, which was later revealed to be lesinurad. I began that study in 2012, taking Uloric and lesinurad in combination therapy before I started noticing improvement with my gout flares.

I'm currently taking part in the extension study, and it has been over a year since my last major flare. I still have discomfort in the joints of my big toes and ankles most likely due to damage from years of gout attacks. In my case, a combination of Uloric and lesinurad has been very positive, and hopefully my experience with it will be helpful in the determination process.

I appreciate your thoughtful consideration of my remarks, and I would be pleased to provide any further information you may require. Thank you for your time and attention and for allowing patients to speak.

DR. NEOGI: Thank you. Will speaker number 3 step up to the podium and introduce yourself, please? Please state your name and any organization you are

representing for the record.

MR. GILENO: Good afternoon. Thank you for the opportunity to speak today on this issue. My name is Paul Gileno, and I'm the president and founder of U.S. Pain Foundation, as well as a person who has gout and a son of a person -- a son of a mother who suffers from gout.

U.S. Pain Foundation is an organization created by people with pain for people with pain, and we recognize and validate the 100 million Americans who courageously battle pain every day. U.S. Pain Foundation works across the country every day to advocate, educate, and empower for the needs of those living with pain, such as David; chronic pain and chronic pain conditions such as gout so they have access to medications their doctors prescribe. We also advocate for new and improved medications, which can help reduce the suffering of pain.

Gout is a painful form of arthritis which affects more than 8.3 million Americans. Gout pain is a chronic condition which debilitates people who have it. When people are debilitated by pain from gout,

they lose productivity, they lose wages, they cannot work, mobility is limited, they have disrupted sleep, and they suffer needlessly. There is no good option for people with gout pain to get relief as of today.

We have heard many stories of desperation from those living with gout pain. The most common ask is for help with the relief of the pain from gout and what can they do and what can they take. When gout pain comes untreated or is undertreated, people suffer longer and gout attacks happen more often, often leaving people debilitated and suffering.

I'm here today to ask you help in giving people suffering with gout pain hope that they can have an option to help relieve the pain from gout. People suffering from gout pain need options, and approving this medication gives them additional options to relieve pain from other therapies that are failing.

In addition to helping relieve suffering, approving this medication can lead to increased productivity at work, increase patient care, and overall lower healthcare costs that come with any chronic condition that goes untreated. We want to

represent people like David to make sure that their voices are heard. So the 8.3 million Americans that suffer with gout pain stand behind me.

Thank you for your time today, and if you have any questions, please let me know.

DR. NEOGI: Thank you. Will speaker number 4 please step up to the podium and introduce yourself. Please state your name and any organization you're representing, for the record.

DR. CRIGHTON: My name is Dr. Andrew Crighton. I'm an Arthritis Foundation board member and chair of the advocacy and access committee, and I'm here representing the Arthritis Foundation.

Gout's known to be an ancient disease. It was first identified by Egyptians in 2640 BC and has been extensively studied and feared throughout the centuries. The pain of gout attack is often described as excruciating. The physician, Aretaeus of Cappadocia, in the first century described it colorfully. "No other pain is more severe than this; not iron screws nor cords, not the wound of a dagger nor burning fire, like hot needles slowly being pushed

into your flesh."

We're here today because despite the long history, gout is very much a 21st century disease, and a cure is yet to be discovered. An estimated 8 million people have gout, which represents 4 percent of U.S. adults.

The incidence of gout has been accelerating in the last four decades. Gout attacks occur after excess uric acid crystals accumulate in joints. When levels of uric acid remain high, the attacks can become increasingly frequent. If not adequately treated over time, gout can become chronic with arthritis, progressive joint erosion, joint deformity, lumps under the skin called tophi, impaired physical function, disability, loss of productivity and quality of life, and not the least, chronic severe pain.

Gout itself is bad enough, but its comorbidities are significant as well. Gout is associated with increased risk of cardiovascular disease, heart attack, type 1 diabetes, kidney failure, heart failure, and early death. Gout self-management, including weight loss, healthy diet, and physical

activity, is an important part of controlling the disease and its comorbidities. But as the American College of Rheumatology states in its 2012 guidelines of management of gout, "Self-management is not enough."

Serum uric acid levels must be reduced to less than 6 milligrams per with strong evidence that less than 5 milligrams per deciliter is more effective. And in most cases, that requires pharmaceutical treatment. Standard first-line treatment calls for a xanthine oxidase inhibitor such as allopurinol to decrease the body's production of uric acid, but not all patients respond adequately to these options.

People who have gout must have access to a broad range of safe therapeutic options for the best chance of treating their gout and hyperuricemia. As such, physicians require a full range of options in order to provide optimal treatment and quality of care to their individual patients.

The Arthritis Foundation does not endorse specific medications to treat arthritis, but we do fully support efforts to ensure that a broad range of treatments are available to people with gout and that

drugs are being developed to cure gout. Thank you for the time.

DR. NEOGI: Thank you. Will speaker number 5 step up to the podium and introduce yourself, please. Please state your name and any organization you are representing, for the record.

DR. EDWARDS: Good afternoon. My name is Larry Edwards. I'm a rheumatologist. And for the past 39 years, virtually all of my research, my academic activities, as well as a large portion of my clinical practice has focused on purine metabolism, hyperuricemia, and gout.

I have had a financial relationship with both Ardea Biosciences and AstraZeneca. In the past, I've been a consultant to them on study design and data interpretation for the early lesinurad trials. I have also given them advice on development of educational tools relating to the mechanisms of hyperuricemia and the management of gout and hyperuricemia. I'm here today on my own dime.

I come to you today as the chairman and CEO of the Gout and Uric Acid Education Society. The society

is a nonprofit organization composed of healthcare professionals considered experts in the field of gout and hyperuricemia and dedicated to educating the public and the healthcare community about gout and the related consequences of hyperuricemia, with the aim of improving quality of care and lessening the burden of gout.

The society and our websites have been in existence for 10 years, and it is the largest non-branded, non-commercial source of unbiased information about gout on the internet. It currently receives more than a quarter million visits per year and has had a sustained annual growth rate of more than 20 percent.

A recent theme of the Gout Society's activities have been the promotion and explanation of the American College of Rheumatology's 2012 guidelines on the diagnosis and management of gout. In particular, we have focused on the internationally accepted goal of treating hyperuricemia and gout patients to a target level of less than 6.0 milligrams per deciliter.

This treat-to-target them has been the

mainstay of our monthly newsletters, the publicity campaign surrounding Gout Awareness Day, as well as several national roundtable discussions involving thought leaders in primary care, physician's assistants, nurse practitioners, emergency room physicians, podiatrists, and orthopedists.

So we as the experts are out there telling these clinicians that they should push urate-lowering therapies until this target is achieved. We feel good about this because the target is data driven and guidelines supported. It is a good target. The rub comes when we are asked by these practitioners how exactly do we do this.

The European and the American College of Rheumatology gout guidelines both have good treatment algorithms describing how a clinician should start with a low dose of allopurinol, 50, 100 milligrams, and gradually increase by doses of 50 or 100 milligrams daily every 2 to 4 weeks until the target is achieved; this along with laboratory monitoring and frequent office visits.

As I describe this to our primary care

friends, they look at me as if I'm crazy. "This is far too complex and time-consuming," they'll say. "And what happens when we get to 300 milligrams of allopurinol daily? I'm not going to go above that dose because I never have. And if you think I should continue to raise the dose, show me the data that the higher doses of allopurinol are safe."

So we have a de facto ceiling of 300 milligrams daily for allopurinol, even if the FDA originally approved its use for up to 800 milligrams daily. We also know from multiple studies over the past decade that at this 300-milligram daily dose of allopurinol, only 35 to 40 percent will achieve the target urate level of less than 6.0 milligrams per deciliter.

An alternative to allopurinol was reviewed by the Arthritis Advisory Committee and approved by the FDA seven years ago. Febuxostat is an excellent medication. It works through the same mechanism of allopurinol but does it better and with fewer severe side effects. But even at the FDA approved maximum dose of febuxostat of 80 milligrams daily, only 60 to

70 percent of compliant pill takers will achieve the target of less than 6.0 milligrams per deciliter.

So here we have allopurinol with its de facto ceiling of 300 milligrams daily that reaches target only 35 to 40 percent of the time under optimal conditions, and you have febuxostat achieving the target only 65 percent of the time. Forty percent, 65 percent, these are both failing grades on any scale. And it is why we as a profession should receive a grade of F for our treatment of gout.

Now is the time for a new approach to gout treatment. Combinations of therapies that have different mechanisms of action is the right course to take. And if this approach gets more patients t o their target urate level, you have done a good job today.

Better monotherapeutic agents may come down the pipeline some time in the future, but they're not within sight at this time. The Gout and Uric Acid Education Society endorses all research and drug development that will improve the treatment of gout and the suffering of our patients. Lesinurad is a good and

worthwhile addition to this armamentarium, and it will help get more patients to the treatment target. Thank you for your attention.

DR. NEOGI: Thank you.

Has speaker number 6 arrived?

(No response.)

DR. NEOGI: If not, are we calling him? Okay. We're just going to move on, then.

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.

(Pause.)

Charge to the Committee

DR. YIM: Good afternoon. As we prepare for the committee discussion and voting this afternoon, I want to provide a brief reminder of the issues, the regulatory framework, and underlying decision-making for marketing applications and the questions to be discussed and voted upon.

As mentioned earlier, the average treatment effect for the proposed dose of 200 milligrams on background xanthine oxidase inhibitor was a decrease of approximately 1 milligram per deciliter in serum uric acid at month 6, and efficacy for clinical outcomes such as flare, tophus reduction, and physical function was not demonstrated during the control period.

Safety results suggest dose-dependent concerns, including renal adverse events and major adverse cardiovascular events. Another consideration is the adequacy of the dose and dosing interval selection in light of these dose-dependent safety concerns.

As per the Code of Federal Regulations, FDA will approve an application after it determines that the drug meets the statutory standards for safety and effectiveness, manufacturing and controls, and labeling. The efficacy standard in the regulations is substantial evidence consisting of adequate and well-controlled investigations that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed,

recommended, or suggested in the proposed labeling.

The safety standard addresses three scenarios which could underlie a refusal to approve an application, including that it does not include adequate tests by all methods reasonably applicable to show whether or not the drug is safe for use; that results show that it is unsafe; or alternatively that results do not show that it is safe under the proposed conditions of use; or finally, that there is insufficient information to determine whether it is safe.

The first question for the committee is to discuss the efficacy data for the proposed dose of lesinurad 200 milligrams and whether the observed decrease in serum uric acid would be considered clinically meaningful. Next, the committee will be asked to discuss the safety of the proposed dose of lesinurad 200 milligrams with a specific focus on renal and cardiovascular safety.

Then the committee will be asked to discuss the dose-dependent toxicity of lesinurad, particularly in light of the safety profile of the 400-milligram

dose and specifically comment on whether you believe the overlapping exposure of the 200 and 400-milligram doses raise concerns about the potential toxicity of the 200-milligram dose if exposed to a broader population of gout patients postmarketing; also comment on whether the justification for once-daily dosing is adequate given that it remains an open question of whether a lower nominal dose given more frequently might have provided similar efficacy with a better safety profile.

Question 4 is a voting question on whether the data provides substantial evidence that lesinurad 200 milligrams once daily provides a clinically meaningful benefit in the treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor.

Question 5 is a voting question on whether the safety profile of lesinurad 200 milligrams once daily is adequate to support approval of lesinurad for the treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor.

Finally, question 6 is a voting question on

the committee's recommendation regarding approval of lesinurad 200 milligrams once daily for the proposed indication of treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor. The voting will be followed up by questions on whether additional studies are recommended either pre- or post-approval.

Thank you, and I will now turn the meeting back to you, Dr. Neogi.

Questions to the Committee and Discussion

DR. NEOGI: 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.

We'll start with question 1. Discuss the efficacy data of the proposed dose of lesinurad 200 milligrams and whether the decrease in serum urate observed would be considered clinically meaningful.

I will also just clarify that if there are any questions about clarification regarding wording, et

cetera, we can also raise that at this time. Dr. Berney?

DR. BERNEY: Seth Berney, Arkansas. I wonder whether the question should be rephrased because the way it's phrased, it's lesinurad by itself. And I view it as more of an adjunct to the xanthine oxidase inhibitor that would be used concurrently.

But the other issue is that I don't know that there's enough time that has passed for us to retrospectively say whether this is clinically meaningful. I wouldn't expect a urate-lowering drug to change the number of flares in only 6 or 12 months. I wouldn't expect there to be significant loss of tophi in 6 to 12 months.

This is really a very chronic illness. It takes years for the tophi to develop. It takes years for patients to have multiple flares. So I think the time frame with which results are being reviewed is the wrong time frame.

Having said that, I think that any significant decrease in uric acid should be considered an improvement, especially given the fact that we don't

have many urate-lowering drugs available to us.

DR. NEOGI: I'll take the next comment. Tuhina Neogi. I agree that I think the question here is really about the incremental decrease in serum urate above and beyond xanthine oxidase inhibition. Throughout some of the presentations, we've heard modest decrease as a descriptor of this.

I still would say I think this is clinically meaningful. I think 1 milligram per deciliter decrease on top of a xanthine oxidase inhibitor on a larger population basis, if we think about millimeters of mercury decrease in blood pressure or decrease in cholesterol, these small decreases in a larger, broader perspective can be meaningful. And in particular here, we're talking about the proportion that are having a serum urate drop below the biologically meaningful threshold of 6 or 5.

So I think given the lack of the number of alternative agents to help those patients that have inadequate management of their serum urate and their clinical gout, this drop is clinically meaningful in my opinion.

Dr. Oliver?

DR. OLIVER: In light of what you just said or to go along with what you said, I actually found the slide the sponsor had shown -- where FDA had shown that, in general, it decreases serum uric acid by 1 milligram per deciliter, the sponsor did show a slide that approximately -- I believe this is right -- 30 percent of the patients in the study group did have at least a 2-milligram per deciliter drop. So there is a fairly significant subgroup that has a larger decrease in their serum uric acid.

DR. NEOGI: Dr. Miller?

DR. MILLER: Don Miller. I just would add my voice also to say that 1 milligram per deciliter doesn't look very impressive on the surface, but in the context of adjunct therapy and the lack of alternatives, I think it is clinically meaningful.

DR. NEOGI: Dr. Tchetgen Tchetgen?

DR. TCHETGEN TCHETGEN: I just wanted to comment about the change of 30 percent of the population experiencing a change of 2 units. That means 70 percent have to experience a change less than

1 so that it averages to 1. So it depends on how you
2 look at it. There is also a significant large group
3 that didn't really experience anything.
4 DR. NEOGI: Dr. Delost?
5 DR. DELOST: Well, the results look really
6 impressive as far as the serum urate. I'm just
7 concerned that we haven't seen any improvement in the
8 symptoms. I think probably part of the problem is a
9 study design that had the first six months with an
10 agent to help prevent the flares. So you basically
11 only had 6 months to really measure flare reduction
12 after that. And I just don't think there's been a lot
13 of time to really see if this is going to be transposed
14 to be a clinically significant thing for people's
15 lives.
16 So that's where I'm at. I'm concerned that,
17 long-term, is this going to be a benefit. I don't know
18 if they proved it or not.
19 DR. NEOGI: If I may take the chair's
20 prerogative. Tuhina Neogi. I don't think we've had
21 this discussion from either set of presenters today.
22 But typical gout management is for prophylaxis at the

initiation of urate-lowering therapy to help prevent the expected gout flares. And in none of the other urate-lowering trials that have been published to date have we seen the clinical endpoints at these time frames because it is -- as Dr. Berney mentioned, it is expected that those clinical endpoints will follow the reduction in serum urate.

There are a number of studies that have supported the use of this serum urate threshold as an appropriate surrogate marker for the clinical endpoints that are important for gout. It's just that trials to date have not extended far enough for us to see that. So I just say that the trial design with prophylaxis is according to standard guidelines.

The next question was Dr. Becker.

DR. BECKER: I was going to agree with you in the sense that it was disappointing. However, if the focus nowadays is to treat target, I think that despite this being a minimal deduction in numerical value, there is certainly, I think, an impressive amount of patients that met that target, and thinking about the long-term effects of that I think outweighs it.

I think the other thing, as a pediatrician that I take very seriously is just the lack of options for therapies. And to have another option, albeit maybe not robust, I think is meaningful in this population of patients that is well studied and we have data on, rather than extrapolating data or utilizing meds off label, which we do all the time. So just for the record.

DR. NEOGI: Dr. Kaboli?

DR. KABOLI: I didn't raise my hand, but I'll say something anyway.

(Laughter.)

DR. KABOLI: I think that the -- as I'm pondering this question, I think the answer is probably yes, based on the preponderance of evidence in the field. But I think it's going to be the balance, which is what we're going to get to later, is sort of the risk. And like anything -- we've seen this with diabetes treatments -- we can maybe lower someone's A1c, but we don't get clinically meaningful improvements and outcomes that are important to the patient and have risks associated with them.

So I think that's where we'll, I'm sure, have a robust discussion on that.

DR. NEOGI: Ms. Chauhan?

MS. CHAUHAN: I was just following on Dr. -- I'm sorry -- Eric's comments. And I felt conflicted with something you said, so I want clarification. Thirty percent of the people were helped is what you said, right? Which leaves 70 percent taking a drug that doesn't help them. But you said benefit matters, and it does. As a patient, I know that.

This may be something we're going to discuss later. The relative risk to benefit when 70 percent of the people taking the drug are not being helped and maybe being harmed, did I heard you correctly?

DR. TCHETGEN TCHETGEN: That's correct, yes.

MS. CHAUHAN: Okay. So then my question would be, is there any ongoing work in looking at is there a genetic profile that you can find that you can sort out that 30 percent and be better able to target the population that needs the drug and gets benefit from the drug without the side effects? Because I also

heard gout is not a lone rider. It is always in the company, almost, of other morbidities, which brings another issue.

DR. NEOGI: Tuhina Neogi. May I just clarify? I think this 30 percent was in reference to Dr. Oliver's comment about the proportion that reached a threshold -- that had a serum urate drop of greater than or equal to 2 milligrams per deciliter, if I remember correctly.

So the actual average benefit overall was a drop of about 1 milligram per deciliter or more. But the clinically meaningful endpoint of dropping to less than 6 milligrams per deciliter is that important biological threshold was a much higher proportion. I think the risk ratio is around 2, so about twofold higher proportion of people achieved that biological threshold than the people who are on the reference group.

I can't speak to the other research issues, but I think one of the FDA speakers did mention pharmacogenomics. So there will certainly be an interest in understanding who may benefit or who may be

at higher risk.

Dr. Reimold?

DR. REIMOLD: Hi. I think you just answered that. I wanted to clarify that, too, just because some of the large proportion may be getting a benefit of less than 1 milligrams per deciliter. There may be other benefits that they nevertheless are getting off of that, especially if they reached a threshold, which is the magic number of gout treatment. So I wouldn't say that only 30 percent stand to gain benefit, but you already made that point. Thank you.

DR. NEOGI: Dr. Caplan?

DR. CAPLAN: I think it's more useful instead of talking about relative risk and the proportion that might benefit to instead look at the absolute numbers and the incidence for gout flares based on your serum urate levels -- uric acid levels.

So a 10, it's going to be virtually 100 percent of folks are going to have flares, and if you get down to 5, it's going to be 10 percent. So for each 1 milligram -- excuse me. For each, yes, 1 milligram per deciliter drop in the uric acid levels

in the blood, you anticipate that about 15 to 20 percent, at that level, are going to have a flare. So that's a very real difference, to be able to reduce 20 percent of the population.

DR. NEOGI: Dr. Berney?

DR. BERNEY: One other thing that needs to be pointed out is we're all presuming that the patients will start at very, very high uric acid levels. And just because there's the perception that the majority will only go down by 1 milligram per deciliter, they're not going to reach whatever the target number is.

What if the patient starts at 8 or at 7? And despite the allopurinol, this other drug is added, and it allows them to drop below whatever the threshold is? I think that needs to be taken into consideration since we really don't have many other alternatives to use.

DR. NEOGI: Dr. Gualtieri?

DR. GUALTIERI: I was questioning if there's data beyond the 12 months because the safety profile is in question.

DR. NEOGI: So I think we will discussing the safety as a separate question. Was there something

specifically for efficacy you wanted to raise beyond the 12 months at this point?

DR. GUALTIERI: Well, I think I was thinking about that for both question 1 and question 2.

DR. NEOGI: Do any panel members want to address the efficacy beyond 12 months or should we ask the FDA or the sponsors to address that? Dr. Tchetgen Tchetgen?

DR. TCHETGEN TCHETGEN: My recollection was that there was no control arm in the extended studies, so there was no comparison that could be made. So all we had was a pooled analysis of one arm looking at the trends, but that could be true in both arms.

DR. NEOGI: Dr. Yim, you look like you might want to comment.

DR. YIM: No, not really. I mean, as Dr. Tchetgen Tchetgen mentioned, you lose the control group and you also have basically people who are doing well staying in the study and other people have dropped out over time. So for those reasons, we find the extensions studies difficult to interpret, as I mentioned earlier. But if you want to hear the

results, I'm sure the sponsor has them.

DR. NEOGI: Okay. So we'll ask the sponsor to show us again the post-12-month efficacy data, please.

DR. STORGARD: If we could see beginning first with the gout flares. Thank you.

As was mentioned, this is data from patients who received lesinurad 200 milligrams in the pivotal study marked CRYSTAL, and then continued into the extension study on 200 milligrams. And with that, we are seeing the continual decline in the flare rate.

As appropriately pointed out, we cannot make any statements about superior treatment effect because we do not have a control arm in this study. But this does support what is seen in clinical practice, that if you can maintain that serum uric acid below target, then you will ultimately start seeing some reductions in flares, as was also commented on.

Similarly, with regards to tophi resolution, again what you're seeing here on the left are the patients who were on 200 milligrams plus allopurinol for 6 to 12 months in the core study, continued on into the extension study with a continuing increase and the

proportion of patients achieving a resolution of at least 1 tophi.

The same is true in the CRYSTAL study with the combination of 200 milligrams plus febuxostat, again, with continued dosing and maintaining that serum uric acid below target, we get an increased resolution rate of tophi. So again, not making any statements about superiority, similarly, but supporting clinical practice of the relevance of maintaining a serum uric acid goal.

DR. NEOGI: Dr. Oliver?

DR. OLIVER: Just to clarify what you said, in those three slides for the CLEAR trial, all of those patients who were in the extended study had a serum uric acid of less than 6 and in the CRYSTAL less than 5?

DR. STORGARD: Dr. Fung, could you remind me? I believe we're looking at approximately 80 -- was it 80 percent of the patients had a serum uric acid less than 5 in the extension? Was the question at the beginning of the extension or during the extension study, please?

DR. OLIVER: During the extension out to 24 months.

DR. STORGARD: Yes, we have that data for you. Sorry. Can we have the serum uric acid? The serum uric acid in the extension studies. There we go. That's what we're looking for. Thank you very much.

So this shows the serum uric acid levels in green with 200 milligrams added to allopurinol in the CLEAR 1 study. So you're seeing the 200-milligram cohort in CLEAR 1 and 2, in solid green, going into the extension, maintaining their serum uric acid. This is the response rate.

When we see the placebo group, the dotted line in gray, the placebo groups were randomized to 200 milligrams of allopurinol, and now you're seeing a similar response rate. So as they now lower the serum uric acid, you're achieving the same -- proportion of patients achieving target.

I'm sorry. Perhaps we could come back to you because I know we do have the slide you're asking for. So what is that serum uric acid level; how many people in the extension studies. So we can come back to you

with that.

DR. NEOGI: Dr. Miller?

DR. MILLER: I think it's important to clarify one issue. In all of these extension slides, we've lost patients along the way. It looks like for slide 70, for example, we had 64 patients up through 12 months and only 48 through 24. So that does bias a comparison.

DR. NEOGI: Are there any more questions or comments for question 1 regarding efficacy?

(No response.)

DR. NEOGI: So I think in general, the committee has an overall opinion that there is efficacy that is clinically meaningful, particularly thinking about this in the context of an add-on therapy being used in patients who are not achieving the serum urate target monotherapy with xanthine oxidase inhibition.

We will move on to question 2. Discuss the safety of the proposed dose of lesinurad 200 milligrams with a specific focus on renal and cardiovascular safety. So first, are there any questions or comments concerning the wording of the question? And then we'll

open the question to discussion.

(No response.)

DR. NEOGI: Okay. So we'll open the question to discussion. Dr. Caplan?

DR. CAPLAN: I had the question about the protocol that was used when there was an elevated creatinine and whether that would be in the dosing instructions to clinicians. As just a general comment, I think sometimes there have been drugs approved in the past without enough of an explicit description to clinicians as to what to do.

I think the response from the company -- or the speaker was that they hadn't tested alternate strategies. So if you have two strategies, one that you use in the protocol and sort of no response or left to private clinicians who aren't privy to this level of data, which one should be promoted? I think it would only make sense to then say, well, we've only tested it in the context of this protocol using these guidelines for clinicians.

So my concern with the proposed -- I guess it's not specific labeling, but what sounds like will

end up in the labeling is that it doesn't follow the protocol that's described. So if there was monitoring and if there was a planned response to these abnormalities, these elevations in creatinine, that should be the default instruction for clinicians to follow because that's the one that was tested not doing anything. Because clearly, if you had to opt between those two, you would pursue -- it would make sense to follow the protocol as described.

DR. NEOGI: Can we have the sponsor clarify what their specific approach will be for addressing these potential AEs?

DR. STORGARD: Yes. So what we are proposing in the proposed label is that if a patient were to experience a twofold serum creatinine elevation from baseline, that lesinurad should be interrupted or also if they report symptoms; and that lesinurad should not be restarted in that patient unless another explanation for the serum creatinine abnormalities could be found.

We're also reemphasizing encouraging the hydration at that point in time. And ultimately, the final recommendations will agreed to with the FDA to

ensure the appropriate use of lesinurad.

DR. NEOGI: Dr. Becker?

DR. BECKER: I was just curious. What's going to be the recommended lab monitoring frequency for that, if you're utilizing creatinine as your focus of intervention?

DR. NEOGI: Will the sponsor address that, please?

DR. STORGARD: The current proposed monitoring is that we will be requesting that serum creatinine be monitored prior to initiation of lesinurad and then periodically thereafter as clinically indicated.

The choice of that language is based upon what's mirrored in the febuxostat language regarding monitoring of hepatotoxicity, but also it's to enable and emphasize the importance of patient focus monitoring because there are concurrent medications and concurrent comorbidities that may require more or less frequent monitoring.

DR. BECKER: I don't think any of us are worried about more monitoring. I guess the question would be less, would there be a possibility of

considering a minimum frequency of lab monitoring? I'm much more worried about somebody going 5 or 6 months or 3 months maybe. Because you monitored every month in the trial, correct?

DR. STORGARD: We monitored every month for the first 6 months, and then every 2 months thereafter in the pivotal studies. So that's how that was initially. The ultimate again, we'll be working with the FDA to ensure that we have the appropriate labeling language regarding monitoring to ensure appropriate use.

DR. NEOGI: Ms. Chauhan?

MS. CHAUHAN: Regarding the labeling, how stringent are you going to be about the issue of patients who have renal failure or who are heart patients, particularly with heart failure? It was mentioned earlier there's a real problem with the liquid requirements if a patient has heart failure problems. And I just want to know the labeling is going to be very stringent and the guidelines very strict.

DR. NEOGI: Will the sponsor address that,

please?

DR. STORGARD: Thank you. Specifically regarding renal function, there will be a contraindication for use in patients who have a creatinine clearance of less than 30 mLs per minute, as well as if they have end-stage renal disease or on dialysis.

We're also recommending use with caution in patients with less than 45 mLs per minute, not because of concerns on efficacy and safety, but the data our study is limited. We had limited numbers. So that will be our recommendation regarding that.

Regarding the fluid, requirement of 2 liters of fluid per day, I also wanted to point out that that is aligned with what is currently in the allopurinol label. The wording is slightly different where there is enough fluid to ensure 2 liters of urine output per day. So that is already in the allopurinol label, and lesinurad is to be added to allopurinol or febuxostat.

MS. CHAUHAN: So are you going to specify anything about heart failure patients?

DR. STORGARD: We will not have any specific

wording at this point in time in our current proposed label. That's correct.

DR. NEOGI: Dr. Kaboli?

DR. KABOLI: My main concern with this question is I think the comment earlier about the narrow therapeutic index, that the minimum effective dose is essentially the same as the maximum safe dose, which that's pretty narrow when you talk about therapeutic indices.

Just a general comment, specifically when it gets back to the recommendations -- and the sponsor may want to respond to this -- about cutoffs for prescribers. And this happens -- I'm a general internist. I'm not a rheumatologist, but it's sometimes very nice to have very specific cutoffs of when you should and shouldn't start something. And you said the cutoff would be a creatinine clearance of less than 30.

Now, in the materials that we were sent ahead of time and didn't come up in discussion today, it looked like the patients with the least benefit were the ones with creatinine clearances less than 45. So

even less than 45, it looks like there's -- and I realize this is a small group, but the N was only 46 patients for studies 301 and 302.

Maybe somebody can explain the physiology that why the people with the lowest creatinine clearance had the least amount of benefit and then potentially are the greatest at risk. This drug seems like it could be potentially greatest -- have the greatest benefit in the people with normal renal function. And anybody below that, boy, I'd be really careful to -- I wouldn't take it.

DR. NEOGI: The sponsor, please?

DR. STORGARD: I'll respond to that question regarding -- overall, the data suggests that we have consistent efficacy and safety regardless of renal function category. And I'll show that by when we take a look at the percent serum uric acid reduction across the various categories -- we do have small numbers in this last category, less than 45, but we're seeing a consistent percent serum uric acid reduction.

It is slightly lower. But now when we take a look at how does that translate into a treatment effect

favoring lesinurad, this is a forest plot that shows when the green dot is on the right of zero, it favors lesinurad. And wee see in the pooled CLEAR studies, it looks like it might be a little lower for the 45 group compared to the 45 to 60. In the CRYSTAL study, it looks the opposite. We think that these differences are due to the small numbers, so that's what we're seeing there.

The question regarding safety in this population, we acknowledge that the patients who have -- well, first, the serum creatinine elevations. What you're seeing here is the creatinine elevation rate in patients with a baseline creatinine clearance of less than 45. And that is not increased with the addition of 200 compared to the overall population. In fact, with 200 milligrams, it looked like it was a little bit lower. Again, we have small numbers.

When you take a look at the renal related adverse events that are reported in this population, this population is a sicker population, so they report more adverse events than the overall population. You can see that in the placebo plus XOI group, almost

4 times as many adverse events. But when we now compare the adverse events reported in the lesinurad 200-milligram group plus XOI to the placebo plus XOI, there are 6 patients actually in all three dose groups. The percentages vary a little bit because of the small sample number. But we're not seeing any suggestion of an increase or a worsened safety profile in this population.

I'll just conclude again with what we showed earlier. When we take a look at the last value of creatinine clearance compared to their baseline in patients across all renal function categories, we're not seeing any meaningful difference in this population. So we're proposing use with caution with less than 45 only because their numbers are small, not because we're seeing any significant alteration in benefit or efficacy.

DR. NEOGI: Dr. Gualtieri?

DR. GUALTIERI: Fully appreciating Dr. Yim's caution, I'm curious about the adverse event reporting in the extension study.

DR. NEOGI: We'll have the sponsor again,

please.

DR. STORGARD: I can first begin with our serum creatinine elevations and talk about the renal safety in the extension studies. The bottom line is what we're seeing in the pivotal studies was observed in the extension studies.

So what I'm showing you here is first our serum creatinine elevation rates. On the left, is 200 milligrams. The first bar is what we observe in the pivotal studies. This is exposure adjusted. That's why the numbers are slightly different than what you saw earlier, which is incidence.

When we look now at the pivotal plus extension, we're seeing a similar exposure-adjusted incidence rate with 200 milligrams, and we see with 400 milligrams, again, those rates are similar. And importantly with this continued treatment, we're still seeing a distinct separation between 200 milligrams and 400 milligrams. This is with regards to serum creatinine elevations.

Now, when we specifically look at adverse event terms, again, we're having similar results here

where the solid bars are the pivotal studies, the hash bars are the results in the pivotal plus extension studies. And as we see with the renal related adverse events, it's comparable with extended treatment for both 200 and 400 milligrams. But importantly, the 200 milligrams is distinct and remains distinct from 400 milligrams with extended treatment.

Similarly with renal related adverse events, our experience in the extension studies mirrors what we're seeing in the pivotal studies. So what we're seeing is a consistent safety profile in the extension studies.

DR. NEOGI: Dr. Miller?

DR. MILLER: Don Miller. I was having a tough time figuring out why the sponsor's efficacy data for less than 45 mLs per minute, creatinine clearance is so different from the FDA's, FDA slide 23. But I think, if I saw your slide correctly a little earlier on efficacy for less than 45, there was a fairly high placebo response in the patients with a clearance less than 45, so that difference is small, kind of artificially small.

Would that be correct?

DR. STORGARD: Yes.

DR. NEOGI: I'm going to pop in a question here. Tuhina Neogi. You know what? I've forgotten my question. I'll move on to Dr. Berney.

DR. BERNEY: I have some concerns about the seemingly arbitrary decision that the creatinine has to double before we worry about stopping the drug. I also have significant reservations about not making specific recommendations about how often to check the creatinine. I think that leaving those decisions up to novices in using uricosurics is very troublesome, keeping in mind that nowadays, most of the rheumatologists in the world are novices in using uricosurics.

I finished my fellowship 20 years ago, and I must say, I haven't prescribed probenecid in over 20 years. So I think that it would be important for the sponsor to make specific recommendations and to rethink their threshold of a creatinine that doubles.

DR. NEOGI: I remembered my question, so I'll pop in here again. Tuhina Neogi. I was wondering if

the sponsors had data on event rates based on duration of exposure to the drugs, so renal AEs and MACE, in relation to duration on drug.

DR. STORGARD: I just wanted to make sure I'm understanding the question correctly. Does this mean on the event as compared to -- the timing of the event or just exposure-adjusted incidence rates?

DR. NEOGI: So my initial question I guess was time to event, but if you have exposure-adjusted incidence rates, that would also be of interest.

DR. STORGARD: So we can review again the data that I had shown regarding serum creatinine elevations. These are the exposure-adjusted incidence rates that we're seeing. And you're seeing here the pivotal studies represented an exposure duration of patient-years of 396.3 patient-years, the pivotal plus extension close to doubling that.

What we're seeing is similar exposure-adjusted incidence rates both for serum creatinine elevations, and we saw the same again here when we looked at our renal related adverse events and serious adverse events. This is again per 100 patient-years. So we're

seeing a consistent exposure-adjusted incidence rate with twice the exposure from the pivotal studies.

So the MACE event rates -- I'm sorry. What we're looking at here, in the top section is the pivotal-based three studies. And you see the placebo plus XOI, lesinurad 200 milligrams, lesinurad 400 milligrams. The pivotal plus extension is below, where we're seeing almost a doubling in the patient-years of exposure, and the 200-milligram plus XOI rates are remaining constant.

On this, we've also referred to our rate in observing the allopurinol 401 study, which was a study of only allopurinol alone in approximately 1700 patients. Again, to show, this was data that was requested by the FDA regarding -- more recent updates regarding our CV signal. And this is now showing again even over greater periods of time.

The first is the core study at the time of the NDA filing. And you're seeing that the 200-milligrams rates are remaining constant over time, and the 400-milligram rates appear to be -- they're still within the original confidence intervals but, again,

very similar now and close to the 200 milligrams. But most importantly is the 200 milligrams are remaining constant over time.

This is not really a reflection because we've lost patients with different demographics. We looked at the demographics from a cardiovascular risk factor perspective. They were similar in the extensions that were in the core. So what we're seeing here is not a reflection of loss of patients with a different cardiovascular profile from the extension versus the core.

DR. NEOGI: Thank you. Dr. Leff?

DR. LEFF: I believe most of the parsing for renal function is usually based on 90, 60, and 30 cutoff values. And the 45 is an interesting analysis because I think it helps us in clinical studies. But I guess my only statement here would be if it gets more widely used, which I think is one of your concerns, would a higher threshold be easier for a general practitioner to interpret, to understand, in the context of everything else that they're doing in the course of the day.

I think having an analysis that shows that there's some level of efficacy at the 45 to 60 is helpful. I think everyone's level of concern goes up as the creatinine clearance goes down. So at least from the perspective when it gets more widely used, I personally was thinking that a cutoff of 60, even though it's higher -- and probably the sponsor behind me isn't smiling -- might be a more reasonable one for when it -- or if it becomes approved, and generally used in the general practitioner arena.

DR. NEOGI: Dr. Chen?

DR. CHEN: Response on the cutoff. This is Jianmeng Chen from FDA again. The 45 cutoff is prespecified in the sponsor's subgroup analysis for efficacy. So the 45 mL per --

DR. LEFF: Was prespecified?

DR. CHEN: Is prespecified in sponsor's subgroup analysis. So that's why we keep that number. For cutoff, we were considering 45, 50, and 60. And the number 50 is there because of the use of probenecid. So we're still having internal discussion and would like to hear from the panel.

DR. NEOGI: Dr. Oliver?

DR. OLIVER: My question or comment's kind of changed since then, and it's back to what you're saying, Dr. Leff, that the two people that required dialysis who were on lesinurad 200 had a creatinine clearance of 51 and 54. So they're right in that kind of gap.

DR. CHEN: If FDA could have backup slide 17? I have a more detailed baseline creatinine clearance on the measure of safety events. And also, while we're waiting for the slide, let me also address for the efficacy based decline renal function, the numbers are small. We see the trend is consistent with the mechanism of the drug, and also the PD, the dedicated renal impairment study. So it seems real to us.

What's seen here is the safety event divided by different cutoffs in renal function. And you can see that for the moderate renal impairment, the safety is worse for moderate renal impairment in general. Between 45 to 60 versus 30 to 45, there's no trend in safety event better or worse. It's happening in both.

DR. LEFF: I mean, it's hard with very small

numbers.

DR. CHEN: Right, it's very hard. I want to note that these are very small numbers.

DR. LEFF: Right.

DR. NEOGI: Dr. Caplan?

DR. CAPLAN: I guess I'm going back to the forest plots that were shown both by the sponsor as well as the one that appears -- I guess it's on slide 22 by the FDA. In keeping with what I think -- it was Peter who mentioned it before, that there appears to be this very tight therapeutic window, particularly below 45.

Is this consistent with the forest plot that was shown by the sponsor for these same groups? There, I thought they all favored the drug, whereas here, they're overlapping zero.

DR. CHEN: In sponsor's plot, this will be study CLEAR 1 and 2. The sponsor also saw the plot for study 304, which they call CLEAR. They didn't do the subgroup analysis for the CLEAR -- we also did a subgroup analysis for the CLEAR, and it's similar to sponsor's results.

While we are waiting for that, we didn't put the CLEAR study here because over there, the number of patients, 45, is really small. This trend of CLEAR, deteriorating renal function, you can see the decrease of efficacy.

May I also have backup slide number 13? This is the dedicated renal function study, and it's in your briefing document, figure 14. I think you can see that the excretion of uric acid decreased with decreased renal function, which is consistent with the efficacy data we saw.

DR. CAPLAN: Can we see the slide again, the first part, back four or five slides ago?

DR. NEOGI: We'll have the sponsor provide that, please.

DR. STORGARD: I think perhaps some of the confusion is that we tend to use the names of the studies, and the FDA was using the numbers. The CLEAR study is study 301 and 302. So this is the pooled study. I believe this is the same reflection of what was shown in the forest -- I apologize. I'm looking at this, and you're not. I apologize.

At the top, the pooled CLEAR studies is I believe reflective of the same analysis forest plot that was shown by the FDA. The CRYSTAL study or study 304 is our analysis also in that study. In that subgroup of patients, there is less than 45. These numbers are small. We can't make definitive conclusions. But the fact that in one study, it's slightly less, the other study, slightly more, I think what this shows when we show the percent serum uric acid reduction is relatively consistent. We are seeing a response that favors lesinurad in these patients.

DR. CHEN: Thank you. This is Jianmeng from FDA again. On that slide, you don't have the efficacy for normal renal function, for on the right side of the curve.

DR. STORGARD: Could we have the last slide that was up, please? This is our analysis looking at the various subgroups of renal function category. This is in the pooled CLEAR studies, so the 301 and 302, showing the green for 200 milligrams of lesinurad plus allopurinol in these studies.

You see that you have consistent efficacy from

the 45 to overall population. The 30 to less than 45 in this pooled population is slightly less than what was seen in the overall population. But as I showed earlier in the CRYSTAL study, it was actually slightly to the right.

DR. NEOGI: Dr. Kaboli?

DR. KABOLI: I think this discussion is sort of illustrating what's going on inside my head in terms of trying to reconcile the safety at these various doses and at the various creatinine clearances that the patients have.

I'm wondering if the FDA has any other summary slides that might summarize some of the safety again for me because I'm still struggling with -- I think some of it is presented differently, so I'm having a hard time telling which is which. I also get confused when anytime the 400-milligram data is thrown in because we're not talking about that anymore because we know there are safety concerns with it. So when it gets thrown in on the efficacy side, it's confusing me.

So I wonder if the FDA has any other summary slides that they could review for me again so that I

make sure I understand this.

DR. NEOGI: Perhaps while they're looking for the optimal piece of data to show us, I will ask Dr. Becker for her comment, please.

DR. BECKER: I think what I was most interested in was in slides 25 and 26, and thinking about what baseline renal impairment and the risk of shifting from one to the next through the course of the study I thought was really intriguing and maybe a little nerve-wracking as we're trying to decide what kind of baseline creatinine clearance is meaningful as far as safety.

I have to say I kind of agree that I don't know if 45 is rigorous enough, and that actually you see some of those patients with moderate renal abnormalities initially being at quite significant risk. And even patients who start normal or mild do tend to progress to more severe renal impairment over the course of the study. And this slide just keeps coming back to me as I think about weighing those risks and benefits. The one before that I thought was also interesting. When you look at that percentage of

patients over time, that may shift from one category to the next.

DR. STORGARD: I'm sorry. I just wanted to point out that there is, from our perspective, an error in the prior slide, in the categorization of the dialysis, severe renal. If you could have that slide that was previously presented, the FDA slide?

In this slide, the patients who had the -- in looking at the placebo plus XOI group in the mild category in the middle, you have two listed there with severe renal adverse events. Those two on the placebo plus XOI, from our analyses, all are in the -- should be on the far right, in the same category, less than 60. So the severe renal events occur equally between placebo plus XOI versus lesinurad plus XOI, in our analyses. So the 2 and 2 should be in the same less-than-60 category.

DR. CHEN: This is Jianmeng Chen from FDA. We used the data set submitted by the sponsor to generate this table, and the baseline renal function was in the data set. And they used the cutoff of 60 to 90 as mild renal impairment.

DR. NEOGI: Dr. Jonas?

DR. JONAS: Just trying to add to Dr. Becker's remarks, as people move from normal to mild or mild to moderate, the other thing that I think, from a safety perspective, that we need to keep in mind is that these are patients that have multiple comorbidities that are also associated with renal insufficiency and progressive renal insufficiency over time; also, on many concomitant medications that they're taking both for their gout and their other comorbidities that may also contribute to the deterioration of renal function over time.

So I think we can't really just look at this in a vacuum. We have to really look at this in the context of the patients. Also, from those of us who see a lot of patients with gout, the patients that we struggle most with actually are the patients with mild to moderate, and sometimes severe, renal insufficiency.

So if we are thinking about a therapy that we are hoping to add on and we have a level of discomfort about its safety in that setting, I think we run the risk that the utility of the drug may not be as great

as we would hope. Yes, we would like to have an add-on therapy, but in the context of all of these comorbidities, other medications, and now what we know about this drug, we really have to consider that.

DR. NEOGI: Tuhina Neogi. I'm still struggling with that slide 25 and trying to reconcile that with the sponsor data showing that the majority of the renal function changes seem to resolve off treatment. I was wondering if the FDA could address that.

DR. CHEN: This is Jianmeng Chen from FDA. May I have the FDA backup slide number 15, please? That table was generated based on the sponsor's submission in the summary of safety. So this is their table. From up to down is placebo, lesinurad 200 milligrams and lesinurad 400 milligrams background of XOI. You can see that there are shifts between renal impairment categories, and there are shifts to the worse, and there are shifts to the better. But overall, you see more shifted to the worse for the lesinurad treatment group.

I don't know if that answers your question.

DR. NEOGI: Tuhina Neogi. I think this is showing a similar message as slide 25, if I'm understanding correctly.

DR. CHEN: Yes.

DR. NEOGI: What I'm having trouble reconciling is this seems to indicate that the subjects in these studies were shifting on average to worse renal function stage. But the sponsor's also shown us some data that shows that those creatinine changes seem to --

DR. CHEN: They reverse.

DR. NEOGI: -- reverse.

DR. CHEN: I will give that question to Dr. Neuner as to the reversibility of creatinine clearance decline.

DR. YIM: Hi. This is Sarah Yim. I think we use the tables that the sponsor submitted and the data sets the sponsor submitted. I believe that Dr. Carome actually in the open public hearing presented the more busier table that we had in the briefing document, where we listed out all the events, how long they took to resolve, and ones that were unresolved at the last

assessment. That was derived specifically from a sponsor table.

So I think the message that we have is that there is a subgroup of people who are not resolving. I'm not quite sure how to explain the sponsor's figures and graphs that look like everybody's resolving.

DR. NEOGI: Dr. Leff?

DR. LEFF: Could you pull up that figure from that last table from the FDA? When I look at that, at those that come in at 30 to 60, some shift to worse, but some shift in the other direction. And I think the FDA, on the easier to read table, was just looking at the ones that shift in the worse direction. So I think in that other one, there are ones that go in both directions, which could explain some of the findings.

I was looking at the lesinurad 200 at the 30 to 60 that's highlighted in the middle, and some that come in at 30 to 60 later on, or 60 to 90, actually a higher percentage there. So I think they were just pulling out the ones that shifted to the worse. I think on average, in fact, it's different.

DR. CHEN: This is Jianmeng Chen again from

FDA. Yes, 4 percent of patients moved to the better category with lesinurad 200 milligrams compared to the 5.6 percent of patients who moved to the better direction in placebo group.

DR. LEFF: Right.

DR. CHEN: Yes. Thank you.

DR. NEOGI: Are there any other questions or comments to be made about the safety question?

(No response.)

DR. NEOGI: So if I may summarize, I think that you're hearing that the committee members are still a little uncertain about the renal safety, particularly as it relates to baseline creatinine clearance. There have been some comments about whether or not the cutoff of caution at less than 45 mLs per minute is a sufficient cutoff and whether or not that should be more conservative.

There were concerns raised about having the labeling be more specific about the minimum frequency of lab monitoring. Questions were also raised about being more specific about other cautions and whether or not the 2 times elevation of creatinine is too lenient

in terms of guidance for prescribing clinicians.

I think overall, there's no concern about the safety signals in individuals with normal renal function, and the question remains about exactly what the data is showing for the small numbers that we do have for those with less favorable renal function.

Does anyone have anything to add to that summary?

DR. YIM: This is Sarah Yim. I think Dr. Kaboli or Dr. Delost had asked for a safety overview again. I think we had a summary slide 55, if you want, from the clinical presentation.

So this isn't really saying anything new, but this is the overall summary again by dose. Was there a specific question you had about that?

DR. KABOLI: Well, just talk through it for me one more time.

DR. YIM: So obviously, this is the entire group. It's not the renally impaired subgroup. But overall, we're seeing an increase in all these categories -- I think all these categories -- yes, all these categories with the 400-milligram lesinurad dose.

The increase for the 200-milligram dose is not necessarily in all those categories, and it's smaller. So you see an increase in overall adverse events and then AEs leading to discontinuation and deaths. And I think we had other slides that had non-serious renal AEs, and there was an increase, a smaller increase, with the 200-milligram dose.

DR. NEOGI: So I'm just being reminded that we've spent a lot of time talking about the renal AEs, but we've not had specific comments about the cardiovascular AEs. Does anyone have any specific comments for that? Dr. Kaboli?

DR. KABOLI: Yes. My only comment is just my unease with the relatively small numbers that we're making decisions on. And I realize that's all you have and that we have to make the best decision based on the data that's available. But I think some of these events are going to be uncommon events but potentially catastrophic.

I think that's what we learned with troglitazone when it came out for diabetes, is that hepatic failure was really rare, and I think there were

about 30,000 patient-years in the trials. But it wasn't until it got used in general use that we found out, oh, wow, fulminant hepatic failure is a pretty serious adverse event when you're talking about one more treatment for diabetes.

So I guess my angst is these very serious events, are we just going to have to roll the dice and see what happens when it's used in the general population and hope that they don't happen or do we ask for more data. That's the internal struggle that I'm having. Just more of a comment. It's not a question.

DR. NEOGI: Tuhina Neogi. I agree. It's very difficult to make conclusions based on these very small numbers. And this was I think reminiscent of what was seen with the febuxostat trials when there was this question of a cardiovascular signal. There's a label for the febuxostat product, and the sponsors have also stated that they will put a label regarding cardiovascular events. I think it's very difficult with these numbers for us to make very specific conclusions.

Dr. Gualtieri?

DR. GUALTIERI: There's been a lot of discussion about the dose, but I wasn't sure the duration or somebody taking this was discussed.

DR. NEOGI: Does the sponsor want to address that, please?

DR. STORGARD: The intention would be that it's for chronic use. Where there's no duration of use limited in the proposed label, it would be for chronic use.

DR. NEOGI: Dr. Reimold?

DR. REIMOLD: While we're talking about this kind of issue, my question was in terms of starting the use of it, the trials were all after a xanthine oxidase inhibitor was on board. So is there any kind of limitation on starting the two drugs together? Would the xanthine oxidase inhibitor definitely have its effect first, and then you could consider the second? I don't think that's been spelled out.

DR. NEOGI: Could the sponsor address that, please?

DR. STORGARD: Our intent is that lesinurad 200 milligrams would be added to a preexisting xanthine

oxidase inhibitor after that patient has failed to achieve their target.

DR. NEOGI: So if there are no more questions or comments for question 2, we'll move on to question 3. Discuss the dose-dependent toxicity of lesinurad in light of the safety profile of the 400-milligram dose. And in your discussion, comment on the following.

A. Comment on whether the overlapping exposure of the 200-milligram and 400-milligram doses raises concerns about the potential toxicity of the 200-milligram dose if exposed to a broader population of gout patients postmarketing.

B. Comment on whether the justification for once-daily dosing is adequate given that it remains an open question whether a lower nominal dose given more frequently might have provided similar efficacy with a better safety profile.

Dr. Caplan?

DR. CAPLAN: I think it's very hard to speculate. That study wasn't done, so I think it's not really fair to ask about anything more than the data

that we have. But I would also just comment that given that there was some rationale in avoiding a twice-daily dose -- twice-a-day dose, rather, based on the concern for flares overnight or whatnot, that instead of it being a daily dose, that it should be specified as a QAM dose maybe. Maybe that makes more sense, and so that's actually what was done.

DR. NEOGI: Dr. Berney?

DR. BERNEY: Seth Berney. I don't know that, regarding question B or comment B, whether one precludes the other. Right now, the discussion is should we consider once-daily dosing. I don't think that precludes the sponsor from necessarily looking into twice daily in the future. I'm not sure why that is being raised as a pertinent issue for today.

DR. NEOGI: If I may, I think one of the rationales for that question is if the therapeutic index is so low that the minimal dose for efficacy is the same as the maximal dose for safety, might we get similar efficacy by doing twice-daily dosing while improving that therapeutic index. On the other hand, the sponsor has also indicated a rationale for why an

evening dose is not an optimal theoretical option.

I have a question for the FDA. Is there any data regarding the bid dosing for probenecid as to whether or not that has negatively affected or has increased the risk of AEs related to probenecid dosing?

DR. YIM: This is Sarah Yim. Yes. I think unfortunately we're left in the same situation where we don't have data for once-daily probenecid dosing. So in the limited data we have from studies of probenecid, it's always twice-a-day dosing.

I will say that, based on my review of the literature, it didn't look like there was an excessive concern about dosing twice daily. For example, in the Pui study, the main adverse events were things like GI intolerance. So it wasn't that all those patients were dropping out because of renal adverse events.

But I understand the rationale, and we're not questioning that rationale. But the concern really gets back to what you were describing, which is if we're very close to what we are considering the maximum tolerated dose, we sometimes make the decision to ask for a change in the dosing regimen before we'll approve

something to improve the distance between the efficacious dose and the maximum tolerated dose, so that we're not quite so close to dropping off the safety curve. So that's why we're asking that.

DR. NEOGI: Would the sponsor like to address that as well, please?

DR. STORGARD: Thank you. Just to respond, I think the concerns that we had with the nocturnal dosing was the history that we have with probenecid with kidney stones. There are some reports that range from 8 to 25 percent of patients have developed kidney stones on probenecid. As we showed in our pivotal studies, the rate of kidney stones was not increased with lesinurad 200 milligrams.

Also, in reference to the studies that quoted I believe that they were not randomized controlled trials -- I think the numbers were in the 50 to 60 range in combination with an XOI. So I think an assessment of renal safety in those studies is not possible. So we agree with that.

DR. NEOGI: Dr. Delost?

DR. DELOST: Kort Delost, community pharmacy.

I think what would happen is if you split that dose up from an efficacy standpoint, it would defeat itself because of compliance issues. In the real world where I'm at, compliance is key. Once a day is so much better than twice a day.

DR. NEOGI: Tuhina Neogi. I have a question for the pharmacologists. I guess this talk of this overlapping exposure and in the graphs that we saw, I think the tail of the 200-milligram dosing that overlapped with the 400-milligram dosing in terms of the plasma exposure, I think that tail was about 10 percent. So as a non-pharmacologist, I wanted input as to how important that overlap is in the real world.

DR. CHEN: This Jianmeng Chen from FDA. This drug is not a highly variable drug. So in terms of PK, it is a normal linear PK drug, meaning the 400-milligram dose, exposure is, in general, higher than 200-milligram exposure. What bothers us here is, again, the therapeutic index. You can see that 10 percent of patients, the exposure was falling [indiscernible] about the 400-milligram median dose, and there you begin to see safety events. So actually,

the exposure overlapping data is consistent with what the real safety data says, meaning the similar safety events were seen in both 200 milligrams and 400 milligrams. But a 200-milligram dose, it happens with much less frequency.

I don't know if that answers your question.

DR. NEOGI: Dr. Miller?

DR. MILLER: Well, I don't think overlap is too surprising in light of patient variation. It's not a particular concern for me.

DR. NEOGI: Dr. Delost?

DR. DELOST: I agree. No concern, no significant concern there.

DR. NEOGI: Dr. Smith?

DR. SMITH: I also concur.

DR. NEOGI: So any other comments or questions regarding question 3? Dr. Yim?

DR. YIM: Sarah Yim. So just to clarify, as a reminder, we don't have any data other than once-daily dosing. So it is kind of unfair to ask you to speculate, but we're sort of -- what we're getting at is would getting that data be important before we

decide to approve this drug, or are you happy with the hypothesis that it could be more dangerous given twice daily.

DR. NEOGI: Dr. Berney?

DR. BERNEY: The lack of the twice-a-day dosing doesn't concern me in terms of considering this as a once-a-day drug, but it would be nice to have it at some point in the future. But I think the data speaks for itself at this point, as well as the safety concerns.

DR. NEOGI: Dr. Becker?

DR. BECKER: Mara Becker. I think one of the challenges we're going to be faced with, with this, is that the frequency of serious adverse events was pretty low, and the likelihood of kidney stones or nephrolithiasis is going to be pretty high. So I think even if we tried to get that data, it might be hard to tease out as well.

I'd be really interested to know the PK data with bid dosing to be able to answer that question a little bit easier. But when I think about, really, the frequency of the nighttime dose of these drugs

increases kidney stones by 20 percent, what I heard correctly, and we have three or four very frequent, single-digit, serious adverse events, I think the reality is we will see way more kidney stones. I'm not sure if we'll see enough serious adverse events early enough to make us change our minds. I'm not sure.

DR. NEOGI: Okay. I think in summary, it seems that there's no specific concerns about the overlap in plasmic exposure and that it's partly to be expected. Then in terms of a comment on question B, I think most people are okay with the once-daily dosing. I think Dr. Becker raises an important -- it's a risk tradeoff that the prevalence of nephrolithiasis is likely to be higher than these rare adverse events. Then others, Dr. Delost, also raised a practical point of adherence, and we may be losing efficacy by putting forth a bid dosing.

Dr. Yim, shall we go on to the subsequent questions?

(Dr. Yim nods in the affirmative.)

DR. NEOGI: Okay. So we'll move on to question 4, which are voting questions. For questions

4 through 6, we will be using an electronic voting system. Once we begin the vote, the buttons will start flashing and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we will go around the room and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did if you want to. We will continue in this same manner until all questions have been answered or discussed.

Question 4. Overall, do the data provide substantial evidence that lesinurad 200 milligrams once daily provides a clinically meaningful beneficial effect in the treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor?

Before we vote, are there any questions or comments concerning the wording of this question?

(No response.)

DR. NEOGI: Okay. So let's proceed to the vote.

(Vote taken.)

DR. BAUTISTA: The vote is now complete. There are 14 yeses, zero nos, zero abstentions.

DR. NEOGI: So we will go around the table to officially put our votes into the record. We'll start with Dr. Leff.

DR. LEFF: I don't vote [off microphone.]

DR. NEOGI: Oh, I'm so sorry. Dr. Berney.

DR. BERNEY: Yes.

DR. OLIVER: Alyce Oliver. Yes.

DR. NEOGI: I'm just going to interrupt for a second. I am off the script here. I forgot to say that I need to have you state your name, the vote, and address subsection A of question 4 and explain the rationale of your vote. I'm not sure what subsection A is.

Thank you.

DR. BERNEY: Seth Berney. I voted yes. I think that the decrease in uric acid, although modest at some times, will end up being clinically relevant in the long run, and that's how I view gout. So I think eventually we'll have the data that says that there were decreased flares.

DR. OLIVER: Alyce Oliver. I voted yes. I think there is a clinically meaningful response in the studies.

DR. GUALTIERI: Lisa Gualtieri. I voted yes, although I was concerned about the use of the word "substantial," but I do believe that they provided evidence.

MS. CHAUHAN: Cynthia Chauhan. I voted a qualified yes. I also was concerned about the use of the word "substantial," but I'm aware that right now, other alternatives are limited. And as long as this goes to a small select population, I think it's a valuable addition to the armamentarium.

DR. BECKER: Mara Becker. I voted yes. I'm primarily focused on the percentage of patients that met the threshold of serum uric acid less than 6 and 5

being meaningful clinically.

DR. REIMOLD: Andreas Reimold. I voted yes. I agree with the other speakers that there's a clinically meaningful effect even though it may be small.

DR. JONAS: Beth Jonas. I voted yes. Again, I think that this is clinically meaningful and likely to have a benefit over the long run, although realizing that we did not really have a chance to look at that long-term data.

DR. CAPLAN: Liron Caplan. I also voted yes because I feel like the 50 to 20 percent of patients who anticipated to benefit from that additional milligram of uric acid reduction makes it worth it.

DR. NEOGI: Tuhina Neogi. I voted yes for many of the reasons already stated. I do think that this is a substantial benefit given that this is on top of xanthine oxidase inhibition. And the average of 1 milligram per deciliter for the broader population I think will amount to a larger proportion, meeting the target that is known to result, in the long term, in clinically meaningful benefit.

DR. MILLER: Don Miller. I voted yes. I took substantial to mean that we do have evidence from a large number of patients that it works. The effect is not large, but it does work.

DR. TCHETGEN TCHETGEN: Eric Tchetgen Tchetgen. I voted yes. The primary endpoint was met. Quite a bit of evidence, compelling evidence, that it works. And based on our discussion, it looks like we will eventually see creatinine co-benefit.

DR. DELOST: Kort Delost. I voted yes, that they met the goals of the serum uric acid levels and that over 50 percent will benefit from that. I still have a little heartburn on the sequelae, and I hope it turns out the way we want it.

DR. KABOLI: Peter Kaboli. I voted yes. If I had to vote at the beginning of the day, I would have voted no, actually because I didn't see in the data I reviewed ahead of time that there was much of a clinical benefit to the patient, and it was more a serologic benefit. But I've been educated now, as a non-rheumatologist, that over time there's a leap of faith that these people will benefit over time with

reduction in flares, reduction in tophi, and health-related quality of life will hopefully improve over time.

DR. SMITH: I'm Bob Smith. I voted yes because I believe, after listening to the discussion, reading the data, that there's objective data that this product will be clinically relevant.

DR. NEOGI: Dr. Yim, any questions?

(Dr. Yim nods no.)

DR. NEOGI: No. Okay. We'll move on to question 5. Is the safety profile of lesinurad 200 milligrams once daily adequate to support approval of lesinurad for the treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor? And please explain the rationale for your vote.

(Vote taken.)

DR. BAUTISTA: The vote is now closed. I'll now read the vote in the record. Seven yeses, zero nos -- sorry, 6 nos, 1 abstention.

DR. NEOGI: Again, we'll go around the table and have everyone who voted state their name, vote, and

the rationale for your vote.

DR. BERNEY: Seth Berney. I voted yes. I think that the similarities between the 200-milligram dose and placebo were enough that I think it's reasonably safe. However, I would like the sponsor to come up with reasonable recommendations for monitoring, and I think it ought to start at 1 and a half times the creatinine, not 2 times creatinine elevation. But other than that, I think it's reasonably safe.

DR. OLIVER: Alyce Oliver. I voted yes. I thought the decision was difficult. I was thinking much like the rest of the committee, back and forth; again, a select number of patients who will have a clinically meaningful use. I think the risk profile is okay. Having said that, again, our numbers that we had to look at for adverse events, particularly renal events and cardiac events, is too low to really understand what's going on. It's going to take postmarketing analysis and other reviews.

DR. GUALTIERI: Lisa Gualtieri. I voted no primarily because I'd like to see a study of longer duration done.

MS. CHAUHAN: Cynthia Chauhan. I vacillated. I voted yes, and then I changed it to no. I thought I was changing to abstain, so obviously, I'm conflicted. I don't think the safety profile is adequate. I think more work needs to be done. So I think my finger did a better job than my brain, and I vote no.

DR. BECKER: Mara Becker. I voted no, too, and I was very conflicted. And I think I probably was most fixated on the current sponsor recommendations for monitoring or safety, and I would like that to maybe be revisited. I don't think that the numbers per se are so terrible. I would just rather have a little bit more specific guidance to providers and maybe limit the exposure to patients who are already compromised from their renal function standpoint.

DR. REIMOLD: Andreas Reimold. I voted yes. I think our views of the safety issues have been colored by the 400-milligram dose very strongly, and I find them quite borderline at the 200-milligram dose. So I voted to proceed. Thank you.

DR. JONAS: Beth Jonas. I voted no. My primary concern is that we don't have a longer term

studies and that also there is some concern primarily about patients with renal insufficiency, and that gave me cause to worry about safety in that population.

DR. CAPLAN: Liron Caplan. I voted yes, but it was a very tough call. I think my yes carries with it a few caveats. And that is that it is on the -- the onus is on the sponsor to demonstrate benefit and safety at the lower estimated creatinine clearance. So if their numbers were low there and heard to tease out, then our default action should be not to recommend it be used in folks below a creatinine clearance of 60 CHF stage 3, 4, et cetera.

DR. NEOGI: Tuhina Neogi. I voted yes. I think there were some qualifications, and the FDA has heard that the panel would like some more specifics in the labeling. Having said that, I actually have to admit that I was impressed that the sponsor came with already a plan for these types of cautions, et cetera, which I've not really seen in most of my meetings that I've been here. So I appreciate that the sponsor has spent time thinking about this and have indicated willingness to work with the FDA to tighten things up

and address these concerns.

So I think that that was a positive that helped sway me toward the yes. And for me not being a pharmacologist, I wasn't really sure what to make of the exposure overlap, that 10 percent, but I did think that just looking at the 200-milligram data, I didn't have any specific concerns.

DR. MILLER: Don Miller. I voted yes. I agree with a need for monitoring, and I think that would be an extra safety margin. But the other thing that influenced me is all of the drugs used for gout have substantial risks, and I don't think, in light of that, the risks for lesinurad are unreasonable.

DR. TCHETGEN TCHETGEN: Eric Tchetgen Tchetgen, the only one who abstained. I was really conflicted just because I think the data are too sparse to be able to tell apart what the story is. And I also thought that the presentation from FDA and the sponsor, it was really hard to tell -- to reconcile a lot of these slides. So that made it for a very confusing -- at least the thought process for me was very, very confusing.

I do think that, based on some of the data that I could make out, the 400 and 200 dose, there was a little too much overlap in terms of the signal for adverse events to make me feel comfortable, actually, like either way. So that's why I abstained.

DR. DELOST: Kort Delost. I voted yes, a qualified yes like the others. I want more attention paid to the creatinine clearance levels and the effects of that, proper labeling, so on and so forth. But as far as the overall safety profile, I didn't see a major issue.

DR. KABOLI: Peter Kaboli. I voted no, and mainly because the narrow therapeutic index of this drug really does concern me, that if we have it out in general use, we're either going to learn that it's safe or we're going to learn that it's not safe, and then we'll take it off the market later. So I really felt conflicted are we going to have something out there that can benefit some people but puts other people at harm.

DR. SMITH: Bob Smith. I voted no primarily because the renal data and the patients I deal with are

mostly diabetic, and they have comorbidities, and it just gives me cause for pause. So I just summed it up and voted no.

DR. NEOGI: We'll move on to question 6. Do you recommend approval of lesinurad 200 milligrams once daily for the proposed indication of treatment of hyperuricemia associated with gout in combination with a xanthine oxidase inhibitor? The following two questions, if you voted yes, are there additional studies recommended post-approval? And if you voted no, what additional studies are recommended prior to approval?

(Vote taken.)

DR. BAUTISTA: The vote is now closed. I'll now read the vote in the record: 10 yeses, 4 nos, zero abstentions.

DR. NEOGI: We'll go around the table again and have everyone who voted state their name, vote, and then address question A, if you voted yes, and question B if you voted no.

DR. BERNEY: Seth Berney. I voted yes. I would like to see three additional trials. One would

be a split dosing, say at 7 and at 2, to look at the efficacy and safety of 100 milligrams twice a day, but the second dose would be earlier in the afternoon. I would like to see whether it truly over several years decreases flares. And three, I'd like a long-term side effect profile or adverse event profile to see if it's really safe or not.

DR. OLIVER: Alyce Oliver. I voted yes. I'd like to see studies looking at longer extension times than 24 months that include a placebo, as well as looking at adverse events, specifically cardiovascular and renal.

DR. GUALTIERI: Lisa Gualtieri. I voted no for exactly the same reasons that my colleagues voted yes. I do want to see the longer term studies, but I'd like to see them before approval.

MS. CHAUHAN: Cynthia Chauhan. I voted a conflicted yes. I think more studies need to be done around safety. I think the comorbidity parameters need to be more closely examined, and -- I can't think of the other word. And I also think that -- I share Dr. Kaboli's concern about when this goes out into the

general population, there's a lot of room for error in the current situation.

So I would really like for the labeling to be very, very specific, not only about renal issues but also cardiovascular issues, and then some general statements about other comorbidities. I think it could be a very helpful thing, but there may be a lot of inherent danger that we have not looked at because the trials have been so small and short.

DR. BECKER: Mara Becker. I voted yes. I switched my vote a few times, and I ended up yes. I think I'm happy with that. I agree with a lot of what has already been said for me. Certainly, I think strict guidelines need to be in place for patients who have baseline renal insufficiency and certainly some of the comorbidities that we see. And I'd really be interested in the long-term safety data as it comes out and as these long-term extension trials are ongoing. I still think the potential benefits outweigh those risks.

DR. REIMOLD: Andreas Reimold. I voted yes. I think I can agree with a lot of the sentiments that

we need a good phase 4 study to look at comorbidities, to look at real-world adverse events. And there's been some discussion that's appropriate about having the label include mention of specific creatinine levels, for example.

DR. JONAS: Beth Jonas. I voted yes. I wondered whether I could vote yes if I thought that the safety was no, which is a little weird. But I think the benefits are big potentially for a lot of patients. The risks are there. Unfortunately, we can't measure them very well, but my overall feeling was that the benefits outweighed the risks, although it was darn close.

I think that real-world data is going to be really important here because we really don't know what's going to happen in large population of patients with multiple comorbidities. So I would urge the FDA to think about lots of post-approval, real-world studies in this population. I also would like to see control data out to 24 months.

DR. CAPLAN: Liron Caplan. I voted yes. And as many of my colleagues have mentioned, I think there

needs to be a specific study looking at patients with lower renal function to see more clearly the benefit versus harm in this medication, and that the labeling needs to be very prescriptive here with a monitoring schedule creatinine of 1.5 being identified. So that's what I would like to see.

I say this often to my patients, that there is no medication that's perfect. There's no free lunch. You don't get a medication with no side effects, but I think that this adds to our armamentarium. And as long as we're very careful with it, I think it's appropriate if it's approved.

DR. NEOGI: Tuhina Neogi. I voted yes. As I said previously, I think the efficacy data is convincing. I think the safety issues for 200-milligram dose were not necessarily clear to me. These are patients who have a lot of comorbidities, and there are a lot of confounding factors that are in place for some of those AEs that makes it difficult to tease apart.

This is a population that has a great unmet need. There are many patients on xanthine oxidase

inhibition or combination therapy. We just can't get them to target, and it would be wonderful to have another option. And I think the discussion about labeling and giving more guidance to prescribing clinicians will help guard against some of these concerns about AEs. I think this discussion has gotten a lot further than what I've seen for some other drugs that have been under discussion that have had similar AE concerns. I think a post-approval study that I'd like to see is specifically in the subset with renal insufficiency.

DR. MILLER: Don Miller. I voted yes. I think the drug does meet an unmet need. I'm not sure I'd recommend any more randomized studies. I think that a twice-a-day dosing study would really be worth the investment. But like everyone else, I totally agree with postmarketing surveillance and the overall to patients.

DR. TCHETGEN TCHETGEN: Eric Tchetgen Tchetgen. I voted no. I think it was mainly my discomfort with the safety data or rather the uncertainty around safety. In terms of what studies

could be conducted, I agree with everything that's been said.

DR. DELOST: Kort Delost. I voted yes. I'd like to see the continuation of the studies on the resolution of tophi and flares. That was my big concern to start with. So I'd like to have that retrospective study in that, as well as looking at the levels for creatinine clearance, you can put in there as well, reevaluated.

DR. KABOLI: Peter Kaboli. I voted no. It was difficult, but what I finally came down to is when I look at things like this, I try to look at the number needed to treat and the number needed to harm. And in this case, the number needed to treat, there are clearly people that will benefit. But I couldn't come up with a number needed to harm that would balance it to say I feel comfortable that this would be approved knowing that we're going to help more people than we're going to harm.

So that's why I felt uncomfortable voting yes. But I think there's great opportunity, if ultimately it's approved, for the sponsor to do some really

interesting studies, some great postmarketing studies, to find out which patients have the greatest potential to benefit from this.

I'm most concerned or most intrigued with the renal issue because I can't tell from the data so far if those are the patients that have potentially the greatest benefit or the greatest of harm, or that they'll get no benefit and maybe very little harm. And maybe some of the events that will happen are going to be more idiosyncratic and we're not going to be able to know who's going to benefit -- I'm sorry, who's going to have the greatest harm. Thank you.

DR. SMITH: Bob Smith. I voted no primarily because I voted no about the safety and couldn't reconcile voting yes.

DR. NEOGI: Dr. Yim or Dr. Chowdhury, do you have any questions or final comments?

DR. YIM: Just to clarify, for those of you who voted no to safety but yes for the overall recommendation, what I'm hearing is that when you're doing the overall risk-benefit, you think that there's going to be more potential for benefit than harm. Is

that right?

DR. JONAS: This is Beth Jonas. Yes, that's exactly how I felt about it, and I think I articulated that. Again, it was hard to vote yes thinking about safety, but I think overall, the benefit outweighs the risk, at least from what we can see right now, realizing that we still have some data to look at, I think.

DR. BECKER: Mara Becker. For me, I'm a newbie, so I wasn't sure how concrete I had to be. And I think after hearing Tuhina say, Oh, I'd like to have more structured guidelines, I thought, "Oh, I can do that. That would make me feel a lot more comfortable." So it was probably just naivete, but I agree. I didn't know how I should vote final when I had no to safety. But I do think that with a little bit of harnessing and some guidelines, and more specific guidelines, I would feel comfortable with it.

DR. YIM: Okay. Well, I want to really thank everybody for your participation today. We really value your input, and we appreciate you taking the time out of your busy schedules to join us.

Adjournment

DR. NEOGI: Thank you. So we will now adjourn the meeting. Panel members, please take all personal belongings with you, as the room is cleaned at the end of the meeting day. All materials left on the table will be disposed of. Please also remember to drop off your name badge at the registration table on your way out so that they may be recycled. And thank you for keeping us on time despite the fire alarm today. Safe travels.

(Whereupon, at 3:19 p.m., the meeting was adjourned.)