FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE
ARTHRITIS ADVISORY COMMITTEE (AAC) AND THE
DRUG SAFETY AND RISK MANAGEMENT
ADVISORY COMMITTEE (DSaRM)

Friday, January 11, 2019
8:00 a.m. to 5:15 p.m.

College Park Marriott Hotel and Conference Center
General Vessey Ballroom
Building 31 Conference Center
3501 University Boulevard East
Hyattsville, Maryland
Meeting Roster

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*(301) 890-4188*
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Call to Order

Introduction of Committee

DR. SUAREZ-ALMAZOR: Good morning. I would like to start by reminding everyone to please silence your cell phones, smartphones, and any other devices, if you have not already done so. My name is Maria Suarez-Almazor, and I'm the acting chairperson this morning. I will now call today's joint meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee to order.

We'll start by going around the table and introducing ourselves. We will start with the FDA to my left, and then go around the table.

DR. SEYMOUR: My name is Dr. Sally Seymour. I'm the acting director for the Division of Pulmonary, Allergy, and Rheumatology Products at the FDA.

DR. NIKOLOV: Morning, everyone. My name is Nikolay Nikolov. I'm an associate director for
rheumatology in the Division of Pulmonary, Allergy, and Rheumatology Products at the FDA.

DR. NEUNER: Good morning. My name is Rosemarie Neuner. I'm a medical officer in the Division of Pulmonary, Allergy, and Rheumatology.

DR. HSUEH: Good morning. I'm Ya-Hui Hsu, statistical reviewer from the Office of Biostatistics, FDA.

DR. GIBSON: Mike Gibson, a member of the cardio/renal panel.

DR. HABEL: Laurie Habel, epidemiologist and associate director for research at Northern California, Kaiser Permanente.

DR. RANGANATH: Veena Ranganath, associate clinical professor at UCLA, adult rheumatology.

DR. OLIVER: Good morning, Alyce Oliver. I'm an adult rheumatologist at the Medical College of Georgia.

DR. KULLDORFF: Good morning, everybody. I'm Martin Kulldorff. I'm a professor and a biostatistician at the Harvard Medical School and Brigham & Women's Hospital.
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DR. CURTIS: Good morning. I'm Jeff Curtis. I'm a pharmacoepidemiologist and rheumatologist at the University of Alabama at Birmingham.

DR. GRIFFIN: Good morning. I'm Marie Griffin, internist and pharmacoepidemiologist at Vanderbilt.

DR. NISSEN: I'm Steve Nissen, and I'm a cardiologist with the Cleveland Clinic.

DR. RUHA: I'm Anne-Michelle Ruha. I'm a medical toxicologist with Banner University Medical Center in Phoenix and the University of Arizona College of Medicine.

DR. WANG: Yinghua Wang, designated federal officer, FDA.

DR. SUAREZ-ALMAZOR: Maria Suarez-Almazor, rheumatologist and clinical epidemiologist at the University of Texas MD Anderson Cancer Center.

DR. CUSH: Good morning. I'm Jack Cush. I'm a rheumatologist from Dallas, Texas. I'm affiliated with the Baylor Research Institute in UT Southwestern.

DR. MEISEL: Good morning. Steve Meisel,
director of medication safety, Fairview Health Services in Minneapolis. And if I can, for the AV folks, the sound at that end of the room doesn't reach over here very well. If the AV folks can look at that, that'd be helpful. Thank you.

DR. WARHOLAK: Hi. I'm Terry Warholak, and I am a professor and assistant dean from the University of Arizona, College of Pharmacy.

DR. HORONJEFF: Good morning. I'm Jen Horonjeff. I am a patient. I'm serving here as the consumer representative on the Arthritis Advisory Committee. I'm also a patient-centered outcomes researcher at Columbia University Medical Center, and I also am the founder of Savvy Cooperative, which is a patient co-op.

MR. WEINER: Good morning. I'm Gene Weiner from Plymouth, Massachusetts. I'm a patient representative.

DR. NASON: Good morning. I'm Martha Nason. I'm a biostatistician at the National Institute of Allergy and Infectious Diseases.

DR. PSATY: I'm Bruce Psaty, a general
internist and cardiovascular epidemiologist at the University of Washington, and as I get older, increasingly a patient.

DR. LIANG: Same here. Morning. Matt Liang. I'm a primary care physician and rheumatologist. A barefoot epidemiologist and trialist from the Brigham & Women's and JP Cooperative Studies Program in the VA.

DR. MILLER: Good morning. I'm Donald Miller, professor of pharmacy practice at North Dakota State University.

DR. McADAMS-DEMARCO: Good morning. I'm Mara McAdams-Demarco. I'm an assistant professor of epidemiology at Johns Hopkins School of Public Health and School of Medicine.

DR. FELSON: Good morning. I'm David Felson, and I'm a rheumatologist and epidemiologist at Boston University.

DR. CHUNG: I'm James Chung. I'm the industry representative. I'm an employee of Amgen and a rheumatologist.

DR. SUAREZ-ALMAZOR: We also have Dr. Scher
on the phone. Dr. Scher?

FEMALE VOICE: He's not on yet.

DR. SUAREZ-ALMAZOR: He's not on yet? Okay.

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, 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 only in the open forum of the meeting.

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

Now, I'll pass it to Dr. Yinghua Wang, who
will read the conflict of interest statement.

Conflict of Interest Statement

DR. WANG: The Food and Drug Administration
is convening today's meeting of the Joint Arthritis
Advisory Committee and Drug Safety & Risk
Management Advisory Committee under the authority
of the Federal Advisory Committee Act of 1972.
With the exception of the industry representative,
all members and temporary voting members of the
committees are special government employees or
regular federal employees from other agencies and
are subject to federal conflict of interest laws
and regulations.

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

FDA has determined that members and temporary voting members of these committees are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest, or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

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

Today's agenda involves supplemental new drug application, sNDA 021-856, Uloric, febuxostat tablets, sponsored by Takeda Pharmaceuticals, which includes the results from the postmarketing safety trial required by FDA to evaluate the cardiovascular safety of febuxostat, entitled Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities, CARES.

Febuxostat is a xanthine oxidase inhibitor indicated for the chronic management of hyperuricemia in patients with gout. The committees' discussion will include the results from the CARES trial, the benefit-risk assessment of febuxostat, and potential regulatory actions.

This is a particular matters meeting during
which specific matters related to Takeda's supplemental NDA will be discussed. Based on the agenda of today's meeting and all financial interests reported by the committee members and temporary voting members, a conflict of interest waiver has been issued in accordance with 18 U.S.C. Section 208(b)(3) to Dr. Jeffrey Curtis.

Dr. Curtis' waiver involves his ownership of shares in a healthcare sector mutual fund valued between $50,001 to $100,000. The waiver allows Dr. Curtis to participate fully in today's deliberations. FDA's reasons for issuing the waivers are described in the waiver documents, which are posted on FDA's website at: www.fda.gov/advisorycommittee/committeemeetingmaterials.

Copies of the waivers may also be obtained by submitting a written request to the agency's Freedom of Information Division at 5630 Fishers Lane, Room 1035, Rockville, MD 20857, or requests may be sent via fax to 301-827-9267.

To ensure transparency, we encourage all
standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. James B. Chung is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Chung's role at this meeting is to represent industry in general and not any particular company. Dr. Chung is employed by Amgen.

We would like to remind members and temporary voting members that if the discussions involve any other products, drugs, 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 committees of any financial relationships that they may have with the firm at
issue. Thank you.

DR. SUAREZ-ALMAZOR: Okay. I believe Dr. Scher is now on the line.

Dr. Scher, would you like to introduce yourself, please?

DR. SCHER: Yes. Good morning. Jose Scher, New York University, rheumatology. My apologies for not being able to be there in person.

DR. SUAREZ-ALMAZOR: Okay.

We will now proceed with the FDA's opening remarks from Dr. Nikolay Nikolov.

**FDA Opening Remarks - Nikolay Nikolov**

DR. NIKOLOV: Morning, everyone. I would like to welcome you to the Joint Meeting of the FDA Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee, for the discussion of the supplemental new drug application 21856 for Uloric, febuxostat, which provides for the results from a postmarketing safety trial required by the FDA to evaluate the cardiovascular safety of febuxostat.

My name is Nikolay Nikolov. I'm a
supervisory associate director for rheumatology in the Division of Pulmonary, Allergy, and Rheumatology Products at the FDA. I'm also an adult rheumatologist.

Before I begin, I would like to thank the members of the panel for taking the time off your busy schedules to come in and provide your expertise. We consider your expert scientific advice and recommendations very important to our regulatory decision-making process.

In the next few slides, I will provide an overview of the key issues for discussion, with emphasis on the results of the postmarketing safety study, the benefit-risk assessment considerations for febuxostat in light of this new information, and potential regulatory actions.

Febuxostat is a xanthine oxidase inhibitor approved for marketing in the United States in February 2009 for the chronic management of hyperuricemia in patients with gout. The application underwent three review cycles before approval, with the primary concerns related to
cardiovascular safety and death, which were also discussed at an advisory committee in November 2008. Further details on the pertinent regulatory history will be presented by Dr. Rosemarie Neuner as part of the FDA presentation.

Upon approval, a postmarketing safety trial was required to further characterize the cardiovascular safety of febuxostat. To address this requirement, the applicant conducted the clinical safety study, which is the subject of today's advisory committee discussion.

The trial titled Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidity, or CARES, as it will be also referred to during today's presentation, was a multicenter, randomized, double-blind, active-controlled, cardiovascular outcomes safety study conducted in the United States, Canada, and Mexico, in a population enriched for major cardiovascular risk factors.

Doses of both urate-lowering therapies were
uptitrated to a maximum dose of 80 milligrams of 
febuxostat daily and 600 milligrams of allopurinol 
daily. The primary endpoint was a composite of 
major adverse cardiovascular events, or MACE, which 
included cardiovascular death, non-fatal myocardial 
infarction, non-fatal stroke, and unstable angina 
with urgent coronary revascularization.

Numerous secondary endpoints included the 
individual components of the MACE composites as 
well as death from any cause. All suspected 
cardiovascular events were prospectively 
adjudicated by an independent cardiovascular 
endpoints committee blinded to treatment 
assignment.

The study was conducted as designed. A 
total of 6,190 patients were enrolled. 
Approximately half of the subjects discontinued 
study visits, however, subjects' disposition was 
comparable between treatment arms. The median 
on-study follow-up was 2.7 years and the median 
on-treatment follow-up time was 2 years.

The prespecified primary analysis, the
estimated hazard ratio of MACE associated with febuxostat relative to allopurinol, was 1.03, with a 95 percent confidence interval, excluding the prespecified risk margin of 1.3.

While the results of the MACE composite endpoint excluded the prespecified risk margin, there was an increased risk of cardiovascular death with a hazard ratio of 1.34 in a 95 percent confidence interval excluding 1. Detailed additional secondary sensitivity and exploratory analysis will be presented by the applicant and the FDA.

We ask the panel for your discussion of the results of CARES study. We also ask for you to discuss the benefits of febuxostat to help frame the benefit-risk considerations, recognizing that febuxostat is an effective urate-lowering therapy, it is one of a limited armamentarium of urate-lowering therapies, and the only alternative so far, xanthine oxidase inhibitor to allopurinol. In the original clinical development program, febuxostat reduced serum uric acid.
Efficacy results in the CARES study were largely consistent with the original clinical development program and also showed a similar benefit on clinical endpoints such as rates of gout flares requiring treatment between febuxostat and allopurinol-treated patients.

Additional considerations for the benefit-risk assessment may include the context of use and the available alternative therapies; also, to what extent the results from the CARES study, which was conducted in a population enriched for cardiovascular risk factors, are generalizable to the broader patient population with gout. This point will be discussed in the context of analysis of the Sentinel Distributed Database to be presented by Dr. Bradley from the FDA Office of Surveillance and Epidemiology.

When faced with new safety information, FDA has a number of regulatory options that we ask the panel to consider for their discussion, as there are multiple approaches the agency may undertake to mitigate risk.
Generally, the first consideration for risk mitigation is labeling. Labeling options include a boxed warning, contraindications, warnings and precautions, limitations of use, and medication guides; in other words, FDA-required patient labeling.

A risk evaluation and mitigation strategy, or REMS, is also a regulatory consideration if it can reasonably mitigate the risk and ensure the benefits of the drug outweigh its risks. In the agency's experience, REMS programs have limited impact on mitigating the risk of MACE or cardiovascular death, and in this case, such a REMS may not have an intended impact. Therefore, we ask the panel to consider the following other potential regulatory actions, and importantly, their clinical and patient care impact.

One option would be to include the results of CARES study in febuxostat label and update the existing warnings and precautions regarding cardiovascular events.

Another option might be to add a boxed
warning for cardiovascular death. A boxed warning

8 can be used to highlight an adverse reaction that

9 is so serious in proportion to the potential

10 benefit that the drug is essential that it be

11 considered in assessing the risk and benefits of

using the drug.

15 Another option may be to also modify the

16 labeling to limit the use of febuxostat to

17 second-line therapy. This could be accomplished by

18 a change in the indication statement and/or a

19 limitation of use.

23 The last potential regulatory action for

24 consideration is the withdrawal of febuxostat from

25 the market. This action was proposed by a

26 Citizen's petition submitted by Public Citizen in

27 June 2018, requesting the immediate removal of

28 febuxostat from the U.S. market, based on the

29 results from the CARES study.

30 Based on these considerations, there are

31 several points that we ask the committee to

32 consider today. The first discussion point refers

33 to the results from the CARES study and the
strength of the findings and the biological plausibility for the cardiovascular mortality, based on the totality of the evidence.

Next, we would like the committee to discuss the benefits of febuxostat to better frame the benefit-risk framework and to consider whether or how the benefit-risk has changed for this product.

The next discussion point follows the benefit-risk discussion and is focused on the potential regulatory actions for the committee's consideration. These include updating the existing warnings regarding cardiovascular events; adding a boxed warning on cardiovascular mortality in the product label; and further, if the committee considers that the benefit-risk has changed for the currently approved population, are there other labeling changes that could define a patient population with a more favorable benefit-risk of using febuxostat?

Lastly, we would like the committee to discuss the consideration of withdrawal of febuxostat from the market and the impact on
patient care and public health.

Following this discussion, the committee will be asked to vote on one question. Namely, is there a patient population in which the benefit-risk profile for febuxostat is favorable for the treatment of hyperuricemia in patients with gout? The answer to this question should be either yes, no, or abstain.

Then, based on your voting, if you voted yes, we ask for your individual discussion on the patient's population with a favorable benefit-risk profile and also to describe any other recommendations, for example, labeling changes you may have for use of febuxostat in that patient population.

If you voted no, we would like you to discuss your rationale, the impact of this recommendation, and any other recommendations you may have.

I would like to note that in light of the nature of this advisory committee and discussion topics, in addition to the standing Arthritis
Advisory Committee, the agency made every effort to invite a panel with diverse expertise relevant to the topic, which we believe will foster a very productive discussion today. Thank you for your attention, and I will turn the podium back to you, Dr. Suarez-Almazor.

DR. SUAREZ-ALMAZOR: Both the 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 applicant's non-employee presenters, to advise the committees of any financial relationships that they may have with the applicant, such as consulting fees, travel expenses, honoraria, and interest in a 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 presentations from Takeda Pharmaceuticals.

**Applicant Presentation - Beth-Anne Knapp**

MS. KNAPP: Good morning, members of the advisory committee, colleagues at the FDA, and members of the audience. My name is Beth-Anne Knapp, and I'm the head of regulatory affairs for the marketed products portfolio at Takeda. It is my pleasure to be here this morning to discuss a bit of the history for febuxostat and highlight the key topics we'll be focused on today.

We're here to examine the benefit-risk profile for febuxostat in light of the CARES data. It is the first cardiovascular outcomes trial in patients with gout who have a history of major cardiovascular disease.
Here is our agenda for our presentation.

Following my introduction, Dr. Michael Becker will describe the current treatment landscape.

Dr. William White will discuss the results of CARES. And then, Dr. Lhanoo Gunawardhana will review the efficacy of febuxostat, followed by Dr. John Affinito, who will review our benefit-risk assessment and communication plans. And lastly, Dr. Lawrence Edwards will provide his clinical perspective and explain why febuxostat is an important option for gout patients.

I would like to mention that Dr. Carroll and Dr. Whelton are with us today to answer any questions you may have.

Febuxostat was approved in February 2009 by the FDA for the chronic management of hyperuricemia in patients with gout. It can be used at a starting dose of 40 milligrams, and after 2 weeks titrated to 80 milligrams to further lower serum urate. It is now approved in 85 countries and has more than 15 million patient-years of exposure. In other countries, febuxostat also has other
indications and can be used at doses from 10 milligrams up to 120 milligrams.

As you will hear from Dr. Becker, urate-lowering therapy is central to the long-term management of gout. There are limited treatment options, and xanthine oxidase inhibitors are the consensus therapy of choice.

Febuxostat meets the American College of Rheumatology recommendation for maintaining serum urate in a sub-saturating range that's less than 6 milligrams per deciliters for most patients. This prevents or reverses gout symptoms and flows progression to disability and impaired quality of life.

Febuxostat reduces the body urate pool and dissolves urate crystals. Over time, this does decrease acute flares and reduced tophus size. Over the past 10 years, it has proven to be an important treatment option.

It's important to note that the majority of patients have some degree of renal impairment. One advantage for febuxostat is that no dose adjustment
is required in patients who have mild to moderate renal impairment, and for patients who have severe renal impairment, 40 milligrams can be used.

I'm going to take a few moments and review a bit of our development history. We've conducted a comprehensive program to support its approval. We first conducted a phase 2 dose-ranging study for which patients could then continue into FOCUS, a 5-year, open-label, extension study.

We then conducted two randomized phase 3 trials called APEX and FACT. These trials enrolled nearly 2,000 patients for which they could then continue into the open-label study, EXCEL. In APEX and FACT, febuxostat 80 and 120 milligram was effective in achieving and maintaining the target serum urate better than allopurinol 300 milligram and placebo. This was also seen in patients with serum urate greater than or equal to 10 milligrams per deciliter, as well as patients who had tophi. The long-term studies also showed a decrease in acute flares and reduction in tophus size. There was a numerical imbalance for CV events.
compared with allopurinol or placebo.

Thus, based on feedback from the FDA, we conducted a third phase 3 trial called CONFIRMS. This study of more than 2200 patients evaluated the safety and efficacy of febuxostat 40 and 80 milligrams compared with the commonly prescribed dose of allopurinol. CONFIRMS, however, did not show a higher rate of CV events with febuxostat compared with allopurinol.

When we pool the data from all three of these phase 3 studies, we do see a numerical imbalance in the number of CV events, which is driven by non-fatal MI and stroke.

While our NDA was under review, this imbalance led to an FDA advisory committee meeting in November 2008. The committee voted 12 to zero to recommend approval with one abstention. They agreed there was adequate efficacy, safety, and quality of febuxostat, however, they felt that the CV safety risk had not been fully elucidated. They recommended a post-approval study to further assess CV safety.
Febuxostat was then approved in February 2009, with a warnings and precautions for cardiovascular events. The label reflects the pooled analysis I showed just a few moments ago. The FDA also required us to conduct a postmarketing CVOT. This study is known as CARES.

CARES was conducted in more than 6,000 patients to fulfill this requirement. The study was designed to assess if febuxostat was noninferior to allopurinol for MACE; that is the composite of CV death, non-fatal MI, non-fatal stroke, and unstable angina with urgent coronary revascularization.

The patient population was enriched with gout patients who had major cardiovascular disease. We reviewed the protocol in depth and gained alignment with the FDA in 2010. Dr. White will discuss the CARES results in a few moments.

As you will hear today, the data from CARES demonstrated that febuxostat is noninferior to allopurinol regarding the primary endpoint of adjudicated MACE. We also observed comparable
rates of non-fatal CV events with febuxostat and allopurinol.

Paradoxical, however, to the primary endpoint result, febuxostat had a higher rate of CV death. To us, this finding was quite unexpected, given what we had learned in phase 3 and the past 10 years on the market. We carefully evaluated multiple potential risk factors, including patient populations and other possible reasons to try to understand this observation. We could not find an explanation within CARES.

We then, also, carefully relooked at our comprehensive development program, the nonclinical program, other clinical studies like the TQT study, observational and other published studies, as well as our postmarketing surveillance data. Here, too, we could not find an explanation or identify a biologically plausible cause.

Accounting for all the information we have, we have uncertainty around the strength of this finding. However, it is important that physicians are informed to consider the benefits and risks of
febuxostat, compared with other treatment options for their individual patient's care.

Takeda has and will continue to widely communicate the CARES data. We carefully considered a number of options, and at this point, based on what we know, we recommend the label should include the CARES data and the CV death observation in the warnings and precautions and other pertinent sections of the label. Following review with the FDA, we will also communicate these important updates in a Dear Healthcare Provider letter.

Considering the seriousness of the disease, the limited treatment options that physicians and patients have, and its established clinical use on the market for more than 10 years, febuxostat continues to have a favorable benefit-risk profile. It remains an important option for gout patients.

I thank you for your time, and I now invite Dr. Becker to the podium.

**Applicant Presentation - Michael Becker**

**DR. BECKER:** Thank you, Ms. Knapp.
Madam Chairperson, ladies and gentlemen, 
good morning. My name is Michael Becker, and I have worked in the fields of purine and uric acid metabolism and associated clinical disorders for five decades.

Today, I will speak to you about the disease burden and background of gout, as well as the current landscape of urate-lowering pharmacotherapy for gout and barriers to its successful application. I'm a paid consultant to Takeda, but I have no financial conflicts of interest to disclose.

Gout is a chronic arthritic disorder with an estimated prevalence in the U.S. of 9.2 million people or about 4 percent of the adult American population. Gout is thus the most common inflammatory arthritis, its prevalence exceeding by about four-fold that of rheumatoid arthritis. Gout incidence and prevalence have increased by 40 to 50 percent over the past three decades.

It's a very painful disorder that often progresses to disability and deformity and results
from inflammatory responses to monosodium urate crystals that form and deposit in connective tissues from urate-saturated extracellular fluids.

A risk for urate crystal formation and deposition is imparted by hyperuricemia defined as serum urate levels exceeding 6.8 milligrams per deciliter, the limited urate solubility. Although hyperuricemia is the major risk factor for gout, only 20 to 30 percent of hyperuricemic individuals ever develop clinical features of the disease, so that hyperuricemia is necessary but not sufficient for the expression of gout; that is in the absence of urate crystal deposition and an inflammatory response to the crystals, the symptoms and signs of gout do not occur.

The natural history of gout usually plays out over many years. The initial clinical manifestation is most commonly a flare of inflammatory arthritis developing over a few hours, involving a single lower-extremity joint and causing disability due to extreme pain, swelling, and loss of joint function.
Early flares usually remit in one or two weeks, but recurrences are the rule after completely asymptomatic intervals of varying length. In most gout patients, however, flares eventually reoccur with increasing frequency and severity and are more likely to affect multiple joints at the same time.

The diagnosis of gout can be definitively established during a flare by identifying urate crystals in synovial fluid aspirated from an affected joint as shown here by polarized light microscopy.

The increasing frequency of flares and their severity are often accompanied or followed by the development of tophi, which are enlarging collections of urate crystals in a chronic inflammatory background that can lead to bone and joint destruction and compromised health-related quality of life.

This slide shows tophaceous gout of the hands, with massive urate crystal burden on three-dimensional CT scan. The last panel shows
gouty bone and joint destruction on a plain radiograph.

Among the many risk factors for gout, some, such as male gender, older age, ethnicity, and genetics, are non-modifiable. Other risk factors are potentially modifiable, such as by management of the important chronic diseases shown here that are commonly associated in gout patients.

These comorbid disorders include hypertension, chronic kidney disease, obesity, insulin resistance, and cardiovascular disease. The disorders are not caused by urate crystal deposition and are, thus, not likely to be direct causes of clinical gout. Nevertheless, the comorbidities and their management often influence the course of gout management and its clinical outcomes.

Also of interest, in the context of this meeting, is the relationship between gout and cardiovascular mortality. In this large, observational cohort study of more than 50,000 male health professionals followed for 12 years, those
with gout had significantly increased risks of all-cause mortality, as well as all cardiovascular death and of fatal coronary heart disease compared with non-gouty study participants.

Management of gout involves both non-pharmacologic and pharmacologic interventions. Lifestyle adjustments and risk reduction measures may help diminish the risk of developing gout and occasionally flare recurrence in established gout, but their major benefit is likely in promoting general health. Thus, they're often continued as adjuncts but only rarely suffice as alternatives to urate-lowering pharmacotherapy in established gout.

An anti-inflammatory treatment is commonly used briefly and intensively in gout flare abatement or for longer periods in flare prophylaxis in the early months of urate-lowering pharmacotherapy. In these settings, anti-inflammatory agents are useful, but they do not affect serum urate levels or prevent gout progression and are only rarely candidates for sustained use. Finally, the majority of patients
ultimately fulfill criteria for initiation of urate-lowering pharmacotherapy.

Urate-lowering pharmacotherapy is a long-term approach to gout management. The goal of therapy is to establish and maintain sub-saturating serum urate levels, which will over time prevent and even reverse urate crystal deposition in gout symptoms, and thus slow or prevent progression to disability and impaired quality of life.

The fact that three mechanistically distinct urate-lowering strategies are disease modifying in gout patients strongly support urate-lowering therapy in gout.

 Accordingly, the American College of Rheumatology 2012 guidelines for the management of gout endorse xanthine oxidase inhibitors as first-line gout therapy. Xanthine oxidase inhibitors reduce uric acid production. This role is by far most often fulfilled with allopurinol or alternatively with febuxostat.

In the event of failure to reach goal urate level with titrated xanthine oxidase inhibited
therapy, second-line therapy is treatment with a uricosuric agent, either combined with a xanthine oxidase inhibitor or alternatively uricosuric monotherapy with probenecid. Uricosuric agents promote renal uric acid clearance. Biological uricolytic infusion therapy with pegloticase, which converts uric acid to a soluble end product, allantoin, is third-line therapy.

ACR guidelines recommend treatment to a serum urate target of less than 6 milligrams per deciliter in most gout patients and less than 5 milligrams per deciliter in patients with tophaceous gout or persistent symptoms.

Treatment should be initiated at the lowest approved dose of the respective agent with serum urate monitored stepwise uptitration to the minimal dose needed to achieve and maintain serum urate target, and where appropriate lower initial incremental doses in gout patients with impaired renal function.

Allopurinol and its major active metabolite, oxypurinol, are purine-based analogues that inhibit
xanthine oxidase but are non-selective in their action and affect a number of other steps in purine and pyrimidine metabolism. Allopurinol remains the mainstay of urate-lowering therapy, as it has been for decades, and is approved in the U.S. at doses of 100 to 500 milligrams per day.

Febuxostat is not a purine analogue. It selectively inhibits xanthine oxidase activity, reducing serum urate and urinary uric acid. Febuxostat is approved at doses of 40 to 80 milligrams per day. Renal excretion of febuxostat is less than 10 percent of the administered dose in the range approved for clinical use in gout.

No dose reduction of febuxostat is needed in mild or moderate renal impairment, and the 40-milligram dose is approved for patients with severe renal impairment.

The clinical benefits of febuxostat have recently been demonstrated in the two-year, randomized, controlled trial in which patients with early gout received either daily febuxostat therapy
titrated to serum urate less than 6 or placebo.

The proportion of febuxostat-treated patients who suffered flare recurrence during the trial period was significantly reduced overall, an effect that was demonstrable in all time intervals beyond 6 months. This finding supports earlier studies reporting nearly complete gout flare suppression among patients maintaining serum urate levels less than 6 milligrams per deciliter, with up to 5 years of urate-lowering therapy.

Several studies have also demonstrated an effect of lowering serum urate on rates of tophus size reduction. In one such study, serial measurement of target urate tophus size were recorded as a function of serum urate levels achieved in patients treated with either allopurinol or the uricosuric agent benzbromarone, or both agents in combination.

As highlighted by the red line marking the serum urate of 6 milligrams per deciliter, considerably more rapid tophus size reduction occurred when greater reduction in serum urate was
achieved. Minimal tophus size reduction occurred as average serum urate levels approached 6 milligrams per deciliter.

Despite the availability of three classes of agents, the ranks of approved urate-lowering therapies are thin and each has clinical limitations. With regard to the two xanthine oxidase inhibitors, only about half of patients achieve target serum urate goals at doses commonly prescribed in clinical practice. That is allopurinol 300 milligrams per day or less or febuxostat 40 milligrams per day.

We've seen in recent years, clinical trials that have shown a high proportion of gout patients, including many with renal impairment, can be safely and successfully treated to target with proper titration of allopurinol, and we should continue to promote this initiative. But we also know that after 50 years of use, optimal dose titration of allopurinol is not frequently accomplished in the practice setting. Optimal utilization of allopurinol is also limited by renal impairment,
intolerance, or drug-drug interaction, and
febuxostat is associated with potential
cardiovascular risk.

The second and third-line therapies are
rarely used, as second-line probenecid requires
multiple daily dosing and usually several titration
steps. It has many drug-drug interactions and
limited urate-lowering efficacy in patients with
moderate or more severe renal impairment.

As third-line therapy, pegloticase is
reserved for patients with clinically-advanced gout
and failure or intolerance to alternative treatment
agents.

There are several other barriers to optimal
management of gout that lead to poor adherence with
urate-lowering pharmacotherapy. First, when we
reduce uric acid levels, flare occurrences are
common, particularly in the early weeks and months
of treatment. Also, there's a lag period, often of
a year or more, before clinical evidence of
urate-lowering therapy benefit is established in
the form of flare reduction or tophus regression,
in part because of the paradoxical early flares and very slow tophus regression.

In addition, dose titration and monitoring strategies with allopurinol are often challenging. And finally, we often see suboptimal rates of urate-lowering therapy initiation or adherence to the necessary long-term course of urate-lowering treatment.

In summary, successfully applied and monitored urate-lowering pharmacotherapy can relieve or reverse clinical symptoms and progression of gout in most patients. At present, however, treatment options are limited to accomplish the same, and renal impairment continues to influence our therapeutic actions.

Xanthine oxidase inhibitors remain the mainstay of urate-lowering treatment, and allopurinol is the most commonly prescribed agent. But many gout patients do not receive allopurinol at all or at doses adequate to achieve and sustain successful urate-lowering.

So febuxostat plays an important role. In a
decade of clinical use, febuxostat has proved to be an effective option for urate-lowering therapy, particularly in patients with renal impairment, or when there is an inadequate response or intolerance to other agents, or in cases where drug-drug interaction precludes the use of other agents, and in patients with severe gout, especially those with tophi or with serum urate levels exceeding 10 milligrams per deciliter who receive inadequate treatment with allopurinol dosing.

Thank you, and I would now like to invite Dr. William White to discuss the results of the CARES study.

Applicant Presentation - William White

DR. WHITE: Thank you very much, Dr. Becker.

Good morning to the committee and to the FDA. I'm Dr. William White. I'm a professor of medicine in the cardiology center at the University of Connecticut School of Medicine in Farmington. I've had a longstanding interest in the cardiovascular safety of non-cardiac drugs, including in arthritides.
In fact, I also chaired the Cardiovascular Adjudication Committee for the CONFIRMS study, which I'll present to you in a moment, as well as the CARES trial, and served as a principal author on the paper in the New England Journal of Medicine last year. I've been serving as a consultant to Takeda for a long time and have received personal fees, but I have no financial interest in the outcome of today's meeting.

The agenda of my talk today will include a brief discussion of the phase 3 cardiovascular safety data, a detailed review of CARES, including its design and objectives, the primary and secondary results, and some of the analyses that we've done to explore this cardiovascular mortality outcome, which was not expected.

I'd also like to review some observational data from a Medicare study that was done and published in October of 2018 in Circulation as of interest; the postmarketing surveillance data of the last decade since the drug has been registered in over 80 countries in the world; and a review of
the design of FAST, which is an ongoing study in Europe scheduled to be completed next year at some time.

So now I'd like to first review these phase 3 pivotal studies that led to the development and approval of the drug in 2008. There were three such studies as you heard from the first speaker, Beth-Anne Knapp, FACT, APEX, and CONFIRMS, totaling over 4,000 patients. These were typical or classic efficacy and safety studies for approval of the treatment of the drug for hyperuricemia in patients with gout, typically requiring patients who had a urate level of greater than 8, with the goal of the study to reduce the level less than 6 and to assess the proportion of patients with whom that happened. These were all randomized, double-blind, and controlled by allopurinol or placebo.

I should like to note that the CONFIRMS trial, which was over 2200 patients, was the subject of the 2008 advisory committee meeting for this drug and which I presented, so let me just show you that real quickly.
This study had 3 arms, febuxostat 40 milligrams, 80 milligrams, and allopurinol at doses of 200 to 300 milligrams, depending on kidney function and entry into the study. After 6 months of double-blind therapy with this sample, there were actually quite a few numbers of major cardiovascular events; none on the febuxostat 40-milligram arm and 3 on the 80-milligram arm, and 3 on allopurinol. You'll note there were no cardiovascular deaths in this study on febuxostat; there were two on allopurinol.

When pooling the other two studies in with the results of the CONFIRMS trial, there was a total of 10 events, that is 0.74 events per 100 person-years on febuxostat and 4 events or 0.6 events per 10 patient-years on allopurinol.

Notably, there were no imbalances in CV death. There was numerically more non-fatal MIs and strokes in this pooled analysis. However, this entire analysis was only based on 14 major cardiovascular events of CV death, MI, and stroke.

The prospectively adjudicated cardiovascular
prevention, the larger pivotal trial, that is CONFIRMS, showed no imbalances, but these results, of course, could not be considered conclusive in 2008 when they were completed and presented to the advisory committee. So the CARES cardiovascular outcome trial was conducted, based on recommendations from the FDA, as a postmarketing study.

CARES stands for the Cardiovascular Safety of Febuxostat and Allopurinol in Subjects with Gout and Cardiovascular Morbidities. This was a multicenter, double-blind, randomized study of febuxostat versus allopurinol given once daily in patients with gout and cardiovascular disease in North American countries. The doses of febuxostat was 40 and 80 milligrams. The doses of allopurinol were 200 up to 600 milligrams in a one-to-one randomized design.

Patients were seen frequently during the first 3 months of the trial for double-blind dose titration, which I'll discuss in just a moment, and then there was frequent clinical tests for the
first year of the study. Thereafter, patients were seen every 6 months for endpoints and other clinical tests.

The drug titration design here was to achieve a serum urate level less than 6 milligrams per deciliter, since that's the known value that typically avoids gout flares in the future. Febuxostat patients were started at 40 milligrams a day, and after 2 weeks if they had not achieved the urate level of less than 6, they were escalated to 80 milligrams regardless of renal function. In either case, this was their permanent dose for the remainder of the study.

For those patients who were randomized to allopurinol, if the patients had normal or mildly impaired kidney function -- that is creatinine clearances of 60 or better -- the initial dose was 300 milligrams, and that was titrated up to a maximum of 600 milligrams in 2-week time periods.

In contrast, if patients had moderately impaired kidney function -- that is with GFRs or creatinine clearances of 30 to 59 mLs per minute,
the initial dose was 200 milligrams and titrated up to a maximum of 400 milligrams.

To be included in CARES, one had to be a man over 50 years old or a woman over 55, with at least 2 years in the menopause; a history or presence of well-defined gout, according to ARA or American Rheumatism Association criteria; and a history of one of the major cardiovascular or cerebral vascular diseases shown in this chart.

You could have more than one of these to get into the study, but you had to have at least one of these diseases, and these are not risk factors; these are diseases.

Exclusionary criteria included a history of an MI or stroke within 60 days prior to the screening visit because we didn't want to put in patients who were too unstable from a cardiovascular perspective; those individuals with secondary hyperuricemia or those who received exclusionary medications within 7 days of the randomization visit, including urate-lowering therapy. And finally, individuals with severe
kidney disease, estimated creatinine clearances of less than 30 mLs per minute, were also excluded from participation in CARES.

The primary endpoint of this study was the time from randomization to first occurrence of MACE, major adverse cardiovascular events. This included a 4-component composite of CV death, non-fatal myocardial infarction and non-fatal stroke, and unstable angina that required urgent coronary revascularization within 24 hours of hospital admission.

The secondary endpoints were the components of this composite and the time from randomization to the first occurrence of what some people call core MACE, which is the older terminology for antiplatelet trialists collaborative composite of CV death, non-fatal MI, and non-fatal stroke.

There were two committees that helped with the infrastructure and oversight of CARES during its conduct over several years. One was the CARES Cardiovascular Endpoints Committee, which reviewed all suspected serious cardiovascular events and all
deaths by a group of expert clinicians blinded to
treatment assignment. I'd like to mention that the
personnel on this committee did not change in the
entire seven years of the trial.

Then there was an independent data safety
monitoring committee, which we call the DMC, which
was an independent group of experts unblinded to
treatment assignment, who reviewed study results at
6-month intervals, and who also performed three
planned interim analyses when there was the accrual
of approximately 25, 50, and 75 percent of the
primary endpoints. Data tables were presented to
this committee by an independent statistician, so
not a member of the DMC, and not an employee of the
sponsor.

The primary endpoint of CARES was analyzed
using a Cox proportional hazard model of time to
the primary endpoint stratified by baseline renal
function. A one-sided, adjusted 97.5 percent
confidence interval was calculated for the hazard
ratio.

The interim analyses at the 25, 50, and
75 percent of events utilized the Lan-DeMets-O'Brien-Fleming alpha spending function to control for overall one-sided significance of 0.025. Non-inferiority would be concluded if the upper boundary of the repeated confidence interval for hazard ratio, that is febuxostat relative to allopurinol, was less 1.30.

Secondary and major exploratory endpoints were also evaluated by a Cox proportional hazard model of time to the endpoint, stratified by baseline renal function with two-sided 95 percent confidence intervals for the hazard ratio.

Now I'd like to show you the primary results of CARES. Starting with the demographic characteristics, the treatment groups, as might be expected, were well balanced for age, gender, race, BMI, and kidney function. In fact, the population averaged 65 years of age, 84 percent men, 70 percent white, with an obese BMI of about 33 to 34 kilos per meter squared. And you'll note that 53 percent of the patients in the trial actually had moderately impaired kidney function. Use of
low-dose aspirin at the screening visit, at randomization, was about 48 percent of the patients.

These patients had high urate levels coming into the study of about 8.7 milligrams per deciliter, and 20 percent of them had a value of over 10. These patients had gout for a long time, averaging 12 years and balanced between treatment groups, and 21 percent of the patients had a baseline tophus.

Cardiovascular disease at baseline were prevalent. The most common, of which that got them in the study, was a history of an MI, history of unstable angina, cardiac revascularization, or diabetes with well-defined, small-vessel disease.

At baseline, about one-third of the patients coming into the trial were not taking any urate-lowering therapies. In fact, the majority had been taking allopurinol, 56 percent in each treatment group, so of course, that may have predisposed the patients coming into the study as tolerating allopurinol a bit better than they would
have otherwise. Note that only 4 percent of
patients coming into the study had been treated
previously with febuxostat.

The cardiovascular therapies of the patients
coming into the study at baseline were the common
ones that you would expect to see in this
population. Somewhere around 80 percent were
taking an anti-platelet drug, 58 percent taking a
beta-blocker, about 74 percent a lipid-lowering
therapy, 70 percent taking a renin angiotensin
blocking drug such as an ACE inhibitor or
angiotensin receptor blocker, and about 40 or
42 percent of patients were taking a diuretic.

The final dose used in the trial for the
febuxostat arm, 61 percent were taking
40 milligrams throughout the study’ 39 percent were
taking 80 milligrams. For allopurinol where the
dose was adjusted based on kidney function, most
patients received either 200, 300, or
400 milligrams, as you see, and very few patients
were actually titrated up to 500 or 600 milligrams
once a day.
Approximately 3100 patients were randomized to each treatment arm in CARES. Eight patients did not take a single dose of study drug, so we excluded these patients from the modified intention-to-treat analysis.

You'll note 43 to 44 percent of patients in the trial were still taking study drug at the end of the trial, so 56 to 57 percent actually at some point in time discontinued study drug, and of those 55 percent in each arm that completed all study visits, most others partially completed study visits.

For those patients who discontinued the study early, about 45 percent of this population, most of them were due to what was called voluntary withdrawal, which could have been lack of efficacy, moving away from the study site, and possibly even adverse events that were not properly reported. Other events, such as adverse events, closure of the site, distaste with being in the study and wanting to go on conventional medication occurred in about 11 percent of patients, and in each
treatment arm, about 7 percent of the patients were lost to follow-up.

Because of this large group of patients who failed to complete study visits, we performed a detailed analysis of those who completed the trial and those who failed to complete the study over the years of CARES. There were 1950 patients in the febuxostat group who completed all study visits versus 1151 who failed to complete study visits, and a similar proportion were seen for allopurinol.

You'll note that the demographic findings, the gout findings, BMI and body weight were actually quite balanced for those patients who completed the study versus those who did not, whether they were randomized to febuxostat or treated with allopurinol during the CARES trial. And in fact, the proportions were also similar between the two treatment groups.

Importantly, for those cardiovascular risk factors and history of diseases that got them into the study, there was also no differences between those who did not complete study visits versus
those who completed study visits, whether it was in the febuxostat arm or in the allopurinol arm.

The study concluded that noninferiority for the primary endpoint had occurred at the 75 percent interim analysis in which there were 488 events exactly the same in each treatment group, with a hazard ratio of 0.99 and an upper boundary of 1.23. However, at that time, the Data Monitoring Committee recommended to the sponsor that the study continue as planned.

We did that, and there was a total of 656 primary endpoints, 10.8 percent on febuxostat and 10.4 percent on allopurinol, with a hazard ratio of 1.03 and an upper boundary of 1.23, so exactly what was seen about 16 months earlier at the 75 percent interim analysis.

Everything I'll be showing you from now on is going to include that final analysis with all events, not the interim analysis.

This is the time to the event for the primary endpoint; febuxostat in red and allopurinol in blue, with 95 percent confidence intervals.
shaded around the time-to-event lines. You'll note the hazard ratio of 1.03, the slope being fairly steady throughout the many years of the study. I'd also like to point out that after 4 years, there was a large drop out in the numbers at risk for the trial.

As mentioned earlier, the composite or primary endpoint showed a 0.4 percent absolute risk difference between the two treatment groups, which was not significant, and it was significant for noninferiority. Also, it was noted that there were 134 deaths in the febuxostat arm versus 100 in the allopurinol arm, adjudicated as cardiovascular in nature, for an absolute risk difference of 1.1 percent, a hazard ratio of 1.34, and a lower boundary of 1.03, which yielded a p-value of 0.03.

The non-fatal events of MI, stroke, unstable angina with urgent revascularization were comparable between the treatment groups with an absolute risk difference of about zero and hazard ratios that were 1 or lower.

The time to cardiovascular death is shown in
this Kaplan-Meier curve, again, febuxostat in red and allopurinol in blue, with the confidence intervals. This did demonstrate comparable rates of accrual of death until about 30 months, then the curve separated in favor of allopurinol and stayed fairly steady until about 48 months.

There appears to be somewhat of a widening later on in the trial, but I caution the way this looks, because of the big drop-off in the denominator, as you'll see in the numbers below the X-axis.

Because of this large number of patients who discontinued study drug early, we actually had built into the protocol a prespecified sensitivity analysis that evaluated cardiovascular events on drug or within 30 days of drug discontinuation for two reasons.

One is the potential of a legacy effect of a drug, and the second is the fact that when people come into the hospital in a clinical trial and they're on a study drug, it's the first thing that gets stopped. Therefore, it could have been
stopped and 2 days later somebody could have died, and it would have been called off-study drug.

The composite primary endpoint occurred in 7.8 and 7.7 percent of patients on the febuxostat and allopurinol treatment groups, respectively, for an absolute risk difference of 0.1 percent, a hazard ratio of 1.0, and an upper boundary of 1.22. The sensitivity analysis showed that the primary endpoint was maintained as it was for the mITT.

Cardiovascular death occurred in 2 percent of patients in this analysis versus 1.3 on allopurinol, for an absolute risk difference of 0.7 percent and a lower boundary of the hazard ratio of 1.01, for a p-value of 0.047. And again, the non-fatal events, MI, stroke, and unstable angina with revascularization, were not significantly different on febuxostat and allopurinol.

All-cause mortality occurred in 7.8 percent of patients randomized to febuxostat versus 6.4 percent on allopurinol. This was largely driven by the cardiovascular death finding with a
hazard ratio of 1.22 and a lower boundary of 1.01.

Substantial attempts were made to gather vital status on all patients enrolled in CARES. A company called OmniTrace was employed to collect data on any deaths that occurred, based on obituaries and other publicly available information.

I would like to point out that this company and their employees and all the sites remained blinded to treatment assignment at all times that the vital stats was being collected and until database lock. They gathered data on an additional 2300 patients and attempted to find mortality. In fact, they found an additional 199 people who had died. Of course, these patients could not be adjudicated due to the lack of clinical information.

When adding these additional deaths to the overall findings of all-cause mortality in the trial, the results were 10.7 percent on febuxostat and 10 percent on allopurinol, for a hazard ratio of 1.09 and a lower boundary of 0.94.
Extensive efforts were then made to investigate whether there was any potential mechanism for cardiovascular toxicity that might be associated with febuxostat that would explain this unexpected finding on imbalances in the numbers of deaths contributed to cardiovascular causes.

Prospectively, we had adjudicated the causes of death, and I'll show you that in a moment. We looked at subgroup analyses for patient populations and the hazard ratios according to them.

We evaluated the vital signs such as blood pressure and heart rate during the study, important electrolytes that may be proarrhythmic if made abnormal, a variety of mechanistic studies, and then also the association of events with serum urate and gout flares because there's some concern that urate is a prooxidant substance, and gout flares create a proinflammatory state that might lend itself towards endothelial dysfunction and cause coronary events to occur.

First, the prospectively adjudicated causes of death, again, 4.3 versus 3.2 percent. The
largest component was sudden cardiac death in
2.7 percent of patients randomized to febuxostat
versus 1.8 percent to allopurinol. The other
categories were much lower in number, some favoring
allopurinol and some favoring febuxostat.

As you know, sudden cardiovascular death is
probably the least precise cardiovascular endpoint
in this kind of process. It is actually typically
an unwitnessed, out-of-hospital event, and it can
be occurring to a variety of causes. The
committee, and most committees that do this these
days, actually take a conservative approach and
attribute unwitnessed and unexpected or unexplained
deaths to a cardiovascular cause.
Non-cardiovascular deaths occurred in 3.5 percent
of febuxostat patients versus 3.2 percent of
allopurinol patients.

As far as the cardiovascular deaths by
subgroups, demographic factors and most clinical
factors showed no differences or no heterogeneity
for the hazard ratio of febuxostat versus
allopurinol, although there were two groups of
people taking medications that were different. One was those patients who came into the trial taking an NSAID. They had a higher risk ratio than those not taking an NSAID, and those who were not taking low-dose aspirin versus those who were.

A couple of caveats about these two subgroups. One is that if people continue to take NSAIDs during the trial versus not, this heterogeneity went away, so it was only seen with the baseline group.

The issue with aspirin was maintained for those people who were taking versus not taking aspirin, but I'd like to point out that the primary endpoint, the primary MACE endpoint, actually showed no heterogeneity for those not taking aspirin versus those taking aspirin during the study. So I think that this finding is probably not very robust because why would somebody have a benefit for CV death but not for an acute coronary syndrome?

The other thing I will tell you is that we evaluated the patients who were not taking low-dose
aspirin and who were at baseline, and their clinical characteristics were virtually identical.

For cardiovascular diseases, history of MI, stroke, revascularization, heart failure, and other risk factors, there was no heterogeneity observed for febuxostat relative to allopurinol.

Blood pressure, whether it was systolic or diastolic, changed very little during the course of the study in either treatment group and were not significantly different between the two treatment groups, and the same is true of heart rate.

Cation, such as calcium and potassium, changed minimally at many checks during the trial, between zero and 72 months. They're almost superimposable for both treatment groups.

Mechanistic studies were done to evaluate the imbalance of sudden death such as cardiac Purkinjие fibers, which is a method of assessing action potential and cardiac function; hERG assay, which is a genomic study to evaluate the movement of potassium across channels and is very important in evaluating the possibility of ventricular
tachycardia and torsade de pointes. Sodium and calcium channels were evaluated; platelet function, INR, prothrombin, and partial thromboplastin, and all of them showed no effects with febuxostat versus a compared or vehicle in these studies.

Then there was thorough QT Study done in human volunteers. This study was done in a fairly fastidious method using both a therapeutic and supratherapeutic dose of 80 and 300 milligrams of febuxostat, contrasting it to placebo, and the quinolone antibiotic, moxifloxacin, which is typically used in these studies as an active control, virtually always increases the QTc by about 10 to 15 milliseconds. So if that doesn't happen, you'd worry about the integrity of the study.

The differences from placebo for febuxostat at both the maximum therapeutic dose and the supra-therapeutic dose were the same as placebo. Moxifloxacin did raise the QTc, as expected, suggesting that there was no effect of the drug and that the study had integrity.
Let me explain also what we do with the urate levels and gout flares. We first looked at two groups, those who did not die during the study -- that's the bold lines in red and blue for febuxostat and allopurinol, respectively -- and then we looked at those patients who died, the 234 patients who died on febuxostat versus allopurinol using interrupted lines.

So first, just focusing on the patients at large who did not die, you note that the urate levels fall in the first month or two of the study, then it became quite stable with febuxostat lowering urate levels a bit more than allopurinol for the remainder of the trial, but very stable levels.

For those patients who had a mortal event, the trends were virtually the same as for the population who didn't have a mortal event, a drop in the first month or two, and stability of urate levels throughout the trial. When we superimpose these two groups, we see really no differences between those patients who did versus did not have...
a CV death. The reason that the patients who died is truncated at 48 months is there were so few urate levels obtained that we couldn't really come up with average values precisely.

Now for gout flares, which were thought to be a potential proinflammatory phenomena that could induce cytokines to cause endothelial dysfunction and other bad things to the vasculature, we found that the gout flare rates went up after the xanthine oxidase inhibitors were instituted, which is exactly what one would expect, a little bit more in the febuxostat group compared to the allopurinol group, red and blue. But they then fell by a year, and then the gout flare rates were low and stayed low for the remainder of the three years of the trial.

For those patients who died, the results were quite comparable, compared to the patients who did not die. And again, by the time that the death rates were starting to go up, at about 30 months, these rates had been stable for some time. So we did not conclude that either urate levels or gout
flares had anything to do with this imbalance in cardiovascular deaths seen on febuxostat relative to allopurinol.

From the standpoint of the CARES trial, it has the strength of being a large, randomized, double-blind, controlled study. In fact, it's the largest study ever done in gout, and it's the only cardiovascular outcome trial in patients with gout.

Febuxostat met its primary endpoint for noninferiority, the primary composite MACE. There were similar rates of non-fatal MI, non-fatal stroke, and unstable angina with urgent revascularization. The rate of all-cause mortality was higher on febuxostat and driven by increases in cardiovascular death, particularly sudden cardiac death.

The limitation of this study is that there was a large dropout in both treatment groups. However, sensitivity analyses looking at patients on drug and up to 30 days discontinuing drug and others, were consistent with the modified intention-to-treat analysis. Baseline
characteristics of those who dropped out of the study early were really quite similar to those who completed the trial, suggesting a lack of differential bias in those patients who dropped out versus those who stayed to the end.

Subgroup analyses showed no real relevant heterogeneity for the treatment effect. Febuxostat and allopurinol exhibited similar effects on clinical laboratory test results, vital signs, and gout flare rates. And finally, an extensive assessment for potential mechanisms for being proarrhythmic for increasing death, particularly sudden death, was not identified in the laboratory or in the thorough QT Study.

Because of this finding, which is perplexing, we have evaluated some additional evidence that has been published or evaluated since the CARES trial was completed in late 2017. This includes a Medicare observational study, some postmarketing data from pharmacovigilance that's been going on for about a decade, and I'd like to review briefly the design of febuxostat versus
allopurinol streamlined trial now ongoing in Europe.

In October of 2018, there was an observational study published by two groups from Boston University and the Brigham, looking at Medicare claims data in almost 100,000 initiators of either febuxostat or allopurinol in people who were over the age of 65 with gout.

They used propensity score matching -- they're real pros at this -- looking at validated claims-based algorithms that have proven in the past to have a positive predicative score of greater than 80 percent. They chose a primary outcome of hospitalization for MI or stroke but were also able to capture all-cause mortality, but not causes of death.

These patients were treated for up to 4 years with a median duration of treatment for about 1.2 years. This first table shows the propensity scored matching analysis of about 25 initiators of febuxostat versus 75,000 of allopurinol. The primary outcome occurred in about
3.4 percent of each of the two drugs for a hazard ratio of 1.01. Of note, all-cause mortality occurred in 4.1 percent of patients treated with febuxostat versus 4.3 percent of patients treated with allopurinol, which was not statistically different.

Of note, they also had prespecified they would look at patients with cardiovascular disease when they initiated the drug, and these were defined as people who had known cardiovascular disease, not just risk factors.

Within their cohort, a little over 12,000 patients, the lower part of this figure, had a history of cardiovascular disease. You'll note that the event rates, not surprisingly, are much higher in this subgroup compared to those without baseline cardiovascular disease, more than double in all the categories.

The primary outcome occurred in 7.8 percent versus 7.9 percent of patients initiated on febuxostat relative to allopurinol with a hazard ratio of 0.97. And of interest, the mortality
rates, all-cause mortality, were 7.1 percent on
patients on febuxostat versus 8.2 percent of
patients on allopurinol for a hazard ratio of 0.85,
which was actually statistically lower.

This Medicare observational study has the
strength of being a large data set that's
well characterized, almost 100,000 people, followed
for up to 4 years. It does represent an older
population than CARES. They were about 76 years
old and CARES is about 65 years old, but this is
more consistent with real-world practice in the
United States. The propensity score matching was
performed by an experienced analytical team.

It's limited by the fact that it's not a
randomized, controlled trial. It's an
observational study, so there can be some imbalance
in exposure. And while the patients were older
than the CARES population, they did have a fairly
high-risk burden, with 12,000 of them being high
risk and a number of others having medium risk,
which I did not show you.

There's no data, however, on cardiovascular
death, but one could conclude from this observational study that there's no evidence of increased CV risk for febuxostat compared to allopurinol in patients with or without underlying cardiovascular disease in clinical practice.

As far as pharmacovigilance data, Takeda and its partners around the world have been evaluating the safety of febuxostat for about 15 million patient-years of exposure; 1.4 million patient-years that are in the United States. This includes ongoing monitoring of case safety reports, literature reviews, and aggregating the safety reports in this global safety base.

They use a disproportional model of indexing to determine whether or not something's different about febuxostat compared to other drugs that are out there on the market, and they review this quarterly. To this point in time, there's been no signal from this pharmacovigilance activity.

Now, I'd briefly like to describe this trial known as FAST, which is being conducted in Europe, with the principal investigator in Scotland, Tom
MacDonald, and this is being sponsored by another company called Menarini, not Takeda.

This study has been ongoing for a few years. It's actually a prospective, randomized, but open-label, blinded endpoint study or PROBE. It's got a somewhat unusual design in the sense that what is being done is that patients are first being treated with allopurinol and titrated to whatever optimal dose they can be achieved on to get a urate level less than 357 micromoles per liter, which is the same as 6 milligrams per deciliter.

Once that happens, the patients are then randomized. Those who had a good response to allopurinol randomized to either that dose of allopurinol or to febuxostat at 80 or 120 milligrams a day. They have over 6,000 patients who've already been enrolled and recruited and randomized into this trial with gout and one or more major cardiovascular risk factors.

Their goal is to have at least 456 MI, strokes, or cardiovascular deaths as the APTC composite endpoint with the expectation that the
average follow-up in the trial will be about 3 years and that the study should be completed next year at some time.

One has to step back now, as I have for the last year-and-a-half or so, and look at the totality of evidence about this somewhat surprising finding in the CARES trial, the imbalance in cardiovascular death.

I would like to mention, having been involved in a number of non-cardiac drug safety studies that, to my knowledge, since about a decade ago when diabetes studies started and arthritis studies, and depression, and obesity, we haven't really seen a study in which mortality goes up, and none of the non-fatal events go up. They're all neutral or lower, so this is somewhat of an outlier finding in this trial, and it's also one of the components of the primary endpoint, which was noninferior.

The mean between group difference we found is in sudden cardiac death, and the proportion of people who had sudden cardiac death as the
The adjudicated cause of death doesn't surprise me at all; that's usually what's seen in all of these studies. But because of the sudden cardiac death, we look for everything. Was there a difference in ventricular arrhythmias or atrial arrhythmias, et cetera? Whether fatal or non-fatal, that was not observed.

No clinical or biochemical variable explained this difference in cardiovascular death; cardiac channelopathies, prothrombotic mechanisms were not observed at all.

I'd like to mention that, in context, CARES cannot define an increased risk of a xanthine oxidase inhibitor per se. There's no placebo group. What we can say is that we don't know of the impact of xanthine oxidase inhibitors on the risk of CV mortality. We just know that there's numerically more CV deaths on febuxostat relative to allopurinol at the doses used in the trial and in the patient population studied.

In contrast, and it's not a randomized trial, but a very well done observational study, it
found no differences in morbidity or mortality between febuxostat and allopurinol, including in patients with cardiovascular disease.

There's been no signal for cardiovascular events or CV death from postmarketing surveillance studies over the last decade in 15 million person-years of use. And finally, we do expect to find some important information from FAST next year in a population of patients with gout who have also had increased cardiovascular risk.

I'd like to thank you for your attention to my long talk, and now I invite Dr. Gunawardhana to the podium to talk about the efficacy findings of febuxostat. Thank you.

**Applicant Presentation - Lhanoo Gunawardhana**

DR. GUNAWARDHANA: Thank you, Dr. White. My name is Lhanoo Gunawardhana. I'm senior medical director at Takeda. Now that you have seen the cardiovascular safety data, I will present the key efficacy data from the development program in CARES to highlight the benefits of febuxostat.

The efficacy data I will present today comes
from 5 of the 6 trials in our development program, as well as the CARES study. I will be presenting data from the three phase 3 trials, APEX, FACT, and CONFIRMS, the two long-term extension studies FOCUS and EXCEL, and finally from CARES.

Before I present the efficacy results, I would like to point out a few key differences between the design of the phase 3 development studies and the CARES study.

First and foremost, the development studies were optimized to assist efficacy. As Dr. Becker explained, treating to serum uric acid target is the best approach for treating gout. Therefore, the serum uric acid reduction is the gold standard endpoint for efficacy studies.

The primary endpoint in these studies was the proportion of patients achieving the uric acid less than 6 milligrams per deciliter, and the entry criteria required that patients have a baseline serum uric acid greater than or equal to 8 milligrams per deciliter. Febuxostat 40 and 80 milligrams were compared with the most commonly
used doses of allopurinol in clinical practice, ranging from 100 to 300 milligram depending on renal function.

In contrast, the CARES study was designed to assess cardiovascular safety. Efficacy was an exploratory endpoint, and the study required a lower serum uric acid entry criteria of greater than or equal to 7 milligrams per deciliter or greater than or equal to 6 milligrams per deciliter in patients with frequent flares or tophi.

Most importantly, as Dr. White explained, doses of febuxostat and allopurinol were uptitrated in both arms to a target serum uric acid of less than 6 milligrams per deciliter.

The demographics of the patient population enrolled in each of the 3 pivotal trials is shown here. These are typical gout patients. As expected for a gout study, the majority were male and many were overweight. The serum urate levels at baseline were high compared to CARES. About a quarter of the patients had tophi, and the mean duration of gout was 11 to 12 years.
The medical history of the enrolled population in each trial is also very important and reflect the comorbid conditions that are typically associated with gout. For example, CONFIRMS is most representative of the general gout population, with 65 percent of patients having mild or moderate renal impairment at baseline. In addition, about half of the patients had hypertension, about one-third had hyperlipidemia, and 10 to 15 percent had diabetes or cardiovascular disease.

It is important to note that in these phase 3 studies, representing the general gout population, the proportion of patients with comorbid conditions was lower than in the CARES study.

This slide shows the proportion of patients in each treatment group who achieved a target serum uric acid less than 6 milligrams per deciliter in the overall population enrolled in each phase 3 trial. Febuxostat 80 milligrams consistently demonstrated superior urate-lowering efficacy over commonly used doses of allopurinol, with 67 to
74 percent of patients achieving a target serum acid less than 6 at the final visit, and in CONFIRMS, 40 milligrams febuxostat demonstrated a similar response compared with allopurinol.

Over the next several slides, I will show you data on some of the subgroups that correspond to the most difficult to treat gout patients who benefit from treatment with febuxostat.

In gout, renal impairment is important and a significant problem. Therefore, we looked at the proportion of patients achieving serum urate less than 6 milligrams per deciliter in the population with mild to moderate renal impairment.

Febuxostat 80 milligrams demonstrated superior urate-lowering efficacy compared to commonly used doses of allopurinol in all 3 studies. We also observed that 40 milligrams of febuxostat was significantly better than commonly used doses of allopurinol in the CONFIRMS study, among those patients with renal impairment.

Another important subgroup are those patients with a baseline uric acid greater than or
equal to 10 milligrams per deciliter. In this subgroup we also saw a consistent benefit of febuxostat 80 milligrams across all 3 studies.

Similar results were also observed in patients with tophi at baseline. As you can see from the data presented here, febuxostat can benefit patients with severe gout who have very high uric acid levels and tophi.

We also have data from the long-term extension studies showing that urate-lowering with febuxostat effectively reduces gout flares. The proportion of patients with flares continued to decline as we maintained urate-lowering therapy. By 3 to 5 years, depending on the study duration, we were able to bring the flare rates close to zero in both studies. It is also important to note that tophi resolved in about 50 percent of patients at two years.

The data from our phase 3 program are further supported by data from real-world studies. Singh et al. evaluated the effectiveness of febuxostat and allopurinol in a real-world setting,
based on medical and pharmacy claims data from a large U.S. commercial and Medicare Advantage health plan from 2009 to 2012.

The study sample included approximately 2,000 patients taking febuxostat and over 14,000 taking allopurinol. In this clinical practice-based study, 83 percent of febuxostat users were on 40 milligrams per day and 17 percent on 80 milligrams; 97 percent of allopurinol users were on 300 milligrams per day or lower.

The analysis utilized propensity score matching and outcomes were assessed during a variable follow-up period of at least 3 months following the index date.

A higher proportion of patients on febuxostat compared to allopurinol achieved a serum uric acid target of less than 6 milligrams per deciliter and less than 5 milligrams per deciliter based on post index serum acid levels, and time-to-reach target serum uric acid was also shorter with febuxostat.

Now I will present the efficacy data from
the CARES study. I would just like to remind you that CARES was a safety study, and the dose of febuxostat and allopurinol was uptitrated in each arm to achieve target serum uric acid less than 6 milligrams per deciliter. That was important to ensure that any observed differences in cardiovascular outcomes were not due to differences in urate-lowering effectiveness.

Shown here is the proportion of patients achieving target uric acid less than 6 milligrams per deciliter over time. On the left is the overall study population and on the right is the subgroup of patients with moderate renal impairment, which represents about half of the patients enrolled.

In the overall population, a higher percentage of patients given febuxostat achieved serum uric acid levels of less than 6 milligrams per deciliter compared to allopurinol at most time points, although the difference was small. On the other hand, the difference between the two treatment arms in the moderate renal impairment
group was somewhat larger than in the overall population.

Next, I would like to share with you the data on flare rates over time. In this study, we observed increasing flare rates during the first year or so with both treatments, which is expected during initiation of urate-lowering therapy, as explained by Dr. Becker.

Thereafter, the flare rates continue to decrease, demonstrating that long-term reduction in serum uric acid leads to reduction in gout flares. There was no difference in the flare rates between the two active treatment arms in this treat-to-target study.

In addition, as Dr. Becker showed, treating to target with febuxostat significantly reduced gout flares over time, compared to placebo. Therefore, all the available data clearly shows the long-term value of treating serum uric acid to target in reducing gout flares.

In conclusion, clinical studies have confirmed the durable and dose-dependent serum
urate reduction achieved with febuxostat. Both the phase 3 studies and real-world evidence have shown that febuxostat is superior to commonly used doses of allopurinol, and febuxostat is particularly effective in patients with mild to moderate renal impairment in those with high serum urate or tophi.

We observed the persistence of serum rate reduction in two long-term, open label, extension studies and in CARES. Finally, long-term maintenance of serum urate at or below the targets of 6 milligrams per deciliter decreased gout flares and achieved tophi resolute on.

Thank you for your attention. I would now like to invite Dr. John Affinito to the podium.

**Applicant Presentation - John Affinito**

DR. AFFINITO: Thank you, Dr. Gunawardhana. Good morning. My name is John Affinito, and I'm the head of global patient safety for marketed products here at Takeda. Based on what we've discussed today, I'd like to summarize our benefit-risk assessment. I'll discuss what we've done and what we propose to do to ensure the safe
and effective use of febuxostat.

Given the CARES data that we've discussed today, we took a new look at the benefit-risk assessment based on a thorough and deliberate framework described and defined by the FDA. First, we considered the condition of gout and the current treatment options. Then we did a comprehensive assessment of the benefits and risk of febuxostat. And finally, we considered what steps could be taken to inform the medical community with the new information obtained from CARES.

As you heard today from Dr. Becker, gout is a serious, chronic, and debilitating health condition, and it's a growing problem. The long-term consequences of gout are evident in these images. Patients may develop significant deformities and experience bone and joint destruction that can severely impact their quality of life. Patients with gout also have a higher risk of cardiovascular disease, renal disease, and mortality.

When we look at the available therapies,
it's clear that the options are limited. Xanthine oxidase inhibitors are the consensus therapy of choice with practically only two available agents, allopurinol and febuxostat. When looking at IMS data, it illustrates that allopurinol is used in the majority of gout patients at approximately 92 percent. Approximately 7 percent of gout patients are prescribed febuxostat. All the available agents have their inherent limitations and safety risks.

Allopurinol is approved in doses up to 800 milligrams a day, but it is rarely dosed over 300 milligrams in current clinical practice. Optimal use of allopurinol is limited by dose titration, renal impairment, intolerance, and drug-drug interactions. The two uricosuric agents are less effective and had significant limitations in patients with moderate to severe renal impairment, and these agents are rarely used.

Finally, pegloticase is the only biologic agent. It is administered IV bi-weekly, and it's reserved for patients with clinically far advanced
gout, can cause anaphylaxis, and must be given in a healthcare setting.

The benefits of febuxostat are well established. It is effective in reducing serum uric acid at target in a simple, one-step titration scheme, which is beneficial to both prescribers and patients. Over time, flares and tophi are also reduced.

There are additional benefits in patients with renal impairment, since no dose adjustment is needed for patients with mild to moderate renal impairment and the 40 milligrams dose can be used in patients with severe renal impairment. Febuxostat is also effective in patients with more severe gout, including those patients with serum uric acids greater than 10 milligrams per deciliter or tophi, and there are no significant interactions with other commonly prescribed drugs. Febuxostat is an important option in a limited treatment landscape.

Now turning to the safety profile, it's well established. We've studied 18,000 patients in
clinical trials, and we have 15 million patient-years of exposure in the real world. As you heard today, CARES was designed to assess if febuxostat was noninferior to allopurinol for MACE, and it demonstrated that noninferiority.

The non-fatal components of MACE were similar between febuxostat and allopurinol.
Paradoxically, there was an imbalance in CV death. We were concerned when we saw the high rate of CV death with febuxostat, so we looked for an explanation. We conducted a comprehensive assessment of the CARES data. We evaluated many potential factors including multiple subgroup analyses, patient populations, laboratory values, clinical data, but we could not find an explanation, so we looked further.

We looked at the original development program, nonclinical data, CV mechanistic studies, and other clinical data such as the thorough QT study. And again, we saw no answer. We also looked at the postmarketing surveillance in literature, including the large Medicare study
Dr. White summarized today. None of the evidence suggests an increased cardiovascular risk.

So when we look at all the available data we have today, we do not see conclusive evidence that febuxostat is associated with an increased risk of cardiovascular death. However, we recognize it's important to communicate the CARES data to the medical community.

Our goal is to provide prescribers with the information they need, so they can make a well-informed treatment decision for their patients. These communications began over a year ago. In October 2017, we communicated the top-line results of CARES to the FDA. The FDA then issued a drug safety communication in November 2017, highlighting the potential for increased heart-related deaths with febuxostat compared with allopurinol in CARES. From there, we have had extensive scientific exchange with the medical community, and the CARES data have been widely disseminated.

A centerpiece of this communication was the manuscript publication in the New England Journal of Medicine.
of Medicine in March 2018. We also presented the
data at the American College of Cardiology Congress
and at the American College of Rheumatology
Conference.

Takeda will continue to communicate the
CARES data to prescribers. We propose updating the
warnings and precautions and other pertinent
sections of the label to include the CARES data and
the CV death observation and advise prescribers to
carefully consider the risk and benefit of using
febuxostat.

We will disseminate these changes to the
label and send a Dear Healthcare Provider letter to
prescribers, pharmacies, and professional
societies. We will continue our postmarketing
surveillance and literature monitoring, and there's
more data to come. The ongoing FAST study will
inform us further on the safety of febuxostat. We
will submit this data to the FDA and respond
appropriately.

In summary, gout is a serious and
debilitating disease with limited treatment
options. CARES demonstrated that febuxostat is noninferior to allopurinol regarding adjudicated MACE, but we observed a higher rate of CV death. We are confident in the robustness of the MACE findings because they are supported by multiple subgroup and sensitivity analyses. However, based on the totality of the evidence, we do not have a similar confidence in the strength of the CV death results.

Nonetheless, the label should be updated with the CARES data to enable providers to make a shared treatment decision with their patients, and we are committed to doing so with your feedback, and in collaboration with the FDA. There remains an unmet medical need for safe and effective treatments for gout, and febuxostat is an important option. Takeda's goal is to find the right balance and do what is best for patients.

I would now like to invite Dr. Larry Edwards up to provide his clinical perspective.

Applicant Presentation - Lawrence Edwards

DR. EDWARDS: Thank you, Dr. Affinito.
Good morning, everybody. I'm Dr. Larry Edwards. I'm a professor of medicine and rheumatology at the University of Florida and have been taking care of gout patients for more than 40 years. I've also conducted basic research and clinical trials in this area. I'm a paid consultant to the sponsor but have no financial interest in the outcome of this meeting. My job today, is to share my perspective on the data that you've heard and discuss how I would use this information when treating my patients.

To reiterate Dr. Becker's comments, gout is a painful and debilitating disease with limited treatment options. It affects approximately 9 million people in the United States, and its prevalence continues to rise. Gout is viewed by many in the healthcare community, and even by the patients and families, as a quirky condition that is certainly painful but short-lived.

In reality, gout is a chronic condition of urate deposition leading to increased frequency of flares in multiple joints, as well as tophus
formation and a persistent arthritis that can lead
to deformities, chronic disability, impaired
quality of life, and even death.

The focus of treatment for gout is to lower
serum uric acid levels. As you've seen, there are
few therapeutic options, and they are all
associated with certain challenges. The guideline
recommended first-line therapies are the xanthine
oxidase inhibitors, allopurinol and febuxostat,
each of which has limitations.

Allopurinol has been used for over 50 years.
However, most patients do not achieve target serum
uric acid levels for multiple reasons. These
include the burdensome dose titration scheme, which
is further complicated by renal impairment,
tolerability issues, and a historic pattern of
underdosing by the medical profession.

Allopurinol is also associated with a rare,
life-threatening, hypersensitivity reaction that is
the basis for some of the concern by physicians and
patients about uptitrating the dose to achieve
target uric acid. Febuxostat is not limited by
renal impairment, but as you've heard, there's some evidence to suggest an increased cardiovascular risk.

This slide clearly illustrates why uptitration of allopurinol is such a challenge. This graph depicts the number of monthly dose escalations required to reach target serum uric acid levels according to the American College of Rheumatology guidelines. Note that the number of escalations of allopurinol depends on whether the patient has significant kidney disease. In those with severe renal impairment, the dose should be escalated by 50-milligrams increments rather than the standard 100-milligrams escalations.

If you increase to the commonly used dose of 300 milligrams, which is also the cap used by many physicians, only about 42 percent of patients will reach target. Even at 400 milligrams, only approximately half will achieve the target serum uric acid level, and this takes several months and several dose escalations.

In contrast, with one dose escalation of
febuxostat, from a starting dose of 40 milligrams daily to a maximum dose of 80 milligrams, 60 to 70 percent of patients will reach target, independent of renal function, and this can be accomplished within several weeks.

This has a significant benefit in convincing the patient to maintain their treatment course, and it greatly minimizes the number of trips to the physician's office and reduces the number and need for ancillary laboratory monitoring.

As you've seen over the past 10 years, febuxostat is effective in reducing the risk of the most painful component of gout, and that is gouty flares. In this five-year study, we see that after two years, we've nearly eliminated the risk of gout flares.

To summarize the benefits of febuxostat, treating to target with xanthine oxidase inhibitors reduces flares and leads to tophus resolution, but allopurinol has been historically underutilized. Less than 3 percent of all allopurinol prescriptions in the United States are for doses
greater than 300 milligrams a day, while the dose
of allopurinol required to achieve the recommended
target in 50 percent of gout patients is
approximately 400 milligrams daily. In contrast,
febuxostat can achieve target serum uric acid
levels in one step in approximately 70 percent of
patients.

There's also an important advantage of
febuxostat in patients with renal impairment.
Because renal excretion of febuxostat and its
metabolites is low, there is no need to dose reduce
in patients with mild to moderate renal impairment,
and febuxostat is approved at a dose of
40 milligrams daily for patients with severe renal
impairment.

Therefore, febuxostat plays an important
role in the management of gout and provides an
effective alternative for patients who cannot take
allopurinol or who have inadequate response to
allopurinol at the doses commonly used in clinical
practice today.

Given what we know today, who would I
prescribe febuxostat for? In my practice, I look at a number of factors when choosing the most appropriate treatment options. Recognizing that allopurinol and febuxostat are both first-line therapies per the American College of Rheumatology guidelines, I usually start patients on allopurinol first, but there are about 10 to 15 percent of patients in my clinic that are currently taking febuxostat.

Two-thirds of those had failed allopurinol either for efficacy or adverse events, such as GI distress, transaminase elevation, or rash. For the other one-third of these patients on febuxostat, or about 5 percent of my clinic population, febuxostat was the first choice.

I've reviewed my clinic notes for the past six months looking to see why those people were placed on febuxostat first. The reasons that I use febuxostat as a first-line treatment in these few patients was, first, a patient reported distant past history of rash or intolerance to allopurinol; second, resistance from the patient's primary care
doctor or nephrologist regarding the use of allopurinol because of significant renal disease; and finally, in a patient that I judged clinically to be incapable of following the allopurinol dose-titration scheme that I had outlined on previous slides.

Before prescribing febuxostat or any gout therapy, I have a conversation with my patient to reiterate the goals of therapy and discuss their options and the relative risk-benefit of the therapeutic change.

Regarding the CARES trial findings, I would tell them that the risk of cardiovascular death would potentially increase from 3 percent on allopurinol to 4 percent on febuxostat. Having had this conversation, I feel comfortable treating patients with febuxostat, even those with cardiovascular disease.

In conclusion, there is strong evidence to support the role of xanthine oxidase inhibitors in counteracting the clinical problems developed in patients with gouty arthritis. Based on the
totality of evidence, febuxostat continues to have a very positive benefit-risk profile in gout patients who are intolerant to allopurinol or who did not achieve target serum uric acid levels with allopurinol.

Although there is a higher rate of cardiovascular deaths in the CARES trial, I believe Takeda is taking appropriate steps to manage the risk. Therefore, febuxostat should continue to play an important role in the treatment of gout. I would hope that your recommendations and the FDA's decision would not impede my treatment decision-making abilities in patients with gout.

Thank you. Now I'd like to invite Beth Knapp back to the podium to address questions.

**Clarifying Questions**

DR. SUAREZ-ALMAZOR: Okay. We will start now with the clarifying questions. We are running about 10 minutes behind, but this is such an important aspect that I'd like to do the full 30 minutes. So it may require if we take the full 30 minutes and also the rest of the morning, that
we go a little bit into the lunch break.

Please identify yourself, for the record, before you speak, and if you can, please direct questions to a specific presenter. Something that would help us is if you turn your sign in a vertical way.

I'd like to start with a question to Dr. White. If I can have slide CS-31?

Most of the subgroup analysis results that you showed are either on the MACE or the cardiovascular death groups, but we can see here, as you stated before, that sudden cardiac death was the main reason for the difference.

If my numbers are correct, the excess deaths were 34 for the full cardiovascular, so 27 of those were attributable to sudden death. I was wondering if you had done any subgroup analysis in that particular group of patients with sudden death?

DR. KNAPP: No, we have not at this time.

We have not.

DR. SUAREZ-ALMAZOR: Okay.

Dr. Psaty?
DR. PSATY: Bruce Psaty, University of Washington. Assuming the cardiovascular death estimate is valid, 1.4 million person-years of febuxostat use translates to 5,000 cardiovascular deaths. So, this is a key question.

I'm struck by the strength of the interaction with aspirin. Those not on aspirin have a doubling of risk in the febuxostat group. And I think it's important to remember that plaque rupture is the most common cause of fatal coronary syndromes, and at autopsy, these plaque ruptures tend to have thin fibrous caps, large lipid cores, abundant inflammatory cells, few muscle cells, and large clots.

So a large thrombus involving activated platelets and coagulation factors often proves to be fatal, and one of the mechanisms might be an increase in case fatality rather than an increase in the incidence.

I did a literature search on febuxostat and platelets, and of the 710 articles on febuxostat, only two mention platelets, and one of them
suggested actually an increased risk of clotting by Kaminski [ph]. Febuxostat partly reversed the anti-thrombotic effect of nitrate as measured by an increased weight of the thrombus.

If febuxostat were to have genuine platelet-activating effects, those not taking low-dose aspirin, which is an anti-platelet agent, might be especially vulnerable to exuberant coronary thrombosis in the setting of plaque rupture.

You've mentioned briefly in two slides that you've studied platelets and coagulation factors, but I'm wondering what these studies were and how robust they might be.

DR. KNAPP: Yes, I'll ask Dr. White to address your question on that.

DR. WHITE: Thank you. Let me first put a slide up for platelet aggregation. It's a small study that mentioned typically the platelets are stimulated with substances like ADP or collagen, and then there's giving increasing doses of the study drugs. TMX-67 happens to be febuxostat at
concentrations from zero to very high or almost toxic doses, demonstrating that there's no effect on the aggregation of platelets in this particular experiment. But I'd actually like to go to a --

DR. PSATY: Do you have comparison with allopurinol because that's --

DR. WHITE: No, this isn't compared to allopurinol. This is actually just a dose response of no vehicle or the actual drug at higher concentrations, so not against allopurinol.

But to answer that question, I think clinically it's more relevant to look at the primary endpoint in these subgroups, which we have analyzed. If we can bring up the forest plot of the primary endpoint, which as you recall, includes acute coronary syndromes.

Slide SS-54 please? This is a fairly similar slide to the one I showed for CV death, but now we're looking at the primary endpoint of MI, stroke, acute coronary syndromes that is angina with urgent revascularization, plus CV death in the composite. And users of low-dose aspirin, yes or
no, towards the bottom part of the figure that did not show heterogeneity, there are some small numeric differences. That's actually driven by the CV death component. But all the other ones are basically the same, having a hazard ratio that's about the same for the non-fatal events.

So while I respect your comment about the possibility of a prothrombotic effect of this drug as a cause of sudden death, I would be surprised that that would happen in exclusion of any differences in acute coronary syndromes or non-fatal MI, or even non-fatal stroke, because all of those are potentially prothrombotic events as well, and they didn't show this imbalance on those users of aspirin versus the non-users of aspirin at baseline.

DR. SUAREZ-ALMAZOR: Dr. Nason?

DR. NASON: Thank you. Martha Nason, I'm a biostatistician at NIAID. I am still struggling to understand the missing data and who was censored, and specifically when you collect MACE data and use it for your primary endpoint, it's time to first
MACE event, I believe.

   I think I read something in what was provided to us before the meeting, saying that you no longer followed people after a MACE event because you'd ascertained their primary outcome. But I've been trying to understand if you -- I would think when you're also looking at the secondary endpoints, the components of MACE, you'd want to know if somebody had, say, angina that had qualified as MACE, then you stopped following them, and then they go on to have a MI or a cardiovascular death.

   I would hope that would be captured, but I couldn't quite tell if it would be from the comment that they were no longer coming in for follow-up after a MACE event. And similarly, I couldn't tell whether those people counted as lost to follow-up then, in your subsequent attempts to go and ascertain mortality or vitality status in participants who'd been lost to follow-up, did that include people who had had a MACE event that was not death, a non-fatal MACE event?
Really just trying to untangle were there more cardiovascular deaths in either group, let's say, among people who'd had non-fatal events but were no longer counted.

DR. KNAPP: Yes, I heard a couple different comments in there, so I'll try to make sure I address each one, and there may be a couple people I pull up. If I don't hit anything, please stop me and remind me.

First, I'm going to ask Dr. Castillo to come up and just address how we followed patients throughout the trial, to just make that point very clear and understood how patients came in and what we were following, and then I'll come back.

DR. CASTILLO: Majin Castillo, medical director for marketed products in Takeda. To answer the latter part of your question, some patients who had a MACE were still followed afterwards, so we do have data on those who continued.

In terms of the lost to follow-up, we did make an attempt to get vital status on those
subjects who were not only lost to follow-up, but also those who were early term from the trial. So we do have data on those lost to follow-up subjects.

DR. NASON: [Inaudible -- off mic].

DR. CASTILLO: Correct, yes.

DR. NASON: Sorry. In the mic, I'll just repeat myself. I was just clarifying that that was including the people who were early termination because they'd had the endpoint.

DR. CASTILLO: Yes, correct. The vital status was performed for all those who were lost to follow-up, as well as those who early terminated for any reason.

DR. NASON: Okay.

DR. SUAREZ-ALMAZOR: Dr. Gibson?

DR. GIBSON: Gibson. Yes. Thank you. I want to build upon what was just said. In a time to first event analysis, if you had revascularization, you could have missed a subsequent MI because the patient was already censored at that time point. So the next question
is have you done a multiple event analysis? I'm not even sure you can do a multiple event analysis because those people were no longer followed up for, say, an MI.

The other issue is you've said there's noninferiority, the criteria was met, but when you have this magnitude of missingness, it drives the hypothesis towards a noninferiority finding.

Have you done traditional methods like a quan analysis, a tipping-point analysis, an inflation analysis, to look at what would happen in those people who you had missing data, had they had an event, to look at the robustness of that noninferiority result?

Finally, have you done a competing risk analysis on mortality, since people who died of other causes, may not have been eligible to die from a cardiovascular event?

DR. KNAPP: Yes, we've done a lot of those analyses. I'll ask Dr. Carroll to please come to the podium and address them for you.

DR. CARROLL: Thank you. My name is Kevin
Carroll. I'm a paid consultant to Takeda, but I have no interest in the outcome of this meeting today, in financial terms.

There were three elements to your question, if I make sure I got them. The first was an element that referred to a patient who might have had, for example, one event, an MI, and then wasn't followed afterwards. I think that was the first part.

The second part was about patients who didn't have complete follow-up, and could they have impacted the conclusion of noninferiority? And I think the third was asking about competing risks on CV death.

I'll deal with them in the order that you've raised. The first, just to clarify, when patients in the study had a MACE event, it is not the case that they were censored thereafter. Those patients were still available for follow-up, and in fact, the data that was shown in Dr. White's presentation, the breakdown, if you look, you add those events, you'll find that the components add
to more than the total MACE, because some patients would have gone on after an MI and had a stroke. Just to be clear on that first point.

The second is obviously an important issue in --

DR. GIBSON: But if that's the case, what did your multiple event analysis show?

DR. CARROLL: Oh, I apologize. I forgot that component of your question.

No multiple event analysis was executed, I'm afraid, so I can't help you with that, but there were multivariate analyses done, but they're not quite the same thing, I think, to address your question.

If I may, I'm going to go to the question about follow-up. Can I have ST-3 please? Thank you.

This slide may be a little bit helpful in terms of just making we understand how much -- to what extent patients didn't have complete follow-up, and then we can talk about those tipping-point analyses. Very briefly, what this
shows you is the primary endpoint, and for the primary endpoint the patient either had a MACE event, so their status as it relates to the primary endpoint is no. There's not a missing component as it relates to those patients. They could have had a non-CV death, so we know the status of the patient, or they could have been censored at the end of the study, because there's a closeout when you close the study and you get all the data and they have a closeout visit.

The first three rows in this table, we know the status of patients as it relates to MACE. It's the last row, where we had some patients who would have dropped out, stopped taking drug potentially, and then from the point they dropped to the closeout visit, we have no information. That group of patients, about 30 percent, they were followed. We have some information. They were followed for an average of 1.7 years. But it's the influence that this group might have had because they didn't have a full follow-up to the closeout.

If I can, there's a backup slide that we
have that looks at the potential impact of these missing events. Here we have it.

For those 30 percent of patients I showed on the previous slide that had an average of 1.7 years follow-up but they terminated early before the closeout visit, so there's some missing follow-up for those patients, for those guys, we can say how many events would be expected could have occurred in these patients who've only had partial follow-up.

The top of this slide shows you the main result that Dr. White has shown you, so just repeating that. The bottom half gives you the information as it relates to this kind of analysis that I think was requested.

You can compute that about 6 and a half percent of those patients who had partial follow-up may have had a MACE event. Then the question is, how extreme does a hazard ratio have to be in these events that you might have missed -- the 6 and a half percent of those without the full follow-up -- how extreme might that have been, or
would it have to be, to change the conclusion of noninferiority of a primary endpoint?

You find that for these 6 and a half percent of patients without the full follow-up who may have had an event, the hazard ratio amongst these missing events, if you'd like, would have to be 1.65. That's an increasing risk that's 22 times higher than the primary endpoint result, which has a 1.03 hazard ratio.

So based on that kind of analysis, which is folding in, I tried to look at what the impact is, possibly, of missing events. I think it's pretty unlikely that you're going to have, amongst those patients, a hazard ratio of around about 1.65.

The reason I say that comes from Dr. White's presentation where he showed patients who had complete follow-up and those who did not, and their baseline characteristics and the disease characteristics, the CV disease history was absolutely identical. I think the FDA also found the same in their analyses.

So there's no reason to believe that you
would have this huge jump in risk in those patients in whom we didn't have full follow-up.

DR. GIBSON: That's the demographics, but I didn't see anything about their cardiovascular risk, like a TIMI risk or some kind of risk score to assess risk, but thank you.

DR. CARROLL: I'm sorry. Answering this question is taking some time. There was a third component, which was asking about competing risk analysis. That was done, and it makes absolutely no difference to the result that we see. Thank you.

DR. SUAREZ-ALMAZOR: Dr. Nissen?

DR. NISSEN: I want to understand who was unblinded to the 75 percent interim analysis?

DR. KNAPP: I'll have Dr. Castillo address your question on the DMC process.

DR. CASTILLO: Majin Castillo, Takeda. When the 75 percent interim analysis was performed, the DMC did via open minutes to some of the Takeda representatives. At that time, we were still blinded. It was not until the October meeting of
2016, which was after the April 2016 meeting from the DMC, the 75 percent analysis, that Takeda was informed that there was an imbalance of the cardiovascular --

DR. NISSEN: I'm still not following you. Was anybody, either the academic leadership or the company, aware of the results of the 75 percent interim analysis prior to the end of the trial?

DR. CASTILLO: When the DMC did notify Takeda, we did have a breakup in the group. So the representatives at Takeda, once they were made aware there were some blinded results being told, that's when they formed a wall, kind of a separation within Takeda. Therefore, those personnel who were running the trial were blinded to those results that were relayed by the DMC.

DR. NISSEN: Then just one more quick question. The missing data, which represents nearly half of all patients in the trial, is unprecedented in cardiovascular outcome trials. And I'd really like the sponsor to explain how did you lose nearly half the patients in the trial,
during the course of the trial? This is relevant, as you are well aware, because it tends to bias the trial towards the null hypotheses.

So I want an explanation of how this level of missingness occurred in a trial where you would never expect -- you would expect 99 percent of the data to be available; what happened here?

Something terrible happened.

DR. KNAPP: What we can say is that it is a very painful disease, so it was hard for us to, in some ways, to predict the level of patients that would drop off their treatments. But we did follow them as closely as we can. I'll have Dr. Castillo come back here and just walk you through --

DR. NISSEN: Sorry, that's not my question.

DR. KNAPP: I'm sorry. Please?

DR. NISSEN: My question is, you did not have complete follow-up on 45 percent of the patients. I'm not talking about drug switching. I'm talking about people who you didn't ascertain outcomes in.

DR. KNAPP: Right. No, I wasn't talking
about drug switching. I was just saying in terms of patients dropping off the study altogether.

DR. NISSEN: Yes. Study drug, that's another issue, but I'm talking about missing data in terms of ascertaining the outcomes. That's the critical question here.

DR. KNAPP: Okay. I'll have Dr. Castillo address that initial question.

DR. CASTILLO: Majin Castillo, Takeda. Can you just clarify the question of what particular --

DR. NISSEN: Well, you had a huge number of withdrawn consent, people lost to follow-up. I mean, you can pull up the slide; it's in your document. But you're missing an enormous number of outcomes.

DR. CASTILLO: Right. For the trial, we understand that we also were concerned with the subjects who were dropping out from study medication as well for the discontinuation --

DR. NISSEN: I'm not asking about study medication. I'm asking about completeness of follow-up.
DR. CASTILLO: Right. We did have a retention program that we initiated at the onset of the trial. Some of these were geared for patients, and in that case, we did have appointment reminders that were sent to these patients --

DR. NISSEN: I'm sorry. This is not my question. My question is not what you did to mitigate this; it's how did you end up missing so many patients? What happened here? What went wrong? I mean this is a failed trial, and the question is how did it fail?

DR. CASTILLO: When we were having -- as part of our retention program, we did meet with some of the investigators, as well as several study coordinators during the inception of the trial. One of the reasons we had this was to discuss some of the challenges that were being encountered during the study, as well as potentially some of the activities that we can do to counter this discontinuation.

What we learned from the study coordinators, as well as from the physician investigators, was
that the first year of the study was the most problematic. As we heard from Dr. Becker's presentation, some of that is due to the increase of flare rates within that first year when you initiate study medications.

So we learned that that was one of the issues why patients were dropping out of the trial, just the concern for the increase in flare rates during that first year.

To counter that, we had a gout flare education program where we developed some materials for these patients, as well as for investigators that describes treatment-initiated flares, as well as the overall effectiveness of urate-lowering therapy for gout.

These were used by the investigators to explain to their patients that they may experience gout flares during that first year, but hopefully it would resolve over time and to maintain that and hopefully stay in the study, and we did get feedback from the investigators that this was helpful in convincing some subjects to stay in the
study.

DR. KNAPP: Dr. Nissen, I want to follow-up a little bit further. I'm going to have Dr. White just come and address it a little bit further, because as you point out with some of the other CVOT trials, you do have a bit more in terms of patient's information. Dr. White?

DR. GIBSON: But to put it in context, you would expect a handful of patients with loss to follow-up in a study like this or zero.

DR. NISSEN: And by the way, if they have a flare, it doesn't mean they're going to be lost to follow-up. Why would you -- okay, you have a flare, all right, so you go off study medication. But that doesn't explain the loss to follow-up. Something's happened here. I don't know what it is.

DR. KNAPP: I'll have Dr. White address that. Thank you.

DR. WHITE: I don't actually have a direct answer to that, other than that this was an experiment that was designed very similar to our
diabetes studies that we've been doing for the last decade, the kind of accrual, the requirement for the number of events and so forth. And we found we had a much easier time with -- let's face it, a much easier time with people with type 2 diabetes who were taking a drug that doesn't cause them any side effects. They're placebo controlled. It's added on to a variety of other therapies.

Here, it's a population of people with gout, who have a lot of other comorbidities. They have the option of going off the study drug and finding a doctor to give them a prescription for the same drugs that they're taking in the study.

So I guess it was somewhat of a learning experience as things were going along, that in a 7-year period of time, which was a very long time for this study to be going on and trying to accrue these events, that people walk with their feet, and they left the trial areas, and they went back into the physician's private practices and were not found again.

Now that's not an excuse for not just
following them for events. That attempt was made. All patients who stopped study drug were invited to continue into the trial for follow-up either by telephone or by personal visits, and about 10 percent of them agreed to do that, and the other 30 percent or so did not agree to do that. That's really all we can say.

DR. SUAREZ-ALMAZOR: Okay. Let's get moving on as we have several members who have questions. Dr. Kulldorff?

DR. KULLDORFF: Thank you. My name is Martin Kulldorff. I'm a biostatistician at Harvard Medical School. I have a question about slide CL-12. It's very clear that the drug, in terms of efficacy, it's a urate-lowering drug, but that's a surrogate endpoint. And when it comes to the clinical endpoints, the APEX trial doesn't show any improvement in terms of flares or tophi, compared to placebo.

The only study I could find where there was some evidence of an improvement compared to placebo is the study on slide CL-12 -- maybe you can put
that up on the screen there -- which is the study by Dalbeth from 2017. In that study, the primary endpoint was CSSHS joint erosion, for which there was no difference between the study drug and placebo.

So my question is, this slide here, is that the only evidence for a clinical outcome where the study drug has shown efficacy compared to placebo, or are there other studies also that show that?

DR. KNAPP: We have other studies where we captured that information. I will ask Dr. Lhanoo Gunawardhana to share that back. He went through it a little bit in his presentation, but I'll ask him to expand for you.

DR. GUNAWARDHANA: Lhanoo Gunawardhana, Takeda. I want to put things in context in terms of your question. Most of patients who are coming into our trials were having the disease for about, let us say, 10 years or so, on average. So by the time they come into studies, they have accumulated large amount of crystals, and when we put them on active medication, they start to reduce urate and
dissolve the crystals. As they mobilize the crystals from joints, it creates these flares.

So it can take about a year or more to clear out these crystals from joints. And when you give two active treatments such as in the CARES trial, which is especially treat to target in both arms, you continue to have these flares, and it takes about 3 to 5 years to clear them out. It's very difficult, in that context, to compare active treatment arms and show a difference.

In the study that you just asked, the early gout study, as you correctly pointed out, the primary endpoint was joint erosion based on x-rays. We did show a reduction in synovitis by MRI, and corresponding to that, we saw significantly reduced flares compared to placebo.

Generally speaking, it's not ethical in advanced gout to do placebo-controlled studies, so you do not see placebo-controlled studies in advanced gout stage, and this particular study was done in the early stages of gout. That's why, as you mentioned, we have not done long-term studies,
placebo controlled, to show efficacy changes.

As for the APEX, FACT and pivotal trials, those were 6 to 12 months in duration. As you saw in the CARES study, the first year or so, you have the significantly increased paradoxical treatment initiative. It's a challenge in gout that when you treat gout with appropriate medication, such as febuxostat and allopurinol, you actually cause more painful flares than the disease itself, which is an issue in management of patients as well as in trials trying to compare the flare rates.

DR. SUAREZ-ALMAZOR: Dr. Curtis?

DR. CURTIS: I wonder if the sponsor could clarify the current disposition of the FAST study. I was a little bit puzzled in trying to reconcile the FDA and the sponsor's briefing documents.

On page 91 of 161 of the FDA document, it said that FAST completed enrollment with 6142 subjects, and as of a year ago accrued 456 targeted MACE events, as of January of 2018, but that we're still going to wait another year until 2020 for the final results.
But then in the sponsor's document, page 57, it didn't imply that, in fact, that was the case, and in fact indicated that that number of events would be sufficient for the final readout for the noninferiority outcome.

So what is the status of FAST, and what has the DSMB told you, if much of anything?

DR. KNAPP: We did send a note to FDA to notify them that that information was not technically correct. Recall this isn't our trial. It's Menarini's, but of course, we've had many discussions with them and with this trial. The study is still ongoing. They have not accrued all the events at this point in time. It's our understanding the results will be available in May 2020.

DR. CURTIS: From the information you presented, have you accrued around three-fourths of the events? It seemed like you had more than 450, which would roughly be close to three-quarters of the events that were seen in CARES when you achieved your primary noninferiority outcome.
DR. KNAPP: I don't have that information in front of me in terms of how many events have accrued at this point. All we know is the DMC has told them to continue.

DR. CURTIS: Okay. Second, and totally separate question, do you have any data in relation to CV events in relation to gout flare, since typically that can be a fairly hyperadrenergic state, and perhaps one could potentially trigger a CV event?

DR. KNAPP: Yes. I'll ask Dr. White to address that for you.

DR. WHITE: Yes, if we could find the slide on the proximity of gout flares in the 3 months before the event. Slide, please. As I pointed out during the core presentation, those patients who had a fatal event didn't necessarily have an event in relationship to their gout flares; it just didn't look that way. But we did do an analysis of the relationships between cardiovascular event, death, MI, and stroke according to a gout flare within 3 months.
This chart looks at the two treatment groups, febuxostat and allopurinol, and whether or not the patient did or did not experience a gout flare within 3 months, did they have an event or not. For example -- and a small number did. CV death, it was 6 percent versus 2 percent for febuxostat and allopurinol for CV death. For MI, it was a bit higher, 14 versus 6. But for stroke, it was balanced 7 to 8 percent, and for unstable angina it was 18 to 16 percent.

These are small numbers. They kind of give one an impression that perhaps it was some temporal relationship between a gout flare and an event in some individuals, but certainly it was in the minority rather than in the majority of patients that actually had a gout flare and then had a subsequent event. We don't really have anything closer than 3 months. There were very tiny numbers in a more proximal time frame.

DR. CURTIS: How do these numbers compare with, say, the background flare rates, just if you chose any other random three month point in time
for people that don't have events?

    DR. WHITE: I apologize. I don't think we actually did that particular analysis.

    DR. CURTIS: Okay. Thank you.

    DR. SUAREZ-ALMAZOR: Dr. Ruha?

    DR. RUHA: Michelle Ruha. I believe I read in the materials that most of the cardiovascular deaths occurred off drug, not on drug, and in particular the first 30 days. I was just trying to figure out if there could be something about going off the drug that was risky.

    I was wondering -- I think it's for Dr. White, and we could look at CS-38. I was wondering if for the subjects who actually stopped the drug, did we measure serum urate in those subjects once they were off drug and follow that?

    I was wondering if just going off might cause a spike. I assume we know this information, a spike in uric acid, and if that could somehow lead to inflammatory reaction.

    DR. KNAPP: Can you just clarify real quick, did you say CS-38?
DR. RUHA: Yes.

DR. KNAPP: I will ask Dr. White actually to address both your questions.

DR. WHITE: Thank you. Let me first talk to you about -- I'll show you the slide again if it's of interest, but it just demonstrates that urate levels were lowered on both drugs. The trends for urate levels over the course of the study in those patients who died versus didn't were really not dissimilar.

I think your question about going off drug is relevant. We actually did an analysis looking at those patients who had an event on drug or off drug for 30 days. If we could bring up that individual patient figure on febuxostat-treated patients for that 30-day period, the colored line graph.

I was interested in this myself, actually, because one of the things that I've seen, being in clinical trials myself for a long time, is that one of the first things that happens when patients come into the hospital with any kind of event, whether
it's pneumonia or cardiovascular in nature, is that
the resident physicians or other physicians stop
their study drug.

Let me show you an example of this
particular phenomenon. Now these terms are not
adjudicated terms. These are actually the verbatim
term by the investigator, but you can get a good
flavor of what happened.

The definition in the protocol is that if
you were not on drug even for one day, you were off
drug when you had an event. If you look at all
those people on the bottom part of that figure,
you'll note that there's a whole bunch of people
who died of some sort of cardiovascular event about
one day after they were not taking the drug. To
me, that's not any different than being on drug,
but we couldn't call it that, based on the
definition in the protocol.

Some of the other events with the longer
blue lines are when an event might have started,
some on drug, some just a little bit off drug, and
then it was perhaps 1 week or 2 weeks that they
actually died.

The adjudication committee, by definition in our charter, if somebody had a non-fatal event that led to death within a reasonable temporal time, like a couple of weeks, we did not call that two separate events. We called it one fatal event. We, of course, had no idea about whether they were on drug or off drug at the time of the adjudication.

So there was a lot of this that occurred in this trial, and I'm sure it occurs in many trials. That's why we prespecified this time window in the protocol, just wondering whether or not we might be picking up extra events in a temporal relationship to the drug. And the same phenomena was seen for allopurinol. It wasn't specific to febuxostat. But I just want to give you an impression.

We don't have data on what people switched to after they discontinued from the study, if they were not treated, or they were treated with a different xanthine oxidase inhibitor. So we have no way of doing an analysis on urate levels or
drugs that were used for the treatment of gout post-discontinuation from the trial, unfortunately.

DR. SUAREZ-ALMAZOR: Okay. We will now take a break. If you can come back at 10:45. Just a few things. We know there are several panel members that have not been able to ask questions, so we can either have those questions after the FDA presentation and clarifying questions, if we have time; or if not, after the public hearing. So we have your names, and we will be sure that we do that.

Panel members, please remember that there should be no discussion of the meeting topic during the break among yourselves or with any member in the audience. Finally, you were all given this form for lunch, so if you're interested in buying lunch, please make sure you fill it and you give it to John Lauttman outside.

(Whereupon, at 10:33 a.m., a recess was taken.)

DR. SUAREZ-ALMAZOR: It's 10:45, so I would like to ask everyone to take their seat, so we can
continue. We will now proceed with the FDA presentation.

(Discussion off the record.)

**FDA Presentation - Rosemarie Neuner**

My name is Rosemarie Neuner, and I'm a rheumatologist in the Division of Pulmonary, Allergy, and Rheumatology Products. Today, Dr. Hsueh from the Office of Biostatistics, and Dr. Bradley from the Office of Surveillance and Epidemiology, and I, will presenting the FDA's review findings for the postmarketing required cardiovascular safety study, the CARES study, for febuxostat, as well as drug utilization data in order to help set the stage prior to today's discussion on the benefit-risk assessment for febuxostat, and your recommendations regarding what risk mitigation actions, if any, that you think the FDA should put into place to ensure the drug's safe use.

My presentation today will include a brief background and overview of the regulatory history of febuxostat, a summary of the CARES safety study.
design and its regulatory history. I will then hand the podium over to my colleague, Dr. Hsueh, who will discuss the cardiovascular safety findings for the CARES study.

She will then be followed by Dr. Bradley, who will discuss usage and utilization data for febuxostat, before I return to present the clinical considerations and benefit-risk assessment for the drug, as well as potential regulatory actions for your consideration and discussion.

There are currently 6 approved therapeutic agents for the management of symptomatic hyperuricemia. These include the first-line agents, the xanthine oxidase inhibitors, allopurinol, and febuxostat; the second-line therapies, the uricosuric agents, probenecid and lesinurad; as well as a fixed-dose combination lesinurad and allopurinol; and the third-line agent, the uricase, pegloticase, all of which are associated with variable degrees of urate-lowering and various inherent toxicities.

Febuxostat or Uloric is a selective xanthine
oxidase inhibitor approved at doses of up to
80 milligrams once a day for the chronic management
of hyperuricemia in gout patients. Its current
label includes warnings and precautions for
increasing gout flares when initiating therapy,
cardiocascular events, hepatic toxicity including
flares, and serious skin reactions.

The drug was approved in 2009, following
three review cycles and an AC meeting, which
discussed its cardiovascular safety. Phase 3
clinical development for febuxostat was comprised
of 2 pivotal active and placebo-controlled studies
of up to 12 months duration. The active comparator
in both studies was allopurinol at doses of
100 to 300 milligrams once a day.

Both studies evaluated a surrogate endpoint,
which was proportion of patients achieving a serum
uric acid less than or equal to 6 milligrams per
deciliter. Complete response actions were taken
for the first two review cycles due to persistent
cardiocascular safety concerns, the basis for which
I will now explain.
At the end of the first review cycle, a complete response action was taken by the FDA, based on the review of the original safety database, which contained a small number of cardiovascular events. The clinical review team determined that febuxostat-treated subjects had a higher rate of overall mortality, a higher rate of mortality due to cardiovascular causes, and a higher rate of cardiovascular thromboembolic events as compared to allopurinol or placebo patients.

To address these cardiovascular safety concerns identified by the FDA, the applicant submitted a re-analysis and post hoc adjudication using the antiplatelet trial as collaboration, or APTC criteria, of both prior clinical safety studies, as well as new data from two ongoing long-term clinical studies, which triggered the second review cycle.

The clinical review team noted in their review of these data a persistent imbalance in all-cause mortality not in favor of febuxostat and a higher rate of investigator-reported primary APTC
events in febuxostat-treated patients and raised concerns regarding insufficient data for post hoc application of APTC criteria, or to confirm events, a lack of dose response for cardiovascular events, and limited exposure to allopurinol due to unequal randomization in controlled portions of studies followed by most patients receiving open-label febuxostat in the long-term extensions.

As shown in this table, there was an initial imbalance of 4 deaths not in favor of febuxostat during the randomized controlled portion of the phase 3 studies, resulting in an all-cause mortality rate of 0.6 deaths per 100 patient-years for febuxostat-treated subjects versus zero per 100 patient-years for allopurinol subjects.

This imbalance during the long-term extension studies persisted with an additional 8 febuxostat deaths resulting in an all-cause mortality rate of 0.38 deaths per 100 patient-years associated with febuxostat.

Based on this total of 12 febuxostat deaths, the overall combined all-cause mortality rate for
febuxostat was numerically higher at 0.43 deaths per 100 patient-years compared to the allopurinol treatment group with zero deaths per 100 patient-years. These imbalances in all-cause mortality could not be explained by differences in duration of exposure between the febuxostat and allopurinol treatment groups. Additionally, 9 out of these 12 deaths were adjudicated by the applicant due to APTC or cardiovascular events.

The applicant next conducted another efficacy and safety study, the CONFIRMS study, which was a phase 3 noninferiority, randomized, double-blind, actively-controlled trial. This study was larger and contained 3 times more subjects than the actively-controlled allopurinol group than the combined 2 phase 3 studies. Additionally, over half the subjects had risk factors for cardiovascular disease. Unlike the other phase 3 studies, it had prespecified cardiovascular endpoints and a cardiovascular adjudication committee. Numerically more deaths in the allopurinol group versus the febuxostat group,
occurred in this study. The overall result suggested the risk of cardiovascular events with febuxostat were the same or lower than allopurinol.

Members of an Arthritis Advisory Committee meeting voted overwhelmingly to recommend approval of febuxostat with the caveat that the sponsor conduct a postmarketing required cardiovascular study to further assess the risks associated with the drug compared to allopurinol.

Additionally, the then review division required the drug's label to include a cardiovascular warning regarding the higher rate of cardiovascular thromboembolic events observed in febuxostat-treated patients in the phase 3 studies, which I have listed on this slide.

Now, as you have heard, the CARES study was a randomized, double-blind, cardiovascular outcome study conducted in the U.S. and Canada and Mexico, in hyperuricemic gout patients with major cardiovascular disease. Its primary endpoint was the composite of major adverse cardiovascular events or MACE. Secondary endpoints included
individual components of MACE and death from any cause.

The study was designed to accrue 624 MACE events for assessing the noninferiority of febuxostat to allopurinol with regard to cardiovascular risk, with 90 percent power to reject a hazard ratio risk margin greater than 1.3 for MACE, and a one-sided alpha level of 2.5 percent, assuming a true hazard ratio of 1.

Both doses of urate-lowering therapies were titrated to maximum doses of 80 milligrams once a day for febuxostat and 600 milligrams once a day for allopurinol, based on achieving a serum uric acid level less than 6 milligrams per deciliter and renal function.

Patients received either colchicine, naproxen, or prednisone for prophylactic gout therapy during the first 6 months. Because of study enrollment difficulties, a timeline extension was granted to the applicant to complete the study, which was completed in May of 2017.

As soon as primary results from the CARES
study were made available, the review division issued a Drug Safety Communication. The sponsor submitted the final study report to the agency approximately a year ago with proposed changes to the current cardiovascular warning, which are listed on this slide.

Additionally, the CARES study was published in the New England Journal of Medicine in March, and data from the study was presented at annual meetings for the American Academy of Cardiology and American College of Rheumatology. In June, the agency received a Citizen's petition to withdraw the drug from the market based on the findings from the CARES study.

The agency also issued an updated Drug Safety Communication in August of 2018 regarding the ongoing agency review of the CARES study, as well as plans to hold this AC meeting to discuss the results from the study and the Citizen's petition request to withdraw the drug from the market.

I will now hand over the podium to
Dr. Hsueh, who will discuss the FDA's statistical findings from the CARES study.

**FDA Presentation - Ya-Hui Hsueh**

**DR. HSUEH:** Good morning. I'm Ya-Hui Hsueh, statistical reviewer, from the Office of Biostatistics. I'm going to present our findings from the statistical assessment of cardiovascular safety in the CARES trial.

Here is the outline of my presentation. First, I will talk about the trial objective and the trial design, then I will go over the statistical methods and present the results of cardiovascular safety. Lastly, I will summarize our findings.

The primary objective of the trial was to rule out a hazard ratio of MACE greater than 1.3 associated with febuxostat relative to allopurinol. The prespecified analyses included 3 interim analyses and a final analysis. The trial met its primary objective at the third interim analysis with approximately 75 percent of the prespecified total events. However, the Data Monitoring
Committee recommended to continue the trial without modification until the final 624 events were achieved.

The results in this presentation are based on the final analysis, including all observed MACE events. All confidence intervals are presented at the nominal 95 percent level. The primary MACE endpoint was defined as the composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and unstable angina with urgent coronary revascularization.

The CARES trial was a multinational, randomized, double-blind, and active control cardiovascular outcome trial about patients with gout and cardiovascular comorbidities, meeting our enrollment criteria, and were randomly assigned one to one to treatment with 40 milligrams of febuxostat, 200 or 300 milligrams allopurinol, depending on their renal function status.

As you heard previously, patients treated with febuxostat could be titrated to 80 milligrams. Patients treated with allopurinol could be titrated...
up to 400 or 600 milligrams. The trial duration was MACE event driven.

The trial disposition and treatment exposure were similar between the two treatment arms. A total of 6,190 subjects were randomized, 3,098 randomized to febuxostat and 3,092 randomized to allopurinol.

In this trial, a subject was defined to have completed the trial if he was followed until the end of planned study visits. Approximately 55 percent of subjects completed the trial. The median follow-up time was about 2.6 years; the maximum follow-up time was approximately 7 years. About 60 percent of subjects had at least 2 years of follow-up. The median treatment exposure time was 2 years.

Subjects' vital status was similar between the two treatment arms. Of the 3,410 subjects who completed the trial, 13 percent of subjects died on study. For subjects who discontinued the trial, the applicant updated the vital status information based on public databases. Of the 2,780 subjects
who discontinued the trial, a total of 199 subjects were found to have died; 89 with febuxostat and 110 with allopurinol.

Please note our analysis in this presentation did not include this additional 199 deaths identified based on the public records, though a sensitivity analysis, including these additional deaths, can be found in the briefing package. A total of 821 subjects had unknown vital status after treatment discontinuation.

A summary of subject's baseline demographic and clinical characteristics is shown in this table. These baseline characteristics appeared well balanced between the two treatment arms. The mean age was 64.8 years; most subjects were male and white. Over half the subjects had diabetes at baseline. The majority of subjects had hypertension and hyperlipidemia at baseline. Approximately 53 percent of subjects had moderate renal impairment.

Now, I will go over the statistical methods for the trial.
The following cardiovascular endpoints were prespecified. The primary endpoint was the composite MACE endpoint, including 4 components. In this particular trial, we refer to it as MACE. However, note that in other programs, this may be referred to as MACE plus endpoint.

The secondary endpoints that are presented in this presentation were individual components of the primary MACE, the composite APTC event, all-cause death, and all-cause death during on treatment plus 30 days follow-up. All events included in this endpoint were prospectively adjudicated.

The analysis population included all randomized subjects exposed to at least one dose of randomized treatment and followed from the time of randomization to the last recorded study visit. We refer to it as on-study population.

The on-study analysis censoring scheme included all events which occurred during the course of the study in both on- and off-treatment periods. All endpoints are presented at the
two-sided 95 percent confidence interval. The prespecified statistical analysis was time to first event analysis. The analysis was based on Cox proportional hazards model with treatment as covariate and stratified by baseline renal function status.

In the next couple slides, I will present the results of the cardiovascular safety assessment.

This table shows the results of primary analysis of MACE on study. A total of 656 MACE events occurred during the trial; 335 events in the febuxostat arm and 321 events in the allopurinol arm. The estimate hazard ratio of MACE associated with febuxostat relative to allopurinol was 1.03 with a 95 percent confidence interval from 0.89 to 1.21. The upper bound of the 95 percent confidence interval ruled out the prespecified risk margin of 1.3.

This is the Kaplan-Meier plot of MACE comparing the two arms; febuxostat, a blue line; allopurinol a green dash line. The X-axis is time
to event in months up to 90 months. The Y-axis is
the observed percentage of subjects who experienced
the MACE, with a scale ranging from zero percent to
30 percent. The two curves show how the events
accumulate over time. The curves were close
throughout the trial and appear to separate
slightly after approximately month 54.

This table shows the observed number of MACE
and the corresponding incidence rate during and
after treatment discontinuation. There were 390
MACE observed on treatment and 266 MACE observed
after treatment discontinuation.

The overall incidence rates after treatment
discontinuation were 9.6 MACE per 100 person-years
for febuxostat and 8 MACE per 100 person-years for
allopurinol. This incidence rate after treatment
discontinuation were about 3 times as high as the
on-treatment MACE incidence rate, 2.6 for
febuxostat and 2.8 for allopurinol.

In order to further investigate the
differences in the rate of MACE during and after
treatment, we looked at the events during different
windows after treatment discontinuation. The highest incidence rate of MACE was observed within the 30-day window following treatment discontinuation.

We have seen a similar pattern in other cardiovascular outcome trials for other indications. A possible explanation for the high rate of events shortly after the treatment discontinuation is that some of the MACE that were recorded during this time may have been associated with the on-treatment adverse events that resulted in treatment discontinuation.

Note that among subjects who discontinued treatment and experienced a MACE within 60 days, we found that 81 percent discontinued treatment due to a pretreatment event or adverse event.

The table also shows while the incidence rate of MACE after on treatment plus 60 days still appears to be numerically higher, the observed incidence rates are more similar between the on treatment plus 30 or 60 days and the period after 60 days post-treatment discontinuation.
While the result of the primary MACE ruled out the prespecified margin, an increased risk of cardiovascular death associated with febuxostat was observed. A total of 234 CV deaths occurred during the course of the trial; 134 events were observed in the febuxostat arm and 100 events were observed in the allopurinol arm.

The estimated hazard ratio was 1.34 with an associated 95 percent confidence interval from 1.03 to 1.73, showing an increased risk of CV death associated with febuxostat.

The Kaplan-Meier plot of CV deaths comparing the two arms is shown in this slide, the febuxostat arm in blue line, the allopurinol in green dash line. This plot shows the imbalance between the two treatment arms appeared to increase after month 24 and continued throughout the trial. The cumulative probability of CV deaths appeared to be higher in the febuxostat arm.

This table shows the results of the secondary cardiovascular analysis. The result of APTC composite endpoint was consistent with the
result of the primary MACE, showing no differences between the two treatment arms. For all-cause death during on study, a total of 243 deaths were observed in the febuxostat arm and 199 deaths were observed in the allopurinol arm.

The estimated hazard ratio was 1.22 with an associated 95 percent confidence interval from 1.01 to 1.47, showing an increased risk of all-cause death associated with febuxostat. The imbalance between the two treatment arms was mainly due to CV deaths, 134 with febuxostat and 100 with allopurinol.

This table also summarized the analysis for all-cause deaths during on treatment plus 30 days follow-up. Fewer than 40 percent of deaths observed on study occurred during on treatment plus 30 days follow-up in both treatment arms. This analysis showed a similar estimated hazard ratio but not statistically significant evidence of increased risk of all-cause death associated with febuxostat.

As mentioned in the previous slide, a high
The proportion of deaths were observed after treatment discontinuation. For CV death, only 37 out of 234 deaths were observed on treatment.

Approximately 55 percent of CV deaths were observed either on treatment or within 60 days of treatment discontinuation. The remaining 45 percent of CV deaths were observed later than 60 days after treatment discontinuation. The timing of all-cause deaths was similar and is not shown on this slide.

We evaluated several subgroup analyses for the association between treatment and CV death. Shown here are only the subgroups that had a nominal significant statistical interaction with treatment on the risk of CV death. They are baseline use of NSAIDs, low-dose aspirin, and any dose of aspirin.

The proportion of subjects taking this medication at baseline was balanced between the two treatment arms. However, as shown in this plot, the estimated hazard ratio of CV death associated with febuxostat was higher among subjects who used NSAIDs at baseline than among non-users, subjects
who were not on low-dose aspirin at baseline than among low-dose aspirin users, and the subjects who did not take any dose of aspirin than among aspirin users.

Due to clinical interest, we also explored the subgroup of baseline renal function of MACE, CV death, and all-cause death. As shown here, we found no statistical interaction with treatment and the baseline renal function status on these endpoints.

I would like to summarize our findings from the statistical assessment of febuxostat in the CARES trial. The CARES trial was designed to rule out a hazard ratio margin of MACE greater than 1.3. The estimated hazard ratio of MACE associated with febuxostat was 1.03 with an associated 95 percent confidence interval from 0.89 to 1.21.

The upper bound of the 95 percent confidence interval successfully ruled out the risk margin. However, the data also showed evidence of increased risk of CV death associated with febuxostat.

Now Dr. Bradley will discuss the drug usage
FDA Presentation - Marie Bradley

DR. BRADLEY: Good morning. My name is Marie Bradley, and I'm an epidemiologist in the Division of Epidemiology II and the Office of Surveillance and Epidemiology. Today, I'm going to talk about the characteristics of febuxostat and allopurinol users in real-world settings and their utilization patterns.

I'm going to present a nationally estimated patient-level and prescription-level data to give a high-level overview of urate-lowering therapy utilization patterns in the U.S.

Next, I'm going to focus on more detailed analyses that we conducted in our Sentinel distributed database, examining the characteristics of febuxostat and allopurinol users, their utilization, and switching patterns.

First, on to the drug utilization from our nationally estimated prescription data, this figure shows the nationally estimated number of patients dispensed a prescription for febuxostat or
allopurinol from U.S. outpatient retail pharmacies from 2013 through 2017. As you can see, allopurinol was the most widely used ULT across this time period with over 3 million patients receiving a prescription in 2017.

This figure shows nationally estimated number of patients dispensed a prescription for either febuxostat or allopurinol by patient sex and age groups from U.S. outpatient retail pharmacies in the same period. Males and patients age 65 years-plus accounted for the largest amount of allopurinol and febuxostat use.

This is similar data by drug strength in the same period, 2013 to 2017, and what we found was that the most commonly dispensed strengths were allopurinol 300-milligram tablets and febuxostat 40-milligrams tablets.

I am going to move on to the analyses that we conducted in our Sentinel distributed database. As a bit of background as to why we conducted these analyses, the CARES trial included a select population of gout patients that was enriched for
CVD. This led to concerns about the generalizability of the CARES trial findings to gout patients in real-world settings. Therefore, we conducted analyses in our Sentinel distributed database to examine if patients in the CARES trial truly reflect gout patients in real-world settings, and also to examine utilization of ULTs in Sentinel.

This is just a little overview of the Sentinel system. Sentinel is a distributed network of data partners, and it comprises primarily commercial insurance claims data. Each data partner contributes medical encounter and pharmacy transaction data, which includes in-patient, outpatient diagnoses, procedure codes, and outpatient drug dispensing data.

Each data partner maintains operational control over their data, which is formatted into a common data model. Customized modular programs, which are compatible with this common data model, are used to run analyses on this distributed database.
We used data from the Sentinel distributed database from January 1, 2009 to September 30, 2016, and this included 17 health plans and over 122 million enrollees. We examined characteristics of the gout population in Sentinel, characteristics of initiators of febuxostat and allopurinol, as well as duration of use of these agents and switching patterns among initiators. We then compared the population of these initiators in Sentinel with those included in the CARES trial.

Now, on to our results. This table shows the characteristics of the gout population in Sentinel from 2009 to 2016. The mean age of the gout patients was 67 years. There were more males than females diagnosed, and allopurinol was the most commonly used ULT following a gout diagnosis, and febuxostat use appeared rare in comparison.

We further examined characteristics of febuxostat and allopurinol initiators, and what we found was that febuxostat initiators were slightly older than allopurinol initiators and had a higher proportion of females.
Additionally, we examined initiators by strength of the initiating agent. We examined those initiating febuxostat 40 milligrams, those initiating febuxostat 80, those initiating allopurinol 100 milligrams, and those initiating allopurinol 300 milligrams.

What we found was that the mean age of the new initiators of these ULTs were similar, ranging from 65 to 69 years. A higher proportion of allopurinol 300 and febuxostat 80-milligram initiators were male compared to febuxostat 40 and allopurinol 100.

Further, we examined cardiovascular disease history at baseline, gout severity at baseline, and chronic kidney disease in these febuxostat and allopurinol initiators. Baseline cardiovascular history was assessed in the 183-day period before these patients initiated the ULT prescription, and we used similar indicators to those that were applied in the CARES trial.

Baseline gout severity measures were ascertained from any point in enrollment in the
database 3 at the index prescription, and chronic
kidney disease was determined in the 183 days
prior.

As you can see, cardiovascular disease at
baseline was similar between both febuxostat and
allopurinol initiators. However, febuxostat users
tended to have more severe gout, which was
indicated by a higher proportion of gout flares, a
higher proportion of gouty arthritis, and a higher
proportion of tophi. Febuxostat users were also
more likely to have chronic kidney disease.

Next, we examined the duration of use among
febuxostat and allopurinol initiators, and we
basically calculated cumulative duration of use
across the study period and divided into the
duration categories that you can see here in the
table.

What you can see is that around 30 percent
of febuxostat and 22 percent of allopurinol
initiators continued use for just 1 to 3 months
within our study period. Very small proportions of
ULT initiators continued just beyond 5 years, and
allopurinol initiators tended to have longer median durations of use compared to febuxostat initiators.

We were also interested in switching patterns among these initiators. Basically, this analyses was once you got your index ULT prescription, if there was a further prescription within that exposure episode for a switch, it was documented here. That switch may have been to a different strength of the same agent or a totally different strength for a new agent.

What we found was that overall the proportion of new ULT users who had switched between ULTs during follow-up in our study was very low; generally, less than 10 percent. The largest proportion of new user switches occurred from allopurinol 100 milligrams to allopurinol 300 milligrams, and febuxostat 40 milligrams to febuxostat 80, which clearly represents some dose titration across follow-up.

We further examined the duration of use before the switch among initiators. The median time to switch was longer among switchers from
allopurinol to febuxostat than from people who switched from febuxostat to allopurinol. Again, approximately 40 percent of febuxostat users and 30 percent of allopurinol users tended to switch after just 1 to 3 months of use.

On to our discussion, what we did with the data that we obtained from our Sentinel analyses is that we compared both demographics and clinical characteristics among ULT initiators in Sentinel with the CARES trial population. Overall, we found that ULT users in the CARES trial tended to be younger than those in real-world settings. There tended to be more males than in real-world settings, and they also had higher prevalence of both cardiovascular disease and chronic kidney disease than we see among ULT initiators in real-world settings.

I'm just going to provide a summary now of our findings in Sentinel, which, of course, reflects what is happening in real-world settings. As I said, allopurinol was the most commonly used ULT, and the 100- milligram strength was the most
common strength for initiation. You may recall, in my earlier slides, when we looked at the nationally estimated data, that the 300 milligrams strength was most common, but that would tend to reflect prevalent use, and we examined initiators.

Febuxostat use was comparatively rare, and few ULT initiators continued long-term just beyond 5-plus years. I think this really confirms what we know about the poor levels of adherence in ULT users. The majority remained on the ULT, their chosen ULT, for 1 to 3 months only. Allopurinol users tended to have better adherence than febuxostat users overall.

In terms of switching, the proportion of new ULT users that switched during our study period was quite low. The largest proportion of switches, as I said, was from 100 milligrams to 300 milligrams of allopurinol, which again, likely reflects dose titration rather than switching. Most patients switched again after 1 to 3 months.

We really identified important differences in the characteristics of the ULT initiators in our
Sentinel distributed base, which, as I said, reflects what is happening in real-world settings. Compared to the population of the CARES trial, in real-world settings, the ULT initiators were older, less likely to have recent cardiovascular disease or chronic kidney disease. Adherence was poorer in real-world settings, and switching between ULTs was low. We believe that these differences need to be considered when interpreting the results of the CARES study.

Thank you. I'm going to pass over to my colleague, Rosemarie Neuner, to complete our presentations.

FDA Presentation - Rosemarie Neuner

DR. NEUNER: Thank you, Dr. Hsueh and Dr. Bradley.

I would now like to discuss the clinical considerations and risk-benefit assessment for febuxostat. To summarize, the results from the CARES study excluded a prespecified noninferiority margin for MACE but showed a significant increase in cardiovascular deaths in patients randomized to
febuxostat. The majority of these deaths occurred following discontinuation of study treatment. A clear cause for this finding was not identified, and as you have heard, the mechanism for this increased risk for cardiovascular death remains unclear.

Unlike the pivotal phase 3 studies conducted in support of febuxostat's marketing approval, the population of gout patients enrolled in the CARES study were at high risk for cardiovascular events, which raises questions regarding the generalizability of the study's findings to gout patients in real-world settings.

The applicant's marketing partner is currently conducting a second cardiovascular outcomes study, the FAST study, required by the EMA. The FAST study is a phase 4, prospective, randomized, open-label, blinded endpoint study, being conducted primarily in the UK and Denmark, in hyperuricemic patients with at least one other cardiovascular risk factor.

Like the CARES study, it is utilizing
treat-to-target dosing of both xanthine oxidase inhibitors. The primary endpoint is the composite of APTC events. Although this study has completed its enrollment with over 6100 subjects, key results from it won't be available until 2020.

Some of you may also be aware of the ongoing comparative effectiveness gout study being conducted by the VA comparing febuxostat versus allopurinol. Safety data collected from the study may contain additional data regarding the cardiovascular risks associated with febuxostat.

I would now like to turn my attention to febuxostat's benefit-risk assessment. On this slide, I have listed several benefits associated with the drug. Its efficacy as a urate-lowering therapy has already been demonstrated in pivotal phase 3 studies that compared 40- and 80- milligram once-a-day doses of febuxostat versus allopurinol, at doses of up to 300 milligrams once daily or placebo.

It can be used as an effective agent in treat-to-target dosing for the management of
hyperuricemic gout patients as recommended by the current treatment guidelines. No dose adjustment is necessary in patients with mild to moderate hepatic or renal impairment, although the dose is limited to 40 milligrams once a day in patients with severe renal impairment.

It is an alternative for patients unable to tolerate allopurinol. This may include the subgroup of patients positive for the HLA-B5801 genotype who are at risk for developing allopurinol hypersensitivity syndrome. Febuxostat has different drug-drug interaction considerations than allopurinol. Xanthine oxidase inhibitors are potent urate-lowering agents, and their administration is less problematic than other urate-lowering drugs.

Risks associated with the administration of febuxostat include serious skin reactions that can run the gamut from minor eruptions to Stevens-Johnson syndrome and life-threatening toxic epidermal necrolysis, as well as hepatic events, including hepatic failure and cardiovascular
events, including cardiovascular death.

I am re-showing this slide to provide additional context for the benefit-risk considerations as it pertains to the arena of approved therapies for gout, all of which have inherent toxicities.

In addition to an increased risk for renal stones, probenecid's efficacy is maximized when it used in patients with creatinine clearances greater than 50 mLs per minute or also able to maintain adequate hydration.

Lesinurad is associated with renal failure and stones, as well as its own cardiovascular risk, and also requires patients to be well hydrated.

Pegloticase must be administered via IV with monitoring in place for infusion reactions and anaphylaxis. It cannot be used in patients with a history of congestive heart failure.

Listed on this slide are factors that need to be taken into consideration during your discussions regarding recommendations for future regulatory actions to be taken by the FDA to
mitigate risk associated with febuxostat. As I reviewed, there are presently 6 approved urate-lowering therapies on the market, each with its own associated safety risks. However, two of these drugs, lesinurad and lesinurad allopurinol fixed-dose combination, will no longer be commercially available in this country as of February 1, 2019.

Febuxostat is the only alternative xanthine oxidase inhibitor for allopurinol. Xanthine oxidase inhibitors are the recommended first-line therapy for the management of chronic gout. In view of the limited number of urate-lowering therapies, there is an unmet medical need and face the growing gout epidemic in this country. It has been estimated that approximately 4 percent of the adult population in this country suffers from gout, making it the most common inflammatory arthritis including RA.

As Dr. Nikolov noted earlier, we would like you to discuss the following possible regulatory actions for this drug: strengthening the current
cardiovascular warning; adding a boxed warning for cardiovascular death; changing febuxostat's indication to make it second-line therapy; and the Citizen's Petition request to withdraw the drug from the market.

On behalf of the FDA's presenters, we would like to acknowledge our colleagues who put a lot of time and effort into the review of the CARES study in preparation for today's meeting. We would also like 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. SUAREZ-ALMAZOR: We will move now to the clarifying questions for the FDA. I'm planning to continue until 12:15, and that way, if we can, we will have some of the questions to the sponsor as well. Again, please identify yourself, and just take your sign and put it vertical so we know that you have a question.

Dr. Warholak?

DR. WARHOLAK: Yes. Thank you. One of the
things that I would have expected to see is a summary of the data from MedWatch on the medication. Do we have that? And if so, can we see it?

DR. SEYMOUR: We didn't show any information from MedWatch. For cardiovascular outcomes and cardiovascular death, postmarketing safety data is really not that informative, and we have the controlled clinical trial data that we're presenting today. So we didn't think it would really add much to the discussion, since that's not really a great resource for those types of events.

DR. SUAREZ-ALMAZOR: Dr. Felson?

DR. FELSON: My question was for the sponsor and not necessarily for the FDA. Do you want to hold it?

DR. SUAREZ-ALMAZOR: Yes, please.

Dr. Griffin.

DR. GRIFFIN: Yes, I also had a question for the sponsor.

DR. SUAREZ-ALMAZOR: Dr. Nissen?

DR. NISSEN: For the FDA statisticians, I
did my own tipping-point analysis, and what I calculate is that the noninferiority boundary of 1.3 would be exceeded if there were 28 additional events in the patients that were lost to follow-up, that we didn't have complete data on.

Can you verify for me whether you've done some tipping-point analyses and whether my numbers are correct; that out of the 2,000-plus missing patients, if 28 of them would have had an additional event in the febuxostat group, that that would render the trial no longer showing noninferiority?

DR. HSUEH: We don't have the tipping-point analysis for MACE. However, we do for the tipping-point analysis for the all-cause death. So I'm not able to verify your --

DR. NISSEN: Can you share anything on your own tipping-point analyses? I'm just eager to understand that. The reason I'm asking the question is when you have massive data loss in a trial, and the tipping-point analysis becomes critically important, it's less important when you
have 99 percent follow-up. We have only 55 percent follow-up, so what happens to those other people becomes critically important.

DR. HSUEH: I can only say for the all-cause deaths, we're using the observed incidence rate. On study, we do the tipping point to calculate. As you can see, the deaths observed on the study, we have 1.22 hazard ratio, and when we included those just based on the public records, the additional 199 deaths, the hazard ratio reduced to 1.09. But when we do the tipping point, we're just using based on the incidence rate on study, and we still find a consistent estimated hazard ratio with the on study.

DR. SUAREZ-ALMAZOR: Dr. Ruha?

DR. RUHA: Michelle Ruha. I'm just wondering, in patients who have taken allopurinol and have a true hypersensitivity syndrome, are there patients who have that history and have taken the febuxostat and done well? On the safety profile, DRESS is included, so I'm wondering if there's cross-reactivity.
DR. NEUNER: That's an excellent question, and I really don't have data or information to answer that because the original phase 3 studies were actively-controlled studies. So there was a risk that patients with a history of allopurinol hypersensitivity reactions could be randomized to the allopurinol arm, so they were excluded from the original study. So we don't have any data to answer your question.

DR. SUAREZ-ALMAZOR: Dr. Gibson?

DR. GIBSON: Yes. What's the FDA's perspective with respect to where cardiovascular death fits into the hierarchy of testing? You had your primary prespecified endpoint, which was a noninferiority endpoint; then you have 4 secondary endpoints. Is there a need to adjust for multiplicity of testing or not?

Then secondly, there was an interaction of aspirin and there was an interaction with non-steroidals, but those were single interaction terms. You have to wonder, though, is there a higher order interaction as well; second order
interaction, where the people not on aspirin, who were on a non-steroidal, had particularly high events.

DR. HSUEH: For the first one, we did not adjust for the multiplicity for the multiple endpoint.

DR. GIBSON: But the secondary endpoints, do you view them as --

DR. HSUEH: Hierarchy?

DR. GIBSON: -- hierarchical?

DR. HSUEH: No.

DR. GIBSON: Do you view them as exploratory? I mean, what do you view them as?

DR. HSUEH: Yes, we see as exploratory only.

DR. GIBSON: And second-order interaction testing with aspirin and non-steroidals, was that assessed?

DR. HSUEH: You mean for the interaction for the low dose of aspirin or the anti-dose?

DR. GIBSON: Either.

DR. HSUEH: Either one, the interaction is significant.
DR. GIBSON: The first order interaction, but the interaction between aspirin and non-steroidals with the endpoint, did you look at that?

DR. HSUEH: Yes, we do. Can I have the slide? Let's show the slide, 19.

You mean in each level, right? So for the low dose of aspirin, the user, yes, there is a difference -- oh, there is no significant in the low-dose aspirin user between the two treatment arms, but for the non-low-dose aspirin user, there's a significant difference between the two treatment arms.

DR. GIBSON: These are the first order interactions. The second order interaction would be the interaction of those drugs with each other with the endpoint, and that hasn't been tested.

DR. HSUEH: Yes.

DR. GIBSON: Okay.

DR. SUAREZ-ALMAZOR: Dr. McAdams?

DR. McADAMS-DEMARCO: Thank you. As we are being asked to consider to be using febuxostat as a
second-line therapy, I thought it would be useful
to know how many patients initiate febuxostat
without previously having tried allopurinol.

Do you have any information on that?

DR. BRADLEY: In our Sentinel analyses, the
febuxostat initiators were clean for allopurinol in
the 183 days, so they're washed out for any
allopurinol use in the 183 days before they
initiated it.

DR. McADAMS-DEMARCO: Yes, but that's not
the question, though. The question is how many
patients start febuxostat without ever having tried
allopurinol before? I don't know if you can answer
that with Sentinel, but I think that's a key piece
of information.

DR. BRADLEY: Yes. We just looked back
6 months before they initiated febuxostat. They
could have, potentially, used allopurinol outside
of that 6-month period.

DR. SUAREZ-ALMAZOR: Dr. Psaty?

DR. PSATY: Bruce Psaty. Can we look at
slide 14 from the statistical analysis? Continue
to the additional -- I'm a little concerned about the event rates. I use them as a way to judge the validity of a trial, and the after-treatment event rates are quite high.

The ones in 1 to 30 days, I'm wondering if they're really after treatment. What was described as someone has an event, they go into the hospital and the drug is stopped, that's not really an after-treatment event, so that may be misclassified.

Then we've got event rates that are at least twice off treatment compared with on treatment, and I don't think it's credible that the drug withdrawal of both drugs would double the event rates. I'm wondering if there are errors in the person-years and the censoring dates? And it really just brings up more questions about the validity of the trial, ones that Steve Nissen and others have raised, in the quality of the conduct of this trial.

DR. ANDRACA-CARRERA: If I may try to answer some of these questions. This is Eugenio Andraca.
I'm a statistical reviewer in the Office of Biostatistics.

As far as the 30-day window, you are correct that sometimes an event might be misclassified as off treatment, and that's the reason why most of our analysis on treatment include a window of 30 days or 60 days after treatment discontinuation, because the behavior that you described, we have seen in other cardiovascular outcomes trials, where a patient will have an adverse event, they will discontinue treatment, and shortly afterwards, they will experience a MACE. And it's not necessarily related to discontinuation but to the adverse event that led to treatment discontinuation.

DR. PSATY: But I'm looking at the rate of 6.6 and 5.8 after 31 days compared with the on-treatment rates of 2.6 and 2.8. I'm just wondering about the quality of the follow-up.

DR. ANDRACA-CARRERA: I cannot directly address the quality of the follow-up, but I think that a more fair comparison of on treatment and after treatment are the three last rows that are
highlighted in the box, because if you include the events that happened within the window shortly after treatment, that increases the rate to about 3.3 or 3.5, which we think is more representative of the rate of events on treatment.

Now, it is true that that still leaves a little bit of a difference between events after treatment and on treatment, and we cannot really explain that. We have so many hypotheses. People who discontinue treatment are not necessarily the same as people who enter the trial as randomized. People who discontinue treatment tend to be, on average, non-responders to drug, more likely to have experienced adverse events, and so on.

So it is not unusual to see differences in rates on treatment and after treatment, but this is just sort of a hypothesis. I cannot explain the total difference between those.

DR. CUSH: Isn't it possible that going off urate-lowering therapy -- I agree with your points about questioning this data, but it is also
possible going off urate-lowering therapy could
lead to a surge in mobilization of urate, and what
does that do, and does that have an immediate
effect of some sort that we don't really know
about?

DR. SUAREZ-ALMAZOR: No answer to that?
DR. ANDRACA-CARRERA: No further comments.
DR. SUAREZ-ALMAZOR: Okay. Just let me ask
you a question. Do you have the same slide for
cardiovascular deaths or just for MACE?

DR. ANDRACA-CARRERA: This slide?
DR. SUAREZ-ALMAZOR: Yes.
DR. ANDRACA-CARRERA: We don't have the
exact same slide, but Dr. Hsueh presented a slide
in which the time for cardiovascular death was
shown on treatment and within windows after
treatment. She presented this slide.

Dr. Hsueh, do you remember what slide number
it is?

DR. HSUEH: Slide 18, by the window of
the --

DR. ANDRACA-CARRERA: Slide 18. For
cardiovascular death alone, you see a similar
pattern, where within the first 30 days, shortly
after discontinuation, you have the highest number
of CV deaths.

DR. SUAREZ-ALMAZOR: Although this one
doesn't have person-years, so it's hard to compare
the rates.

DR. ANDRACA-CARRERA: Yes.

DR. SUAREZ-ALMAZOR: Okay. Dr. Nason?

DR. NASON: Thank you. I actually have two
questions. One of them is on Dr. Bradley's
presentation about the switching patterns; if you
don't mind, slide 17 from that. I was struck by
the fact -- and this was not something that you
highlighted. But I was struck by the fact that
there were many more, percentage-wise, people going
from febuxostat to allopurinol than vice versa,
whereas this had been presented to us as maybe an
alternative for people who had failed or could not
tolerate allopurinol.

So I was wondering -- I also noted that you
didn't point that out in this slide. I'm looking
at the second row and then the last row, the 9.7 versus 2.7. I was wondering if there was a reason not -- like if I'm being misguided to look at that because maybe people switched off it at the time when the CARES study results came out and there was a warning, or something that would qualify that, because that surprised me to see so much switching going the direction I wasn't expecting, having come in here thinking of this as something was being offered, largely, to patients who couldn't tolerate allopurinol.

I do have one more question, which is somewhat different. So if you don't mind, if there's an answer to that, can I keep my mic after?

DR. BRADLEY: The thing is we don't have the reasons for switching, so --

DR. NASON: But you have the calendar time. It wasn't like there was a big burst right around the time when a -- maybe you didn't look at that.

DR. BRADLEY: These switches, basically, the patient would have initiated febuxostat and then switched to allopurinol within that exposure
episode, but that exposure episode could be a number of prescriptions that don't have big gaps.

DR. NASON: Okay.

DR. BRADLEY: It's between 2009 and 2016, but we don't have that data to hand right now.

DR. NASON: Okay. The other question that I just want to ask, which is really both to the sponsor and the FDA in the sense that it's an inconsistency I can't reconcile.

This was not in the slides, but in the document we got from the FDA, there was a statement about the protocol containing the following withdrawal criteria; that is once the subject had experienced a CV event that was positively adjudicated as MACE, that patient was no longer followed up by the study site.

It lists that a CV event that was positively adjudicated as MACE would lead to withdrawal of the subject, and I think the sponsor said the opposite this morning. So I just wanted somebody to clarify for me because those seemed to be contradictory, whether somebody was, indeed, withdrawn from the
study if they'd had one of the non-fatal MACE events.

DR. SEYMOUR: I think we would defer that to the sponsor since they conducted the study and they can tell us what they actually did.

DR. SUAREZ-ALMAZOR: Do you have an answer now or you need to look for that?

MS. KNAPP: Dr. Castillo will address that. Thank you.

DR. CASTILLO: Majin Castillo, Takeda. You are correct. It is in the protocol. The protocols will say it's at the study personnel. The sponsor would notify the sites. My time, we never notified the sites to withdraw the patients from the trial because they had a MACE, so there are some subjects who had a MACE who continued in the trial.

DR. NASON: Just to make sure I understand, it was in the protocol but not necessarily implemented that way.

DR. CASTILLO: Correct.

DR. NASON: It kind of could go either way in practice.
DR. CASTILLO: Correct, yes.

DR. NASON: Okay.

DR. SUAREZ-ALMAZOR: Dr. Kulldorff?

DR. KULLDORFF: Thank you. In the background material, you don't -- not only [indiscernible] a percent hazard ratio but also the numbers needed to harm, and that's very informative. I think that's very helpful to understand what is the clinical importance of the findings.

For the cardiovascular death, the 1.34 hazard ratio corresponds to 278 person-years to see one additional death in the study design. Do you have a confidence interval for that 278?

DR. HSUEH: You mean for the number needed to harm?

DR. KULLDORFF: Yes.

DR. HSUEH: I don't have here. I don't have here. I'm sorry.

DR. KULLDORFF: Okay.

DR. SUAREZ-ALMAZOR: Dr. Liang, we have you in the list; do you still have a question now?
DR. LIANG: [Audible - off mic]. It's been answered already.

DR. SUAREZ-ALMAZOR: Dr. Curtis?

DR. CURTIS: I have two questions. One of them is as the CARES trial was being designed, I was curious about discussions about whether low-dose or any dose aspirin should be required. It felt like this was a high enough CVD risk population that might warrant that for secondary prevention, and yet more than a third of people in the study were not on it. And I guess that gets to Steve's question about should they have been if there's really an interaction?

The second question relates to Martha's question about the switching. I wanted to confirm, in the Sentinel analysis first, that fee for service Medicare patients weren't there since I think that's an important demographic when we think about generalizability. The second is just to inform the switching, because my perception is that it's exactly as we understood; that people are mostly starting with allopurinol first and
switching to febuxostat. But if you make people
naive to everything for 6 months and you don't let
the naive to switcher people in that analysis, then
you'll skew your results.

In fact, I think we see that in the
Zhang et al. paper that looked at Medicare, where
about a third of people who started febuxostat had
been on allopurinol in the prior year, and
0.4 percent, so less than 1 percent, of the reverse
was true, meaning lots of people who were on
allopurinol went to febuxostat, but almost nobody
did the reverse; and yet, it didn't feel like
that's what we saw from Sentinel.

DR. BRADLEY: To answer your first question,
CMS Medicare was included, and we now have that as
a data partner in Sentinel. It was one of our 17
data partners, so we had a good range of ages, not
just lower than 65; so we had that.

Can you repeat your second question?

DR. CURTIS: Sure. The issue about the
switching, if you have 6 months naive to
everything, then if someone starts allopurinol and
then subsequently switches to febuxostat, you'll see that, but in fact, you will miss the people that are starting febuxostat that had been previously on allopurinol when you're talking about the new users of febuxostat.

So essentially, a prevalent allopurinol user starting febuxostat, is that reflected in how you did the switching? Because it seems quite at odds with the Zhang et al. paper that found a lot of people starting febuxostat had been on allopurinol, but the reverse was never found.

DR. BRADLEY: The Zhang et al. paper, I think, washed out for one year, and we only washed out for 6 months.

DR. CURTIS: But they didn't wash out for a year. They looked a year back and said what were you on?

DR. BRADLEY: That's what I mean, so they looked back a year. In Sentinel, there is sometimes -- that was Medicare, and people tend to turnover less. In Sentinel, often people turnover a lot and we might lose a lot of people if we
actually look back a year compared to 6 months, so that was the reason that we chose that. But you're completely right, that someone could have been on allopurinol outside the 6 months, switched to febuxostat, and then switched back to allopurinol, potentially, for adverse events or something like that.

DR. CURTIS: But someone who had been on allopurinol and then switched to febuxostat wouldn't have been in your febuxostat cohort, because they weren't naïve to everything for 6 months?

DR. BRADLEY: So --

DR. CURTIS: You excluded them if they had previously been on allopurinol in the prior 6 months and started febuxostat.

DR. BRADLEY: Yes.

DR. CURTIS: Okay.

DR. BRADLEY: Yes. It would be, yes. They'd have to be naïve in the 6 months, but yes.

DR. CURTIS: So all the people who were using second line, as I think many of us might have
intuited its use, would have been excluded from that analysis, in the febuxostat cohort.

DR. BRADLEY: Yes. Absolutely, yes.

DR. CURTIS: Okay. Then the other question about the aspirin use as a potential requirement for the CARES trial, you may not be the right person to answer that.

DR. BRADLEY: No, I think someone else can answer.

DR. NEUNER: In the review of the concomitant medications, it's noted that low-dose salicylates were permitted, but I don't recall if the sponsor required, as part of the entry requirements, that all patients, because this was a high-risk population, be on aspirin. It was meant to be an actual-use trial, so maybe the sponsor could answer that question.

DR. SUAREZ-ALMAZOR: Sponsor?

DR. KNAPP: Dr. Castillo?

DR. CASTILLO: Majin Castillo, Takeda. The question was whether there was a requirement to be on aspirin to be in the trial?
DR. CURTIS: Well, maybe more why it wasn't a requirement perhaps.

DR. CASTILLO: That was not one of the inclusion criteria where a patient had to be on aspirin. That was left to the normal care of the patient under their physician.

DR. SUAREZ-ALMAZOR: Dr. Griffin, do you still have a question?

DR. GRIFFIN: Yes. I'd like to clarify with the FDA, maybe Dr. Neuner, about why the postmarketing study was required, because we got a little bit different feel from the sponsor's presentation and your presentation. From your presentation, my understanding is it was required because of a signal of all-cause mortality and cardiovascular death.

DR. NEUNER: I think there was considerable uneasiness within the FDA at that time because this was at the same time that we were discussing or grappling with the cardiovascular risk associated with NSAIDs, that there were concerns related to what had been seen on the first two review cycles.
with this drug, and then we had a large phase 3 study come in that showed the opposite, or suggested the opposite, that febuxostat actually had a lower cardiovascular risk.

That is why, due to those safety concerns or persistent safety concerns, the people who were -- the review team in charge of this application decided to request the postmarketing required study, and at the same time FDAAA had just been introduced and we had the ability to ask for it.

DR. NIKOLOV: This is Dr. Nikolov. Just to add to what Dr. Neuner mentioned, I think there were additional considerations about the benefit-risk assessment during the initial review cycle, and that pertains to the efficacy of febuxostat, which was originally established based on the surrogate endpoint rather than the clinical endpoints.

Again, we acknowledge that serum uric acid has been accepted. It was even discussed at an advisory committee as a clinical endpoint, although
a surrogate of a clinical benefit. But the
clinical program has demonstrated efficacy on serum
uric acid without additional data to show direct
clinical benefits. That was additional
consideration, in addition to the concern about
cardiovascular safety.

DR. GRIFFIN: I guess I just wanted to
clarify that I think the original signal was
all-cause mortality and cardiovascular death in the
extended studies, which aren't in all the tables.
But it was the EXCEL and FOCUS, I think, where
those deaths occurred.

So I just think it's noteworthy that the
signal we're seeing from this study is also
all-cause mortality and cardiovascular death.

DR. SUAREZ-ALMAZOR: Dr. Nissen?

DR. NISSEN: Yes. I'd like to get the
perspective from the FDA statisticians about the
likelihood of informative censoring, and let me
tell you the context of the question. We see these
very different event rates on treatment and off
treatment, and I want to know whether you agree
with me that that's a very strong signal, that there's the potential here for a high degree of informative censoring. That's the elephant in the room here, obviously, when you have a trial where 45 percent of the patients are not continued throughout the follow-up period.

What are your thoughts about this?

DR. ANDRACA-CARRERA: Eugenio Andraca, Office of Biostatistics. We looked at the characteristics that were measured among people who discontinued, and they were comparable in both treatment arms. There are, of course, the possibility of unmeasured characteristics being different. But in everything that we could measure, we didn't see a difference that would lead us to believe that one arm was discontinued differently.

Also, the reasons for discontinuation were similar. The proportion of people who discontinued both treatment and the study due to adverse events, voluntary withdrawal, and so on, were similar between treatment arms. That doesn't mean that
there's not a high rate of discontinuation; you're right about that. But as far as we could measure, we couldn't see anything that would be a smoking gun that there was any difference between the two treatment arms.

DR. NISSEN: I guess what I'm getting at here is that when you see, after people go off study drug, these very high rates of events, then you would believe -- in most cardiovascular trials, it means something bad was going on with those patients prior to their discontinuing study drug, and they are therefore different from the patients that stay in the study.

My concern here is that this may create a very large degree of bias, and it's going to be bias that's going to go toward the null hypothesis. So my worry here is that there's a signal here in the fact that the event rates are so high when you go off study drug, that these are the sickest people that were enrolled.

DR. ANDRACA-CARRERA: I don't have any comments about that. We don't have any information
with MACE on people who discontinue study. We have
some information about mortality that the sponsor
collected based on public records, but we do not
have any information on MACE after they
discontinued the study.

DR. NISSEN: By definition, you can't, but
the MACE rates -- I mean the CV death rate's pretty
high.

DR. SUAREZ-ALMAZOR: Dr. Gibson?

DR. GIBSON: Yes. I'm still confused for
MACE, not for death, but for MACE, if a MACE event
causd someone to discontinue drug or did
discontinuation of the drug cause the MACE event.
In other trials, we know the exact military time of
drug discontinuation and whether that followed or
preceded the MACE event, particularly when we're
looking at bleeding and thrombotic events.

So is there granularity in the data to know
whether the drug discontinuation happened before
these MACE events or not? Then my question for the
epidemiologist is, is there any epidemiologic data
that substantiates these very high event rates
after discontinuation of these drugs in the real world?

DR. ANDRACA-CARRERA: This is, again, Eugenio Andraca from the Office of Biostatistics. Within the first 30-day window after treatment discontinuation, this is not unusual for this cardiovascular outcomes trial. We have seen a similar pattern in other cardiovascular outcomes trials, and that's why we considered these different windows.

It is not unusual for somebody to go to the hospital with an adverse event, to be discontinued from treatment, and then to have an adjudicated MACE within a window of 7 days.

DR. GIBSON: But again, do we know if the MACE event happened or was ongoing before drug discontinuation or did drug discontinuation precede the MACE event? Is there granularity in the database to know what?

DR. ANDRACA-CARRERA: For those subjects, it's hard to tell. You have an adverse event that is not adjudicated as MACE, but it could be a
precursor of MACE on treatment; then you have the
date of treatment discontinuation; and then you
have the date for the adjudicated MACE.

So you have all those dates, but you might
have to look at those reports.

DR. GIBSON: But beyond dates, do you have
military time on a date of drug discontinuation,
whether it preceded the military time of the event?

DR. ANDRACA-CARRERA: That, maybe the
sponsor can talk about how those dates are captured
in your data set and the possibility to have some
miscoding.

DR. GIBSON: Yes, because we deal a lot with
this with bleeding, the exact time of the bleed,
and the exact time the drug was discontinued.

DR. SUAREZ-ALMAZOR: Okay. Maybe the
sponsor can clarify afterwards, when you get time
after the public hearing. We're going to give some
time for the sponsor to clarify.

Dr. McAdams? And please remember we'll have
time for discussion, so just limit the time to
questions now.
DR. McADAMS-DEMARCO: Thank you. I'd like
to address this question to the statistical
review -- sorry, Mara McAdams-DeMarco -- and again,
the sponsor can comment on this later.

This study population was not treatment
naïve; 56 percent of the study population had a
previous exposure to allopurinol, so then by
design, the patients who were enrolled in this
trial had to have survived up until the time of
enrollment.

To me, it almost wasn't surprising to see an
association with cardiovascular death, given that
you had the selected population that gets enrolled
to the trial, who has been previously exposed to
allopurinol, at a differential rate to that of
febuxostat.

So my question to the statistical reviewer
and then eventually to the sponsor, is whether
anyone has looked at the effect measure
modification or the interaction between previous
exposure to allopurinol and their treatment
assigned group, to see whether or not there's an
interaction between previous allopurinol exposure
and the current exposure on the outcome.

DR. HSUEH: I don't have that analysis down.

Perhaps the sponsor has done that.

DR. McADAMS-DEMARCO: Thank you.

DR. SUAREZ-ALMAZOR: Dr. Ranganath?

DR. RANGANATH: I may have missed this, but
do we have any data -- we know that high levels of
uric acid can contribute to cardiovascular risk.
Is there any data on trials, where patients have a
cardiovascular risk factor and they've been
randomized to febuxostat versus placebo, looked at
MACE outcomes; whether the FDA has any of that
data?

DR. HSUEH: For the CARES, there's no
placebo arm over there, so I don't.

DR. RANGANATH: From prior studies that have
been analyzed?

DR. NIKOLOV: This is Nikolay Nikolov. I
think we may defer this question to the sponsor, if
they have any additional information.

DR. SUAREZ-ALMAZOR: I had a quick question.
Have you done any analysis according to the dose of either allopurinol and febuxostat and whether there were any differences?

DR. HSUEH: Yes.

DR. SUAREZ-ALMAZOR: Because it seems to me that for the pivotal trials and also perhaps here, the dose of allopurinol was comparatively lower to what the dose of febuxostat was.

DR. HSUEH: Can I have slide 13 up? Sorry, 26. This was the CV death rate by the baseline renal function and the final dose. As you can see, the CV death is higher in the subjects with moderate renal impairment in each dose and in both treatment arms.

As you can see, for the febuxostat, if you titrate to 80 milligrams, the CV death rate is higher. The same to the allopurinol, if you titrate up to 400 milligrams, the CV death rate is higher. But we would not say this is a dose response because the dose titrated is based on the serum uric acid level and has not randomized the dose.
DR. SUAREZ-ALMAZOR: Okay. Thank you.

We have about 7 minutes, so we will go back to the questions to the sponsor. We may not be able to complete all six questions or all six panel members questions, but the first one that we had in the list was Dr. Griffin.

Do you still have a question for the sponsor?

DR. GRIFFIN: Well, maybe Dr. White could just comment on his slide CS-6, which shows the previous data and really doesn't indicate much of a signal. Again, I'm wanting to know what was the signal, and why didn't we see the results of the EXCEL and the FOCUS extensions in your analyses?

DR. KNAPP: Your CS-6 that you asked Dr. White to present this, this was the pooled analysis with CONFIRMS, APEX, and FACT, the randomized controlled trials. The two trials that you referred to are the long-term extension studies that were open label and did not have real good control on those, so that was something that we did not include but was part of the discussion with
FDA. But what this shows here is what is in our label.

DR. GRIFFIN: So that was not part of the consideration for requirement for the postmarketing study?

DR. KNAPP: I would turn that back to the FDA because that was really their decision.

DR. NIKOLOV: Yes, it was a consideration. That was the main reason we required the postmarketing study.

DR. SUAREZ-ALMAZOR: Dr. Meisel?

DR. MEISEL: Thank you. Steve Meisel. I want to go back to the patients who stopped taking the drug. About 60 percent of the people who came into the study were on something -- 55 or so percent were on allopurinol, another 4 or 5 percent were on Uloric -- yet 57 percent of the people discontinued.

It's a chronic condition, and they were on it before, and then they just stopped the drug early on in the course. When I look at the data, 22 percent voluntary withdrawal, but it doesn't say
why, 10 percent says other, and that's not defined. I heard Dr. White say, well, a lot of these people went back to their primary doctors and got prescriptions, but if that's the case, then they were taking drug.

I need more clarity. I just don't understand, in a study of this magnitude, how such a large portion of people just quit the study.

DR. KNAPP: Yes. I will have Dr. Carroll come up and address your comments, and I think it also relates to some questions that we've been hearing around the panel this morning.

DR. CARROLL: Dr. Carroll, statistician. There's obviously an issue here, I think, in relation to an understandable concern about patients who weren't completely followed up. I think there's been a couple of comments that are confusing patients stopping taking randomized therapy and the ascertainment of the primary endpoint, which are not the same thing. So I'll try and deal with this briefly because I think it's helpful to try and get this straight.
If we look at this slide, which I showed earlier, the real question we're dealing with is what fraction of subjects were not ascertained for the primary endpoint? That's different than patients who stop taking drug because they can still be followed.

What you see, what you have to look at, is the last row on this table, where there were, in fact, approximately 30 percent of patients in whom there was follow-up, and the average of that follow-up was 1.7 years.

So it wasn't as if we didn't have any data. And that data was included in the analyses you've seen presented by Dr. White, but they didn't have a closeout visit, so we didn't know at the point of closeout, whether they might have had a MACE event between when they stopped coming in for visits and the closeout visit.

It's actually 30 percent of patients, which is still a large number -- and I'm not trying to downplay that -- but it's not 45 and it's not 50. There's 30 percent of subjects who had some
follow-up but didn't have total follow-up.

Now, the critical question then is -- before I move to that, this degree of patients without ascertainment of the event is clearly not favorable in the sense that you want to have full follow-up. Anybody who says they don't, you would question them. But it's not unique. There have been recent trials where there has been this lack of ascertainment. I, myself, was involved in a trial in 18,000 patients in acute coronary syndromes, where about 1800 patients did not have full ascertainment.

So the question at that time, and then right now for CARES, is to what extent -- and I think Dr. Nissen raised this -- could the lack of ascertainment in this fraction of patients undermine the primary endpoint results. For that --

DR. MEISEL: I'm sorry. Could I just interrupt? Because you're not really getting to my question. My question is 57 percent of people quit taking the drug. Why? I mean, this is a chronic
condition. Most of the people who came into the study were on it. I've never heard of a 57 percent fallout rate from the therapy in a major clinical trial. Why? Why did they stop taking the drug?

DR. CARROLL: If I may, I'm going to hand that to Dr. White. One thing to remember, this is a unique trial. Nothing like this has ever been done in gout. You haven't really got a yardstick to know what you would expect in a gout population, I think. It is unique. And I'm sure Dr. White will address your question, if that's okay.

But the really critical issue is, is this a so-called failed trial? Can we interpret the results? And I think -- and the FDA, I think, concluded similarly in their review, and they can correct me if I'm wrong -- it is not a failed trial. The issue here is you do have patients who weren't fully followed up, so then the question is, to what extent could they have undermined the results? I'll do that quickly, because I think that's on the next slide.

Of those 30 percent who didn't have full
ascertainment, you can look and see how much time was missing. You can then compute the number of events you would expect to be missing, so you compute that.

This is a tipping-point analysis. Of those patients who didn't have events, didn't have full follow-up, you can compute that about 6.5 percent of the 30 percent, from the previous slide, would probably -- based on all the data we have, would likely have had an event if they had full follow-up.

So then you say, what if I plug those back in, those additional events that we've missed, what would they have to look like to undermine the primary endpoint and you'd lose noninferiority? The risk ratio amongst these events that you might have missed, you have to have an increased risk of 65 percent, and that is approximately 22 times higher than the excess risk you see in the analysis with the hazard ratio of 1.03.

The question then is, what is the likelihood, in these missed events, that you'd have
a 22-fold higher increase in risk? And both the sponsor and the FDA went carefully and compared those and you had full follow-up and those who had partial follow-up, looked at the baseline characteristics, the disease characteristics, the characteristics in terms of CV risk, and there was absolutely no difference.

So there's no plausible way that you're going to get an excess risk amongst those in whom you might have had an event but you didn't get it; that's going to be that degree higher. There's no data to support that, whatsoever.

So I think the NI result is, despite the unfortunate fraction of patients in whom we only had partial follow-up, is not something that we can't rely on because we can compute what would have happened and what happens if we plug them in, and then we can ask about the plausibility.

So I think that's kind of important. The last comment I will make on this is you can do the same thing for vital status. Remember, because of this fraction of patients in whom follow-up wasn't
complete, the sponsor initiated a follow-up for
d vital status, in which we got vital status in
87 percent of the population, and that gives a
hazard ratio of 1.09. I think we may have that.
Let me see if I can put that up.

DR. SUAREZ-ALMAZOR: Very briefly, because
we're running out of time.

DR. MEISEL: I'm sorry. Can you actually
answer the question? What you're getting at here
is, despite all that fall off, the data is valid
anyway. That wasn't the question.

The specific question that I'd like an
answer to -- if you can forget the, don't worry
about that, it's still valid -- why did 57 percent
of people leave the study? And I'm seeing
22 percent is voluntary with no explanation;
10 percent says other, with no detail. I want to
know those details, and I'm trying to ask the
question as to what really happened here.

If you can be that granular, I'd really
appreciate that. And please leave the analysis of
this is valid anyway; that's not my question.
DR. CARROLL: No, I understand, and Dr. White will address your question in about 20 seconds, and I'll just finish this. It's important, and I won't go through the detail for vital status.

We can do the same exercise in vital status; 13 percent didn't have vital status ascertained. The characteristics, they're identical. The FDA did it; Takeda did it. There's no suggestion that you're going to have more deaths in those that would bias. You can do the same calculation, and there you need, again, a huge relative risk in those patients who you didn't have a vital status to undermine the overall result for vital status.

I just need somebody, and Billy's going to come. I think it is not correct to characterize the study as a failed study. We definitely didn't have complete ascertainment. That, of course, is an issue. Nobody's not taking that seriously. That was examined very carefully in terms of exactly what would it take to destroy the results. You have to have really crazy results in those
patients in whom we didn't have full follow-up to undermine the results that you've already seen in CARES.

So I think it's important to realize that you can have confidence, at least in MACE, and vital status in CARES, and now I'll hand it over to Billy.

DR. SUAREZ-ALMAZOR: Okay. I think we're going to break now for lunch because we've already --

DR. WHITE: I can answer it in 5 seconds.

DR. CUSH: So, the answer would be --

DR. SUAREZ-ALMAZOR: Ten seconds.

DR. WHITE: Thank you. Two things in response to this question. Like the patients with osteoarthritis, rheumatoid arthritis, in PRECISION, the CARES study had a large dropout from drug. I think it was higher in PRECISION.

These are two studies that have never been done before with a population that has pain. So when the patients came into the trial and got a gout flare, they left the study. They didn't want
to be on a drug that caused a gout flare. If there was a perception of lack of efficacy by the investigator or the patient, they would leave the drug and leave the study. If they had any perception that they weren't being taken good care of, they would do the same thing.

I've been doing these kind of clinical trials for 35-37 years, and all you have to do is have an argument with somebody and the patient's going to leave the study.

This particular patient population is a very difficult one. They have a lot of other problems. There's a lot of alcoholism. There's a lot of obesity. There's a lot of other cardiovascular disease, and they're ornery. They're unhappy. They're in pain all the time from their disease.

So the first thing they're going to do when they get a gout attack is say, this doctor's not doing something good for me, I'm leaving the study.

So I think that that's part of -- we didn't know this was going to happen. No one would have predicted that half the patients in the trial were
going to discontinue study drug, but at least we could say one thing, and that it was equal in each treatment group.

DR. SUAREZ-ALMAZOR: Okay. I think that we need to stop now this discussion and just take the lunch. I realize there are several of you that still have questions to the sponsor, so we'll do that after the public hearing. The sponsor will have 10 minutes after the public hearing, as well, to answer some of the questions from before.

So, once again, please come back at 1:15, and take any personal belongings with you, and just remember that we are not supposed to be discussing this topic among ourselves.

(Whereupon, at 12:21 p.m., a lunch recess was taken.)
AFTERNOON SESSION
(1:14 p.m.)

Open Public Hearing

DR. LEWIS: 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 committees 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 committees 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 the committees place great importance in the open public hearing process. The insights and comments provided can help the agency and these committees 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.

Speaker number 1, please step to the podium and introduce yourself. State your name and any organization you're representing, for the record.

DR. BARAF: I am Dr. Herbert Baraf. I'm a rheumatologist in this area, and let me start my
comments this way and will give you what potential conflicts there may be.

Good afternoon. I appreciate the opportunity to address the panel and FDA officials in this open public hearing. I have reviewed the briefing documents provided by the FDA and by Takeda, and I appreciate the careful, thoughtful work that has gone into the preparation for this meeting by all of the parties.

If my comments are, in any way, redundant, and they likely will be, of what has been said this morning, I apologize in advance. I'm a private practice rheumatologist and have worked full-time the past 41 years caring for patients. I am the managing partner of Arthritis and Rheumatism Associates, a 21-member rheumatology group, in the D.C. area, and I have served as a principal or subinvestigator for over 400 clinical trials, including about two dozen focused on gout therapeutics.

I have also authored or co-authored numerous peer-reviewed gout publications. I have
participated in trials for Takeda, Savient, Ardea, Horizon, and Selecta Biosciences, among others, and I have consulted with most of these companies.

I was a principal investigator for the CARES study. I was also an investigator for the three, phase 3 febuxostat trials earlier today. I attended the FDA advisory committee meeting in 2008 that led to the mandate for Takeda to further evaluate the cardiovascular concerns that arose from the FACT and APEX trials.

I actively manage many patients with gout, and I am often called by colleagues in neighboring practices and around the country to assist in the management of difficult-to-treat gout patients. Thus, I come to this meeting with a depth of clinical experience as a practitioner and investigator with the matters at hand today.

Gout is a major health concern. The widely cited 8.3 million number of Americans suffering from gout we heard this morning has been updated to in excess of 9 million over the last 11 years. The economic impact of undertreated gout on the patient
and their family, and on society, and the negative effects on quality of life, and disability, are significant.

Control of hyperuricemia in patients with gout has a disease-modifying effect, and disability from gout with appropriate management is entirely preventable. So I believe it is critical to be able to treat hyperuricemia effectively, and febuxostat is an extremely important therapeutic option.

The findings in the CARES study give those of us who manage gout pause, and it is correct for us to consider the meaning of the findings and their implications for managing hyperuricemia in gout patients. Yet, there is abundant evidence that hyperuricemia is a risk factor associated with or causal of multiple chronic metabolic diseases, which are, in turn, risk factors for cardiovascular and renal morbidity.

For example, Choi and Ford's observational study, discussed in the briefing documents, revealed a linear relationship between serum urate
levels and prevalence of the metabolic syndrome, indicating that a serum uric acid of greater than 10 milligrams per deciliter conferred an almost four-fold likelihood of prevalent metabolic syndrome than a serum urate level of 6.

In looking at the results of the CARES trial, can we conclude that febuxostat is more dangerous than allopurinol or simply less likely to confer cardiovascular benefit? My review of the CARES study leaves me with many questions, many of which were addressed this morning.

From the vantage point of the clinician, there are few treat options to manage hyperuricemia. To review, these options fall into two categories, diet and drugs. The practical management of hyperuricemia in patients with gout should always include a discussion of diet. However, though time honored control of a patient's hyperuricemia solely with a low purine diet, in my opinion, is a fool's errand. At best, a patient compliant with a low purine diet is able to lower their serum uric acid little more than a point; not
enough to reach the therapeutic target of less than 6 milligrams per deciliter in most patients.

There are three classes of drugs discussed earlier today, and I'll review them from my perspective: uricosurics, xanthine oxidase inhibitors, and enzyme-based therapies.

Uricosuric drugs can be effective, but only in patients with normal renal function and without a history of nephrolithiasis. Of the three agents of this class approved in the United States, sulfinpyrazone is no longer available, and we learned this morning that lesinurad is coming off the market next month.

Probenecid is the sole uricosuric drug available as a monotherapy. Proper initiation of treatment with probenecid and dose titration requires the alkalization of the urine and an increase in fluid intake to achieve a target serum uric acid value. These requirements and the BID or TI dosing of probenecid presents challenges to compliance, and it is not surprising that fewer than 2 percent of prescriptions for uric acid
lowering therapy, in the United States, are for probenecid.

Xanthine oxidase inhibitors are the second class of drugs, the class we are discussing today. Allopurinol has been the cornerstone treatment of hyperuricemia for more than 45 years. Until febuxostat was approved, allopurinol was the only available agent of this class, and patients with an allergy to allopurinol or other adverse experiences in the pre-febuxostat era had poor treatment options, and none if their renal function was diminished.

Further, since the mid-1970s, physicians were acutely aware of the risks of severe allergic reactions to allopurinol. Allopurinol is one of the few drugs that has a syndrome named after its unique, albeit rare, toxicity, the allopurinol hypersensitivity syndrome or AHS. AHS includes the Stevens-Johnson syndrome and toxic epidermal necrolysis.

In response to increasing alarm about these severe adverse events, two changes impacting the
management of hyperuricemia occurred beginning in
the mid-1980s. First, in a 1984 paper published in
the American Journal of Medicine, Hahn recommended
dose reduction at initiation of allopurinol
treatment in patients with renal insufficiency
because lower doses of allopurinol at the outset of
treatment were believed to be less immunogenic.
Hahn's paper resulted in the habitual underdosing
of allopurinol, resulting in less satisfactory
outcomes in the management of hyperuricemia that
continues to the present.

Second, the serum urate was removed from the
SMA-12, a multichannel chemistry panel, the
forerunner of the CMP. This removal was intended
to reduce the treatment of asymptomatic
hyperuricemia with allopurinol, thus lowering the
incidence of severe hypersensitivity reactions.
But as an unintended consequence, the removal of
the serum urate from the panel has led to the under
diagnosis and under treatment of gout in the
primary care setting.

When febuxostat was approved by the FDA in
2009, we at last had a therapeutic option for allopurinol-intolerant patients. Is febuxostat more effective than allopurinol? I don't think so. Properly dosed, they're both effective. Outside of today's question of cardiovascular safety and the rare AHS events, the safety profile of these two drugs is pretty comparable.

The third class of drug management of hyperuricemia is enzymatic therapy. Pegloticase was approved in late 2010, indicated for patients with gout, refractory to or intolerant of xanthine oxidase inhibitors.

I was actively involved in this drug's development as a clinical investigator. The patients studied in the phase 2 and phase 3 trials had severe manifestations of gout. This severity was a function of the lack of a therapeutic alternative to allopurinol at the time of the trials.

Pegloticase is a 2-week IV therapy and is not a long-term alternative for gout management. Though very effective, it is not tolerated by all
patients, and only about half of patients achieve a sustained response. It is extremely expensive. Even in responders, there will come a time in all patients when it should be stopped, and an alternative treatment instituted to maintain urate control. At the point, if the patient is intolerant of allopurinol, what will that treatment be?

To illustrate what the allopurinol refractory patient looked like in the era before febuxostat and to drive home the importance of having febuxostat as a therapeutic option, I would like to show you images of three patients, each of whom was either intolerant of or not responsive to allopurinol.

In each of these patients, severe tophaceous disease had developed as a result of uncontrolled hyperuricemia, and in each, the serum uric acid was controlled with pegloticase. This control resulted in relatively rapid resolution of tophi.

This gentleman had this photograph taken after 6 months of placebo in the phase 3
pegloticase trials. This is what his right hand looked like at the end of 6 months of treatment. If you look at his index and his ring fingers, you'll see a marked reduction in the size of tophi. This is his left hand; look at his thumb and his middle finger.

This is the second patient. The first patient I treated with pegloticase after the drug was approved. This patient was insensitive to allopurinol. These were his hands 5 months apart with treatment intervening, and these were his feet. My infusion nurse was so excited when he came in 2 months later wearing shoes for the first time in 7 years.

This patient, a cardiologist from Baltimore, intolerant of allopurinol, presented this way in January of 2012. After a period of 7 or 8 months of treatment, his hands looked like this, and 4 years later, like this. Most of that time on febuxostat therapy. Because febuxostat was available by 2009, once functional, clinical, and therapeutic targets were reached with pegloticase,
it could be stopped and febuxostat initiated.

   In each of these patients, control of serum
uric acid and sustained suppression of clinical
manifestations of gout were achieved with
febuxostat, with an enduring response, like this
fellow.

   I asked to speak at this hearing to make a
request. For the panel advising the agency and for
the agency to be mindful of the importance of
febuxostat as a therapy for gout, the lack of
certainty about the meaning of the findings in the
CARES study should be apparent to everyone here.

   There will continue to be patients for whom
febuxostat is the only viable option for treating
their gout. Many patients have been successfully
treated with febuxostat for many years. I would
not want the continuity of their care disrupted,
and I want physicians and patients who need gout to
be treated, to be comfortable with febuxostat as an
option when it is the best option and not be unduly
frightened by an overstatement of the findings
we're discussing today.
What actions would I like you to take?

There's no question the findings from the CARES trial should be incorporated in thefebuxostat label. These findings should appear in the warning and precautions, and the adverse reactions sections. Wording that overstates the meaning of the CARES trial would be unfortunate. CARES leaves us with more questions, I'm afraid, than answers.

Patients who need febuxostat will pay the price for overly aggressive labeling. Trials in progress should inform the issue of febuxostat cardiovascular safety.

The conservative recommendation that I favor is both rational and justified by the benefit-risk ratio of febuxostat. To compromise use of this agent on the basis of the current information may well compromise its later use if and when the CARES findings are not supported. Please help those of us who care for patients keep their options open.

Thank you for your attention.

DR. SUAREZ-ALMAZOR: Will speaker number 2 please come to the podium and introduce yourself?
DR. SUAREZ-ALMAZOR: Will speaker number 3 step up to the podium and introduce yourself?

(No response.)

DR. SUAREZ-ALMAZOR: Will speaker number 4 please come up to the podium and introduce yourself? Please state your name and any organization you are representing.

DR. CAROME: Good afternoon. I'm Dr. Michael Carome, director of Public Citizen's Health Research Group. Public Citizen and I have no conflicts of interest.

On June 21, 2018, Public Citizen petitioned the FDA to immediately require the removal from the market all medications containing febuxostat, because, one, the drug increases the risk of death compared with alternative therapy, and there exists other effective medications that are approved by the FDA and have not been shown to have this risk. We urge the committee to recommend that the FDA grant our petition.

Serious concerns about increased risks of
adverse cardiovascular events and death predated
the approval of febuxostat and resulted in the
agency issuing complete response letters to the
first two NDA submissions. The sponsor submitted
the initial NDA in 2004, seeking approval of 80-
and 120-milligram doses of febuxostat tablets
dosed daily for treatment of hyperuricemia
associated with gout.

The company requested priority review, but
that request was rejected because of insufficient
evidence of the superiority of febuxostat to
existing therapy and the existence of a reasonably
effective uric acid lowering treatment currently on
the market.

The initial NDA included efficacy and safety
data from a 28-day, dose-response, phase 2 trial
and its long-term extension trial, FOCUS, and the
phase 3 FACT and APEX trials, and their long-term
extension trial, EXCEL.

FACT was a double-blind, randomized trial
comparing febuxostat at doses of 80 or
120 milligrams with allopurinol at a dose of
300 milligrams once daily for 52 weeks in 760 subjects with gout and hyperuricemia.

APEX was a double-blind, randomized trial comparing febuxostat at doses of 80, 120, or 240 milligrams with allopurinol at doses of 300 or 100, depending upon renal function, and with placebo once daily for 28 weeks in more than 1,000 subjects with gout and hyperuricemia.

The primary endpoint of both trials was a surrogate marker, a serum uric acid level below 6 milligrams per deciliter at each of the three follow-up monthly measurements.

In their assessment of the initial NDA, FDA reviewers noted that 8 deaths had occurred in the febuxostat group subjects in the phase 2 and 3 trials and the long-term, EXCEL extension trial, including 2 deaths due to myocardial infarction, whereas no deaths occurred in the allopurinol and placebo comparator groups. Most of the deaths occurred after 170 days of febuxostat exposure.

FDA reviewers also expressed significant concern about an excess of serious adverse
cardiovascular events in febuxostat subjects, based on data shown in this table here. For example, in the ischemic coronary artery disease category, there were 17 such events in febuxostat subjects, 2 in allopurinol, and zero in placebo.

In terms of efficacy, FDA reviewers concluded that there was substantial evidence of efficacy to support the sponsor's proposed indication for the drug. However, the FDA reviewers noted that no trial had presented evidence of a reduction in gout flares, one of the most important clinical endpoints in gout treatment for febuxostat compared with allopurinol or placebo.

The lead FDA clinical reviewer concluded at the time that the risk-benefit analysis is not favorable for febuxostat. The FDA decided not to approve the NDA for febuxostat, and in October 2005 issued a complete response letter, primarily because the application raised concerns regarding the potential for febuxostat to cause clinically significant cardiovascular adverse events in excess
seen with allopurinol or placebo, even when exposure over time is factored into the analysis.

In February 2006, the sponsor resubmitted the NDA for approval of 80 and 120-milligram once-daily febuxostat for the same indication. The resubmission included a re-analysis of the prior clinical trial data, augmented by new safety data from the then ongoing long-term extension clinical trials, FOCUS and EXCEL.

FDA reviewer's analysis of the updated clinical safety data continued to raise concerns that febuxostat increased the risk of all-cause mortality, cardiovascular mortality, and serious adverse cardiovascular events, compared with exposure to allopurinol or placebo.

Overall, there had been 4 deaths in the randomized, controlled trials, and 8 deaths in long-term extension studies among febuxostat-exposed subjects, compared with zero deaths among allopurinol and placebo group subjects. Nine of the 12 deaths among febuxostat exposed subjects were attributable to
cardiovascular causes, including 5 related to MI.

In a reanalysis of safety data categorizing adverse events according to the APTC primary event and secondary event criteria, FDA reviewers noted a numerical excess of investigator-reported primary and secondary APTC events in febuxostat-exposed subjects.

In the phase 3 randomized FACT and APEX trials, 0.9 percent of febuxostat-exposed subjects had an investigator reported treatment-emergent primary APTC, and only 0.2 percent of allopurinol-exposed subjects had such events.

The director of the Division of Anesthesia, Analgesia, and Rheumatology Products made the following comment in his summary review during the second cycle.

"This complete response does not adequately address the cardiovascular safety concerns noted during the first review cycle for the application. I am convinced by the review team's assessment that a clear signal of risk remains even in the most cautious analysis."
"The apparent increase in cardiovascular thromboembolic adverse events in febuxostat-exposed subject population results in my continued concern that the risk associated with this product may outweigh the benefits. This is especially a concern for a product where the approval would be based on a surrogate uric acid reduction, not a clinical outcome assessment.

"To approve a drug on such a surrogate, when an unresolved signal of potential serious adverse cardiovascular effects is outstanding, does not appear warranted."

Therefore, the FDA, again, appropriately denied approval of febuxostat and issued a second complete response letter in August 2006 that required further data to clarify the cardiovascular risks of the proposed doses and to provide data on the safety and efficacy of lower doses of febuxostat in order to ensure that a dose level with favorable risk-benefit characteristics had been defined.

In June 2008, the sponsor resubmitted the
NDA for febuxostat. In response to the FDA's ongoing concerns regarding cardiovascular safety, the sponsor undertook the CONFIRMS trial, a double-blind, randomized trial that compared febuxostat at 40 or 80 milligrams with allopurinol dosed over 6 months in subjects with gout and hyperuricemia.

The primary endpoint for the trial was a serum uric acid at concentration below 6 at the final study visit. The trial involved more than 2,200 subjects.

Results of the CONFIRMS trial showed that febuxostat 40 milligrams was noninferior to allopurinol in achieving the primary endpoint, whereas febuxostat 80 milligrams daily was superior to both febuxostat 40 and allopurinol. However, the trial did not show any statistically significant difference in the proportion of subjects who experienced gout flares between the three groups during the study.

In terms of safety, there were 2 deaths among febuxostat-exposed subjects and 3 among
allopurinol-exposed subjects. Three subjects in the febuxostat 80- milligram group and 3 in the allopurinol group experienced adjudicated APTC events, whereas none occurred in the 40- milligram febuxostat group.

Although the CONFIRMS trial did not find the same safety signal for adverse cardiovascular events associated with febuxostat exposure compared with allopurinol exposure that had been seen in the earlier randomized trials, FDA reviewers noted that the upper bound of the 95 percent confidence intervals for relative risk of APTC events for febuxostat at 40 and 80 milligrams compared with allopurinol was 2.7 and 4.9, respectively, which indicated that the trial could not exclude an increased risk of adverse cardiovascular events with the drug.

Importantly, FDA reviewers concluded that the small number of adverse cardiovascular events in the CONFIRMS trial made, quote, "any results fragile and conclusion speculative at best" end quote. Multiple FDA reviewers noted that questions
and uncertainty remain about the cardiovascular safety of febuxostat, based on the available data from the premarket trials.

In February 2009, the FDA approved febuxostat for the chronic management of hyperuricemia in patients with gout. However, the FDA required that the sponsor perform a large, randomized, controlled, postmarket trial to determine whether the use of febuxostat is associated with a moderate increase in the risk of serious adverse cardiovascular outcomes, as compared to allopurinol.

Notably, approval of febuxostat might not have occurred without the ability of the FDA to mandate postmarketing clinical trials under the authority granted by the Food and Drug Administration Amendments Act of 2007, FDAAA, a provision that took effect in March 2008.

Indeed, in his summary review, the director of the FDA's Office of Drug Evaluation II, stated that, "Had we not had the authority given under FDAAA, which gives me some confidence that we can..."
dictate a study that we can get a definitive answer, my conclusion on whether to approve or not may have been different."

Likewise, because of concerns about cardiovascular safety, some members of the Arthritis Advisory Committee were only willing to recommend approval due to the recent passage of FDAAA, which provides the agency with regulatory authority to require studies and to implement strict timelines for completion.

The CARES trial was a double-blind, randomized, multicenter trial, comparing once daily febuxostat with once daily allopurinol. Doses of both medications were titrated based on a goal serum uric acid level less than 6 and based on renal function.

From April 2010 through May 2017, the CARES trial investigators enrolled 6,190 subjects who had major cardiovascular disease before randomization, gout, and hyperuricemia. Patients with severe renal impairment were excluded from the study. The primary composite endpoint of the trial was the
first occurrence of cardiovascular death, non-fatal stroke, non-fatal MI, or urgent revascularization for unstable angina.

The secondary safety endpoints included a composite of cardiovascular death, non-fatal MI, or non-fatal stroke, as well as the individual components of the primary endpoint, and death from any cause was one of several additional prespecified safety endpoints.

The mean duration of follow-up was 968 days for febuxostat-exposed subjects and 942 days for allopurinol-exposed subjects. Premature discontinuation of study medications was high in both febuxostat group subjects and allopurinol subjects, more than 50 percent, and the percentage of subjects who did not complete all trial visits was 45 percent for both groups.

Importantly, such factors would be expected to bias towards the null hypothesis, underestimating the potential risks of febuxostat use.

There was no significant difference in the
composite primary cardiovascular endpoint, hazard ratio 1.03, as shown in this table that you've seen before, and this Kaplan-Meier curve, also seen before. However, there were statistically significant differences in all-cause mortality and cardiovascular mortality between the two groups as shown in table 25 and figures 6 and 7 from the FDA briefing document.

During the trial, 243 or 7.8 percent of 3,098 subjects in the febuxostat group died, and 199 or 6.4 percent of 3,092 subjects in the allopurinol group died, which corresponds to a hazard ratio for all-cause mortality of 1.22 with a 95 percent confidence interval of 1.01 to 1.47 and a p-value of 0.04.

This difference in all-cause mortality was driven primarily by differences in cardiovascular death. There were 134 cardiovascular deaths in the febuxostat group, or 4.3 percent of subjects, compared with 100 such deaths in the allopurinol group, 3.2 percent of subjects, which corresponded to a hazard ratio for cardiovascular mortality of
1.34 with a confidence interval 1.03 to 1.73 and a p-value of 0.03.

The most common cause of cardiovascular mortality was sudden cardiac death, which occurred in 83 febuxostat-treated subjects, 2.7 percent, and 56 allopurinol-treated subjects, 1.8 percent. The majority of the deaths, 63 percent, did occur more than 30 days after discontinuation of the trial drug. However, the trends towards excess cardiovascular and all-cause death in febuxostat group subjects was seen when data were analyzed in each of the following overlapping time frames: during drug exposure, during drug exposure or within 30 days of discontinuation of the trial drug, and total duration of follow-up.

The FDA statistical reviewer also conducted a series of analyses of cardiovascular death and all-cause death by various time windows, after discontinuation of the study drug, shown in table 28 of the FDA briefing document, and it's shown here.

Notably, the point estimates for all hazard
ratios are in the same direction and indicate that the finding of an increased risk of cardiovascular death with febuxostat, compared with allopurinol, is robust.

In addition, a sensitivity analysis by final dose of treatment drug showed a higher rate of MACE, cardiovascular death, and all-cause death, in subjects whose final daily dose of febuxostat was 80 milligrams compared with those with the final dose of 40 milligrams, shown here, which is consistent with a possible dose-related toxicity.

Thus, the data from the CARES trial provide the strongest evidence to date, confirming the earlier concerns that treatment with febuxostat carries an excess risk of fatal cardiovascular events.

There's also a lack of clinically meaningful benefit with febuxostat compared to other gout therapy, in particular allopurinol. There is no convincing evidence that febuxostat is more effective than allopurinol to prevent clinically relevant outcomes.
As discussed previously, all phase 3 clinical trials in the febuxostat clinical program were designed to demonstrate febuxostat's ability to lower serum uric acid levels. However, the premarket trials and the large postmarket study found no advantage with use of febuxostat over allopurinol for preventing gout flares, and some trials showed an increased risk of gout flares with febuxostat-exposed subjects compared with allopurinol-exposed subjects.

There also is no evidence from the randomized clinical trials that use of febuxostat at 40 or 80 milligrams dosed daily results in faster resolution of tophi than use of allopurinol. A Cochrane Library systemic [sic - systematic] review article published in 2012 concluded there was no significant difference in effectiveness between the two drugs.

Finally, the most striking finding in the FDA's analysis of allopurinol and febuxostat utilization between 2009 and 2016 -- where the proportion of new users of allopurinol who switched
to febuxostat, which was only 2.7 percent, whereas the proportion of new users of febuxostat who switched to allopurinol was 9.7 percent.

In summary, there is substantial evidence that the serious cardiovascular harms of febuxostat outweigh the clinical benefits. Febuxostat, therefore should be immediately removed from the U.S. market to avoid preventable serious harm to patients.

Although initial clinical trials strongly suggested an increased cardiovascular risk with febuxostat and appropriately caused the FDA to repeatedly deny approval of the NDAs for this medication, a later phase 3 randomized clinical trial of inadequate duration and power unfortunately provided temporary false hope that perhaps febuxostat was safe.

The result of the FDA mandated postmarket trial provides additional strong evidence of a causal link between treatment of febuxostat and increased risk of all-cause death and cardiovascular deaths, which must be presumed to be
a real finding. The FDA almost certainly would have denied approval of febuxostat if data from this trial had been available at the time of the third NDA submission.

   Consistent with the precautionary principle of public health, Public Citizen strongly urges the committee to recommend that the FDA grant our petition and remove febuxostat from the market. Thank you for your attention, and I'd be happy to answer any questions you have about our petition.

   DR. SUAREZ-ALMAZOR: The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. The sponsor had requested additional time to cover some of the questions from this morning, so you will have 10 minutes. Please no more than 10 minutes. After that, we'll continue with the clarifying questions that we were not able to go through this morning, and then we will go into the discussion.

   DR. KNAPP: Thank you very much. Yes, there are three things we wanted to cover that were asked
earlier this morning. The first was some clarifying questions around our phase 3 data and what led to the CVOT. Second was around the event rates post-discontinuation, so we'll walk through that, as well as prior urate-lowering therapy use and what we saw with the data from CARES for those patients who had been treated with prior urate-lowering.

For all three of those points, I'd like to ask Dr. White to come and address that for the committee. Thank you.

DR. WHITE: Thank you very much for the time to clarify some of these issues. The first question I know came a couple of times, the slide that I showed about the phase 3 program and the concern about the imbalance in APTC events from the phase 3 program from the FDA slide.

What I thought would be important to do is to -- well, you remember that I showed that there was 14 primary MACE in the phase 3 program in the randomized trials. To complement that, I want to show you a slide that I actually showed 10 years
ago at the FDA advisory committee meeting on the long-term extension study.

If you recall, patients who came into the two trials, FACT and APEX, could spill over into a trial known as EXCEL, and then there was a small phase 2 study that could go into FOCUS, but that was a much smaller N.

The way this was done, in order for you to understand this enormous imbalance in person-years on febuxostat versus allopurinol, was at the end of those 2 trials, patients were randomized and still for the investigators blinded to treatment, 3 to 1 febuxostat to allopurinol into the extension.

Subsequently, the investigators had the ability, based on efficacy, based on urate-lowering efficacy, to switch either from allopurinol to febuxostat or febuxostat to allopurinol. And there was about a 10-fold more likely chance that patients were switched from allopurinol to febuxostat.

So by the end of this period of 3 years in the EXCEL extension and 5 years in the FOCUS
extension, there was 15 and a half times more person-years on febuxostat than there was on allopurinol; 26/61 versus 172 on the top part of the slide there. So the number of events has to be characterized by this very large difference in the number of subjects exposed for all those years and the person-years.

The cardiovascular deaths were 7 versus zero, which doesn't sound good, but you've got to keep in mind that there was a lot more people treated with febuxostat. I presented these data 10 years ago at the ADCOM, and this was, of course, a source of concern. I'm not saying that it wasn't, but it was certainly not the same as the findings in the randomized trial, in which the events were prospectively adjudicated and so forth.

The one other thing I might mention is that there's some, I think, disagreement about these cardiovascular deaths. I personally looked at all of them and all their narratives, and two were definitely due to myocardial infarction, but then there were 2 that were due to bleeding, and there
was a couple that were due to respiratory failure and sepsis; so we very conservatively call these cardiovascular deaths.

I hope that, in part, addresses some of the discrepancy between what I showed in the core presentation today and then the long-term extension data, which is not randomized anymore or blinded.

The second slide, SS-4, there was a lot of questions about why are there more events in this trial off study drug than on drug. Of course, I think the thing that I found interesting was why there are so few events on drug. That partly is due to the fact that was a discontinuation of study drug in many patients earlier rather than later, although we do have about 40 percent of the patients on drug until the end of the study.

We also have an analysis here that looks at on drug plus 30, 60, 120, and 180 days. I know the FDA did a similar analysis on plus 30 and plus 60, but as you look at those 2 groups under the red line, you note that there was 2 percent versus 1.3 percent with on drug plus 30, and then as you
go down, the number of events accrue.

There's also a narrowing of the confidence intervals around the hazard ratio because now there's more power and greater events. But the absolute risk difference becomes somewhat smaller as time goes on, but the trend is really not terribly different. The hazard ratio at the end, after 6 months off drug, is still 1.24, but now the lower boundary is lower and it's no longer statistically significant.

I'm not sure that we can say that going off drug increases hazard; all I can say is that the longer we watch people in the trial, the more events we're accruing, and that's one of the phenomena that happened in this particular study.

Finally, for the question of if you were pre-disposed to events, if you had not been on a urate-lowering therapy or you were, we have this only for cardiovascular death. But for those patients who came into the study with a history of being on a urate-lowering drug, which was 56 percent allopurinol or 4 percent febuxostat
versus not being on an agent at all, which was about 33 to 34 percent of the cohort, the hazard ratio for cardiovascular death was similar for both of those two subgroups, and there was no heterogeneity for the interaction p-value.

That's all I was going to show. If there's any other questions, I'd be happy to address them, if I can, or one of other members of the panel.

Clarifying Questions (continued)

DR. SUAREZ-ALMAZOR: Okay. We will go on to the clarifying questions. Dr. Felson?

DR. FELSON: Thanks, Maria.

Dr. Felson here. I have a question for the sponsor. The main signal seems to be in cardiovascular death and not in overall MACE events and not in cardiovascular events that don't lead to death. I think someone earlier tried to gain insights into that by asking about plaque rupture, and I think Dr. White earlier in his presentation implied that they were concerned about arrhythmia as being a source of that potential difference.

So the question is why does this drug
potentially lead to an accelerated risk of death
due to cardiovascular disease but not to
cardiovascular events, per se, that don't lead to
death? And one explanation -- and I'm not a
cardiologist, so for the cardiologists here, please
correct me -- is that this is leading to fatal
arrhythmias, somehow, acute fatal arrhythmias.

In that context, I wanted to ask whether the
company had done Holter monitors on anybody, had
data on previous arrhythmias in patients in the
CARES trial or those on antiarrhythmic therapy, and
whether there was more or less signal in those
patients.

I want to also just make a comment on how
would one explain an increment in risk that seems
consistent during treatment, and for a little while
after treatment, in febuxostat, yet the rates for
both febuxostat and allopurinol-related events go
up as treatment is discontinued.

It seems to me that there's a reasonable
explanation that's dual. One is that lowering uric
acid substantially actually lowers the risk of
cardiovascular death, which, frankly, is consistent with current literature, and that when you stop lowering uric acid, the risk of cardiovascular events and death goes up. But in the context of that effect, febuxostat is more dangerous than allopurinol is.

So that would explain all of the data we're looking at now. I don't know that all of that's true, but it would, at least, come up with an explanation that makes sense, given the data we're seeing.

But let me go back to the sponsor question, which is you gave us a lot of strata-specific risk estimates before by non-steroidals, by aspirin use. Do you have a strata-specific estimate for those in the CARES study who had a history of arrhythmias, or do you have something like Holter monitor data on any of them, or do you have data on any who were actually on antiarrhythmics to try to determine whether arrhythmia is a concern here?

DR. KNAPP: I’ll ask Dr. White to come and try to address your questions as best he can.
DR. WHITE: If we could please bring up my second subgroup analysis slide on cardiovascular death from the core presentation. I just want to show you one thing that sort of helps that or sort of relates to that.

We do not have patients stratified or, excuse me, analyzed according to arrhythmia per se, but we do have heart failure. Most people who have heart failure and have poor left ventricular function end up dying from arrhythmias, particularly ventricular arrhythmias. As soon as their ejection fractions are 40 percent or less, they are at high risk for that.

In a way, that group, yes or no having heart failure, are somewhat of a surrogate for people at risk for arrhythmias, and we didn't find heterogeneity for those with a history or those without a history of heart failure.

We did not actually have a subgroup specifically for people with arrhythmias. Most of those arrhythmias would have been atrial arrhythmias, not ventricular arrhythmias anyway,
coming into the study, and to my knowledge, there wasn't a specific dedicated Holter arrhythmia study done with febuxostat because the QTc study was so benign-looking with 300 milligrams of the drug.

Thank you.

DR. SUAREZ-ALMAZOR: Dr. Scher on the phone?

DR. SCHER: Yes, thank you. Can you hear me well?

DR. SUAREZ-ALMAZOR: Yes.

DR. SCHER: Okay. More people essentially have been raising concerns about the high attrition rate for the CARES study, the way in which it can actually affect the validity of the conclusions.

Something that perhaps has not been discussed and may be of relevance is the fact that when you breakout the proportion of patients who failed to complete their study visit, and you do it by country in which the study was conducted, you find that, on average -- and this may be relevant again.

This is from the supplementary table on the publicly available New England Journal of Medicine.
Participants in the United States failed completion in about 41 percent of the cases. If we compare that to the other major place, which was Mexico in this case, the failure of completion is about 12 percent.

So they seem to be, in my eyes, completely different studies in terms of follow-up. My question to the sponsor is what was the discrepancy these attrition rates attributed to? Number two, was there any subgroup analysis performed comparing both primary points and specifically cardiovascular death by geographic area or even study sites?

DR. KNAPP: I'll ask Dr. White to come to the podium. I will say it's a little hard to hear you. He may have to clarify a few things.

DR. SCHER: Okay.

DR. WHITE: I apologize. I think one of the questions might have been differential findings according to country of randomization. Was that correct or not?

DR. SCHER: That's correct. Yes.

DR. WHITE: All right. I have one slide on
that, which we actually published in the supplemental appendix of the paper, demonstrating that the bulk of patients were clearly in the United States. Much smaller numbers were in the other two North American countries. Overall, the rates of cardiovascular death were higher in the United States than they were in Canada and Mexico. In fact, there was no difference for Canada and Mexico. But again, the event rates were really tiny for those two countries.

The other thing I believe I heard you asking was whether or not there was a differential dropout or discontinuation from the study by the country of origin. Is that also correct? Was that another --


DR. WHITE: Yes. Here we have those data from discontinuation by country. The only finding there was it looked like there was a slightly higher rate of discontinuation in patients in Canada on the febuxostat arm versus allopurinol. But again, this is based on only 7 patients in the
trial, so I didn't really make a huge amount of
that. I thought that the discontinuation was
pretty consistent among the 3 countries in the
trial.

That's the two things I heard. Was there
anything else?

DR. SCHER: No, but I [inaudible - audio
feedback].

DR. WHITE: Okay. There was a very loud
feedback.

DR. SCHER: My apologies. I'm insisting on
the point that there seems to be a significant
discontinuation rate difference between the United
States and Mexico, for instance.

DR. WHITE: Yes, that's correct. It's a
much bigger sample, but it's also a larger
discontinuation in the U.S. versus Mexico.

DR. SUAREZ-ALMAZOR: Dr. Horonjeff?

DR. SCHER: Could that --

DR. SUAREZ-ALMAZOR: Oh, yes. Dr. Scher?

DR. SCHER: Thank you. I just wanted to ask
that question. I appreciate it.
DR. HORONJEFF: Thank you. Jen Horonjeff, and I'm here as the consumer representative. I want to dig in a little bit more to talk about some of the other benefits that we haven't really talked about. I know that the primary and secondary endpoints are looking at cardiovascular risks. But I am curious if the sponsor has any data on any quality-of-life or PRO measures that you had looked at to see how we might weigh that out.

I appreciated Dr. Edwards, in his presentation, mentioning even just the impact and the burden of the steps that one would take to reach the correct therapeutic dose. I'm trying to understand, again, what other factors the patient may be taking into account.

DR. KNAPP: No, we did not do that in the CARES trial.

DR. HORONJEFF: How about in any of the other trials?

DR. KNAPP: No, we didn't.

DR. SUAREZ-ALMAZOR: Mr. Weiner?

MR. WEINER: Thank you. Gene Weiner,
patient representative. In the information
provided prior to the meeting by the FDA, I seem to
recall a section mentioning the initiation of the
tests in Spain and that there was a higher
incidence of CV death, and that it was not
included.

Can someone explain what happened, or what
the result was, or what the result would be if it
had been pursued further? Thank you.

DR. KNAPP: Can I ask you to repeat? It was
hard for me to hear you. Were you talking about
the study from Spain? Is that what you were asking
about? Okay. There was a study in the literature
on Spain, if you may recall, so I'm going to ask
Dr. Gunawardhana to address that for you.

DR. GUNAWARDHANA: Lhanoo Gunawardhana,
Takeda. To clarify, this is from our briefing
document. This was a small cohort study in one of
the hospitals in Spain. This is from an abstract
presented at the ACR meeting, so the information is
still limited.

In that study, they saw a higher rate of
events with febuxostat compared to allopurinol. But we do not -- they mentioned that they have matched the patients, but one of the things that has happened since the launch of febuxostat, all around the world, is that patients who were not able to be on allopurinol due to, for example, their renal impairment or the comorbid conditions, or other non-tolerance, et cetera, were put on febuxostat.

So basically, those who were on worse conditions got put on febuxostat, so one of the possibilities that we have to look at when we get all the details in that type of a study is whether febuxostat-treated patients were worse off coming into that study. I cannot answer that question right now. Thank you.

DR. SUAREZ-ALMAZOR: Dr. Cush?

DR. CUSH: My question is for Dr. White. I want you to do an explanation, once again, for something I think went a little too fast for me, about the importance -- CS-32. You flashed up the NSAID and ASA associated increased odds. CS-32 is
the slide. Thank you.

You flashed up those, and you explained it
in a way that I didn't get it. I think that we're
left in the audience thinking, and the panel
thinking, that this is an important factor in maybe
predicting some of these outcomes. Do you have
another alternative explanation?

Then I want you to answer the question for
me, where we do have an increased hazard ratio, is
that to be interpreted as an increased risk
associated with febuxostat or that febuxostat is
not as protective as allopurinol, or does it make a
difference to you?

DR. WHITE: Well, I'll do the first one
first because the other one I don't really -- and
no one has an answer for it. It's really the huge
question about all of this between two xanthine
oxidase inhibitors. But let me try and explain and
give some more detail on these two subgroups.

These two findings, for NSAID use and the
lack of low-dose aspirin use, are at baseline. So
if somebody came into the trial on an NSAID versus
not on an NSAID, these were the findings, 2.17
versus 1.13 and a significant interaction.  
Similarly, they came in on low-dose aspirin versus
did not. If they did, their hazard was 1.99 versus
0.85, and that was a significant value.

If we look first at NSAIDs, more closely,
these are the risk ratios for NSAIDs if you were at
baseline, which I just showed you, or if you
continued to use NSAIDs during the double-blind
period. So part of that could have been
prophylaxis, but actually most people took
colchicine for prophylaxis. Very small percentages
took naproxen, which was the recommended NSAID, in
case there was a flare.

So you look at this, and you might think,
well, if I see there's only people coming in at
baseline, maybe that's a somewhat different group,
but as far as a drug-drug interaction, it didn't
persist. If patients were actually still taking
NSAIDs while they were actually in the trial, the
risk ratios were fairly similar for CV death on
both of those subgroups.
So we didn't believe that was a very robust finding for the subgroup of patients who were taking NSAIDs at baseline.

DR. CUSH: Is that any non-steroidal use?

DR. WHITE: Any non-steroidal typically would have been naproxen, ibuprofen.

DR. CUSH: No, I mean talking about did they get 2 doses --

DR. WHITE: Oh yeah, they get --

DR. CUSH: -- or could this have been 2 months, 6 months? I mean did you quantify use?

DR. WHITE: No, it was anybody who used NSAIDs for any duration during the trial.

DR. CUSH: Right. So you have, yes, any non-steroidal use during -- I'm not sure if that's going to be different if it's people got an occasional use for headache, or people who had regular use during the trial, because midway they weren't well controlled, so half the trial was spent on non-steroidals.

DR. WHITE: Yes. I also should point out the numbers of events in that yes group were pretty
small, for both at baseline and during treatment, which was another thing that influenced us thinking that this was possibly a confounded finding.

Every time I look at subgroups in our trials, I always get worried about what they mean. We tested a lot of subgroups without controlling for multiplicity, so it's very possible that this was just one of many of those kind of findings. So I really can't delve into it too much more because it's a small number of events that occurred in the yes group during treatment.

Now, the finding with aspirin, which is the other heterogeneity finding, if we can bring up the group on aspirin during the trial versus at baseline for CV death, and then we'll follow that with the MACE finding, please.

This is a little bit more, I guess you could say, complicated. We had evaluated low-dose aspirin, that is less than 325 a day at baseline. That's what you saw in the figure during the core presentation. That's the very heterogeneous finding. Then when we looked at any dose, people
that could be taking a higher dose than 325, it was still significant, but the trends were not as substantial looking as they were for low dose.

Then when we look at the patients who were still taking low-dose aspirin during the treatment period, the findings were consistent with the baseline use of aspirin, and the same thing for any dose, although that had lost statistical significance at the higher doses of aspirin.

We're left with what to do with this, and the question would be how does aspirin protect somebody on allopurinol as a xanthine oxidase inhibitor, but not on febuxostat? So that was our pharmacologic question that was sort of unanswerable.

Then, as I showed you, I think earlier in the key clarifying questions -- I just want to show you this really quickly -- one would think that the use of low-dose aspirin would also be protective against acute coronary syndromes and MI, and that the lower part of that figure, low-dose aspirin use, yes or no, didn't show heterogeneity for all
of these prothrombotic non-CV events.

So I don't know how to interpret just mortality as a standalone versus all of the other things that should have been protected by aspirin if there was a real, true drug-drug interaction between aspirin and febuxostat versus aspirin plus allopurinol.

I think that's where we're left, and we didn't ascribe a huge amount of clinical significance to this finding, even though it is pharmacologically of interest.

DR. SUAREZ-ALMAZOR: Okay. We only have a few minutes left. There were an additional three people that had requested this morning, clarifying questions. We will have discussion later on, so if you have any pressing questions, please let's do it quickly so we can move to the discussion.

The first one was Dr. McAdams? Anything else?

DR. McADAMS-DEMARCO: They answered my question earlier. Thank you.

DR. SUAREZ-ALMAZOR: Okay. Dr. Psaty?
DR. PSATY: Bruce Psaty. This was a noninferiority design, and poor conduct of a noninferiority design tends to bias the result toward the null. So, the finding of cardiovascular death and total mortality is pretty stunning. And what is not clear is how people were followed up during the trial.

The briefing documents say that follow-up was discontinued after a first event, and there was some response this morning that suggested at least some were followed and maybe others were not. There was a slide with 30 percent of the people who only had partial follow-up. The FDA briefing document says "Subjects who had discontinued study treatment but had not withdrawn consent were contacted every two months for the duration of the study or until the patient had experienced a MACE, that was adjudicated as such."

Basically, what is the person-years of follow-up that are missing during this trial? What would have been the total person-years and how much person-year data is missing with potential missing
events and missing deaths. The deaths is a different question because you did the other follow-up, but how much is missing here? It seems like a lot.

DR. KNAPP: We did have partial follow-up as you note. I would like to ask Majin -- or excuse me, Dr. Carroll to come. And he can just walk you through, because we did put up that slide early around the partial closeout and the median study fallout.

DR. SUAREZ-ALMAZOR: Okay. Please remember it's a brief question, so just a brief answer related to the question.

DR. CARROLL: Dr. Carroll, statistician. Slide up. Just briefly, the amount of time where patients could have been followed is captured in the bottom row, and it's an average of 1.7 years for the patients in the orange bottom row.

So they were followed for 1.7 years. The amount of time that, if you like, is missing, the missing patient-years, is approximately the difference between about 3 and a half years and
1.7 years, and that gives you the average length of
time that those patients were missing in their
follow-up. Thank you.

DR. NASON: I just don't understand the top
row of that. Sorry, can you put it back up? The
top row says -- well, it's only for MACE events,
right? So this question about whether people are
followed after MACE events for the question of
cardiovascular death or all-cause mortality, that
top row would also have some unknowns in it,
correct?

DR. CARROLL: Yes. Unfortunately, I don't
have a similar table for cardiovascular death, but
I could go through. We do have the OmniTrace
follow-up where they got 87 percent of the patients
to get total mortality. So we know we have
mortality in the majority of patients.

DR. SUAREZ-ALMAZOR: Dr. Gibson?

DR. PSATY: So it's about 4,000 person-years
of follow-up that are missing? Is that right?

DR. CARROLL: It's going to be about in that
region. And again to be brief, the issue that
arises is what proportion of events you might have missed? You have to compute from that number of events that you might have missed, and we did that earlier, and about 6 and a half percent of the 30 percent might have had a MACE event during that total period of follow-up time, and then would they have changed the result, which I discussed earlier.

DR. SUAREZ-ALMAZOR: Dr. Gibson?

DR. GIBSON: I think someone could go missing one day before the end of the trial, they would count as missing, but they would have 99.9 percent of their follow-up time available. And I don't think you've answered the question about the amount of time missing.

Is there any evidence of other thrombotic events like pulmonary embolism and DVT, and is there a landmark analysis from drug discontinuation through 30 days, just focusing on that potential rebound period after drug discontinuation?

DR. KNAPP: Dr. White?

DR. WHITE: We have a figure of the base-plus we can show. We didn't do a specific
landmark analysis, as you're referring to, from the
time of drug discontinuation using standard
Kaplan-Meier curves and standard methodology, but
at least if we can show the table of the expanded
events that were just requested. Thank you.

All of these were prospectively adjudicated
during the course of the trial. This is an
expanded endpoint that included the primary
discontinued endpoint plus hospitalization for heart failure,
arrhythmias, venous thromboembolic events such as
pulmonary embolism and DVT, and transient ischemic
attack that was well characterized and
hospitalized. One of our endpoint members was a
vascular neurologist.

So we didn't have any significant
differences for the total expanded endpoint, and
for all of the subsidiary ones, if you will, heart
failure, arrhythmias, and thrombotic events, none
of them achieved statistical significance. We had
a fair amount of them, as well, in the study as it
was being conducted. Those are the totality of
that information.
DR. SUAREZ-ALMAZOR: Okay, thank you.

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. Dr. Nikolov will provide us with a charge to the committee.

**Charge to the Committees - Nikolay Nikolov**

DR. NIKOLOV: Good afternoon. As we prepare for the committee discussion and voting this afternoon, I want to provide a brief reminder of the scientific issues, the regulatory framework, and the questions to be discussed and voted upon.

In CARES, which was the prospective, multicenter, randomized, double-blind, active-controlled, cardiovascular outcome safety study, the prespecified primary analysis, the estimated hazard ratio of MACE associated with febuxostat relative to allopurinol, was 1.03, excluding the prespecified risk margin of 1.3.

While the results from the MACE composite endpoint excluded the prespecified risk margin, there was an increased risk of cardiovascular
death, with a hazard ratio of 1.34 and a 95 percent confidence interval of 1.03 to 1.73.

We ask for your discussion of the results of CARES study, certainty and strength of the findings, of the cardiovascular mortality based on the available data, presented today by both the FDA and the applicant.

We also ask for you to discuss the benefits of febuxostat to help frame the benefit-risk considerations, recognizing that febuxostat is an effective urate-lowering therapy, and one of a limited armamentarium of urate-lowering therapies, and the only alternative xanthine oxidase inhibitor to allopurinol.

When faced with important safety and new safety information, FDA has a number of regulatory options that we ask the panel to consider for your discussion, as there are multiple approaches the agency may undertake to mitigate the risk.

Therefore, we ask the panel to consider the following regulatory actions and, importantly, their potential clinical and patient care impact.
For example, adding the results of the CARES study to the febuxostat label; for example, updating the existing warning and precautions section regarding the cardiovascular risks.

Adding a boxed warning to the febuxostat label, and as I previously mentioned, a boxed warning can be used to highlight an adverse reaction that is so serious in proportion to the potential benefit from the drug that it is essential that it be considered in assessing the risk and benefit of using the drug; an option maybe to also modify the labeling to limit the use of febuxostat. This could be accomplished by a change in the indication statement and/or a limitation of use.

The last potential regulatory action for consideration is the withdrawal of febuxostat from the market. As previously mentioned, this action was proposed by the Public Citizen's petition submitted in June last year, requesting the immediate removal of febuxostat from the U.S. market based on the results from the CARES study.
Based on these considerations, there are several points that we ask the committee to discuss today. The first discussion point refers to the results from the CARES study and the strength of the findings and the biological plausibility for the cardiovascular mortality, based on the totality of the available data.

Next, we would like the committee to discuss the benefits of febuxostat to better frame the benefit-risk framework and to consider whether or how the benefit-risk has changed for this product.

The next discussion point follows the benefit-risk discussion and is focused on the potential regulatory actions for the advisory committee consideration. These include updating the existing warnings regarding cardiovascular events and cardiovascular death; and adding a boxed warning on cardiovascular mortality in the product label.

Further, if the committee considers that the benefit-risk has changed for the currently approved population, there are other labeling changes that
could define a patient population with a more favorable benefit of using febuxostat.

Lastly, we would like the committee to discuss the consideration of withdrawal of febuxostat from the market and the impact on patient care and public health.

Following this discussion, the committee will be asked to vote on one question. Namely, based upon the available data, is there a patient population in which the benefit-risk profile of febuxostat is favorable for the treatment of hyperuricemia in patients with gout? The answer to this question should be either yes, no, or abstain.

Then, based on the voting, if you voted yes, we ask for your individual discussion on the patient population with a favorable benefit-risk profile for use of febuxostat. Also, we ask that you describe any other recommendations, for example, labeling changes, you may have for the use of febuxostat in that patient population. If you voted no, we would like you to discuss your rationale, the impact of this recommendation, and
any other recommendations you may have.

With this, thank you for your attention, and again, I'll turn back the podium to Dr. Suarez-Almazor.

Questions to the Committees and Discussion

DR. SUAREZ-ALMAZOR: 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.

Okay. This is the first question. Discuss the results of the cardiovascular safety of febuxostat and allopurinol in patients with gout and cardiovascular morbidities, CARES study, particularly major adverse cardiovascular events, MACE, and cardiovascular mortality.

Please consider the following in your discussion: a) biological plausibility of cardiovascular mortality; and b) strength of the findings for cardiovascular mortality, considering
the totality of available data.

Are there any questions or comments related to the question per se before we start the discussion?

(No response.)

DR. SUAREZ-ALMAZOR: No? Okay. Then we will start the discussion. Again, please make sure that you let us know if you have any comments by raising your -- or turning around your name label.

Dr. Kulldorff?

DR. KULLDORFF: Thank you. As a statistician, I don't have any comments on the biological plausibility, but I'm looking forward to other people commenting that. But on the strength of the findings, there are two issues. One is the magnitude and one is this a chance occurrence or not, and that's where I can contribute as a statistician.

In terms of the magnitude, the number needed to harm one person with CV death was estimated to be 278. We don't have a confidence interval of that, but in my head, I would estimate that in the
worst-case scenario, we will treat between 100 and 150 person-years to get one CV death as the worst-case scenario. The best-case scenario, it would be about a couple of thousand person-years.

That's the range based on the confidence interval that we have in terms of the damage of this drug. I guess if we turn it around, if I had a drug that would prevent this number of cardiovascular deaths in a population with people who are at risk of cardiovascular death, that would probably be a pretty good drug to actually give as a prevention of cardiovascular death, but in this case, of course, it's a question of harm.

In terms of the randomness, I think one of the reasons for this CARES study was that there were an excess of cardiovascular deaths in earlier studies. I'm not too worried about the multiple testing here because it was clearly one of the reasons why this study was conducted. I think it was a good reason to do this study and for FDA to require this study.

But the confidence interval is very close to
1, so is it a true effect or is it the random
effect? I think it's harder to tell only based on
that confidence interval. But the fact that when
you look at the aspirin users or not, and the NSAID
users or not, for those who do not use aspirin, the
confidence interval is very, very far away from 1,
so the p-value would be very, very small, less than
0.0001 probably.

To me that's extra evidence that this is not
a chance occurrence, and the same with the NSAIDs,
those who take NSAIDs have a higher risk. Those
subanalyses, in my mind as a statistician, is
evidence that this is not just a chance occurrence.
There's something really going on here. And why, I
don't know, but that's my comments on both of
these. Thank you.

DR. SUAREZ-ALMAZOR: Dr. Cush?

DR. CUSH: Well, I left it up from before,
but I also have no guess on biologic plausibility.
I applaud the effort to look into that. My best
guess, and this is a guess, is that febuxostat may
be a little more effective maybe a little faster
than allopurinol in getting to a target SUA, and that could be the Achilles heel if you believe that maybe rapid changes in uric acid may impose some risk, but again, that's way out on a limb.

Again, I do think, like others, as has just been said and has been said, before, that I would have expected the null here, given the hazards of the trial and the downside of the trial.

My explanation on why there's such a large dropout and why there's this missing gap is because, one, this is a trial that's not been done before. It's a long-term trial. The other trials were short-term trials. This includes gout, which is mostly males, and they're horrible patients, and they're gigantically non-compliant, and they never come back, and it's just -- you pull your hair out when you're just managing gout patients in the clinic, and then try to do a trial with several thousand, and this is what you get.

Yet, we still are left with this cardiovascular mortality, which is going to be meaningful. And I would say, along with the
totality of evidence, means that this data needs to be acted upon.

DR. SUAREZ-ALMAZOR: Dr. Griffin?

DR. GRIFFIN: Yes, Marie Griffin. Yes, I see this as far as confirming a signal, I think that makes it much stronger to think that it's not just chance because the signal we had before was all-cause mortality or cardiovascular mortality.

I think the hazard ratio was highest for the people on drug or on drug within 30 days. So even though there were a lot of deaths after drugs were stopped, 21 of the 34 excess cardiovascular deaths occurred on drug plus 30 days. I think that's really important because I think that's another signal that this may be real.

Third, I think inflammatory conditions, like rheumatoid arthritis and gout, are associated with an excess of cardiovascular events that are not explained by traditional risk factors. There's a lot we don't know about it, and we don't know what to measure to find out what's putting them at risk; maybe CRP and other things. But I think it's just
we don't know a lot about how to measure the risk associated with these inflammatory conditions.

I think because of those things, I think it's not a slam-dunk, but I'm very concerned about the plausibility of this association.

DR. SUAREZ-ALMAZOR: Dr. Nissen?

DR. NISSEN: Colleagues, let's look at what happened here. On not one, but two occasions, the division declined to approve this drug and gave a complete response letter because of concerns primarily with cardiovascular mortality.

They required a large trial to confirm or refute that risk, and that trial was conducted. It was conducted in a way that biases the trial toward the null hypothesis, and in spite of that, it shows an excess of cardiovascular mortality.

So once is an accident, twice is a happenstance, and three times -- I think this is third -- or three tries at it, now you've got the confirmatory evidence. So I believe there is an excess risk. Is it a hundred percent certain? No.

I can tell you that if these data were
available prior to approval, I have no doubt that
the predecessor committee to this one would have
deprecated to approve this drug. So we have a drug
that's on the market, that if we had these data,
would not have gotten on the market.

The issue of biological plausibility, first
of all, we should not overstate the importance of
that issue. A favorite phrase of mine, you can
find this on the internet, if you google it, is
that, "The road to hell is paved with biological
plausibility."

Whenever you see a safety signal, the first
thing that sponsors say is, well, it's not
plausible. We don't have an explanation for it,
and therefore it must not be real. I don't think
we need biological plausibility to have a finding,
but there is biological plausibility.

I was very struck by Dr. Psaty's and
Dr. Gibson's comments because the two interaction
terms that are very strong, both are reflective of
arachidonic acid aggregation. That is aspirin,
which is anti-aggregatory and then NSAIDs, which
block the efficacy. Some of them block the
efficacy of aspirin. So you have two findings,
both of which are in the realm of platelet
function.

Now, the sponsor showed us ADP aggregation
data. Well, aspirin doesn't affect ADP
aggregation; it affects arachidonic acid
aggregation, and NSAIDs don't affect ADP
aggregation. They do affect the influence of
aspirin on arachidonic acid aggregation. So I do
think that there's plausibility.

Now, why don't you see it in the MI data?
We don't always know these things. We don't know
how many, for example, sudden deaths were actually
MIs, where the patient never made it to the
hospital, and that certainly is a possibility.

One final comment, I do not believe that the
trial met the standard, the regulatory standard,
for noninferiority for the primary MACE endpoint,
in spite of the fact that the upper confidence
interval was below 1.3.

Why do I think it didn't meet that? Because
the trial conduct was so poor that it so biased the trial toward the null hypothesis, that if you do any imputation of the data, it doesn't take very much data to get the upper confidence interval to be 1.3 or greater.

So I don't think we want to set the regulatory precedent that you can do a trial, lose 45 percent of the patients, have a whole bunch of people off a study drug, and then come in under 1.3 and say that's good enough. So I do not think the noninferiority finding is robust, and I'm very concerned about that.

Finally, will we get new data? Well, if you look at the design of this European trial being done, it's smaller, it has only 450 events. It's not very robust. It's open label. I think that that isn't going to answer the question. I think we've got as much good data as we're going to get, and I do not think this trial was done to demonstrate that the drug was noninferior, and I don't think it's demonstrating noninferiority.

DR. SUAREZ-ALMAZOR: Dr. Psaty?
DR. PSATY: Thank you. I'm not a big fan of biologic plausibility either, because if you show somebody the results and then say, oh, that's reversed, somebody will come up with an explanation for them.

I'm also not a fan of a lot of subgroup analyses, but I thought the subgroup analysis for aspirin was powerful, and it's even made more powerful by Dr. White's showing that it persists during the trial. So that leads to the hypothesis that there may be something about febuxostat that affects platelets, that affects innate or adaptive immunity, and plaque rupture.

So this isn't the usual thing the FDA worries about, like QT intervals. This is an exuberant thrombosis that takes a plaque rupture to a large MI, a large fatal MI, and it is not a mechanism of QT interval or QT prolongation or arrhythmia.

So there be other mechanisms here, and there's a distinct lack of information about the potential effects of febuxostat, as Steve just
pointed out, on some of these potential biologically plausible mechanisms.

DR. SUAREZ-ALMAZOR: Dr. Meisel?

DR. MEISEL: Steve Meisel. I couldn't say anything more eloquently than Dr. Nissen did just a few moments again here. I think you took all the words out of my mouth, but you multiplied them ten-fold.

A couple of points. First of all, I also want to emphasize the issue of biological plausibility. I think that's sort of red herring. Just because you can't explain something doesn't mean it isn't real. As people have said already, there are all sorts of things that you can only explain after years and years and years of further research. There could be some metabolic pathway that nobody's even identified yet that it's affecting, and that sort of thing.

When I was first looking at this, the data -- and I'm no statistician, and I don't pretend to articulate this really well. But I looked at those confidence limits at 1.03 and 1.01,
and it's really close to the 1.0, and p-values of 0.03, 0.04, and I was taught back in college in my statistics class, the only thing I remember, is that that is what is the likelihood that the result is by chance? If it's a p of 0.04, that means 4 percent likelihood that it's by chance.

Maybe it's just you measure enough things in the right way and it's just a chance occurrence. If you did a 99 percent confidence interval, the p-value would likely show non-significance.

But then, all of the other studies, and I mean all of them, the Zhang study, the early ones before the drug was approved, although albeit at higher doses than we have on the market today, all show the same trends, all of them. The Zhang study showed it was not statistically significant, but if you look at the out-years -- it was a short-term study, but if you look at years 2 and 3, and so on, the spread begins to show. It begins to break apart, and if every study has the same trend, then it's probably real.

Now, does that mean that the drug gets
pulled from the market? We'll talk about that later, but I think it's real. And I think it's also quite true, Public Citizen is absolutely right, had this study been available back in 2008, this drug never would have made it to market. This drug would have been -- there would have been a complete response letter, and that would have been it, and we've never seen again.

But of course, it isn't 2008, it's 2019, and it's a different world, and we'll have to think about what the implications are. But it's quite true, these data presented in 2008 would have prevented this drug from coming to market.

DR. SUAREZ-ALMAZOR: Dr. Gibson?

DR. GIBSON: Yes, I think we have to look at the amount of missingness here. We have 234 cardiovascular deaths. That is overshadowed by 449 patients who are lost to follow-up, which really clouds our ability to interpret these imbalances in cardiovascular death.

I do think it's possible to follow patients up. I know in the trials Dr. Nissen's done,
handfuls of patients lost to follow-up. I completed a 7500-patient trial with zero patients lost to follow-up, so it can be done. I think, though, the p-value for the cardiovascular death signal is fragile in the overall population at 0.03. When you looked at the within-30-day analysis, the p was 0.047, so one patient going one way or the other might have offset that. Then when you look at the on-treatment analysis, it's not significant.

Now, when the investigators used death registries to collect more data, I was reassured that when you had 87 percent of the vital status in, there was no difference in all-cause mortality. You could not look for cardiovascular death in that analysis because you didn't know why people died; you just knew whether they were dead or alive. So you're kind of taking all-cause mortality as a surrogate for cardiovascular death in that kind of analysis.

Getting back to sudden death, when someone is found dead in a lazy boy recliner with a remote
control in their hand or dead in bed, you really
don't know why they died. You don't know if it is
an arrhythmia, heart failure, an MI, a pulmonary
embolism, which there was a slight imbalance going
against the agent, or if it's a non-cardiovascular
death.

Those deaths that were outside the hospital
were attributed to cardiovascular death, when in
fact, they may not have been. They may not have
been cardiovascular deaths. Looking back at some
of the earlier phase 3 analyses, there was a
numeric increase in MI and stroke, which was not
confirmed here. There was not strictly -- there
was a numeric excess, but not a significant
increase in cardiovascular death in those trials.

I also was somewhat reassured, looking at
the KM curves for cardiovascular death, that there
was no divergence over the first 3 or 4 years.
That's a period of time when most people seem to be
taking or tolerating these drugs in the real world.

I do also agree about the comments about
biologic plausibility, although I have to say, we
didn't see any direct interactions with platelets and the QT and calcium channels, et cetera. What I didn't see is any data about CRP and lipids and lipid lowering and LDLs.

I agree with Dr. Nissen and everyone. I'm most concerned about the interaction with aspirin, which was very pronounced in the non-steroidals. It looked as though if you were on aspirin, you may have had a protective effect, but if you weren't, you were at risk, which was bothersome to me, and of course, non-steroidals can be pro-aggregatory in this kind of setting.

In terms of biologic plausibility, I'm just not sure. It looked like a lot of the excess in events was clustered in those 30 days after discontinuation. We didn't see a landmark analysis looking at that period, but you could postulate that discontinuing the drugs led to a pro-inflammatory state, which led to either plaque rupture or some other cardiovascular outcome.

DR. SUAREZ-ALMAZOR: Dr. Miller?

DR. MILLER: Yes, I just wanted to add
something in terms of plausibility, that's been
brought up lightly a couple of times so far. There
are at least observational data that allopurinol
may be cardioprotective in patients with gout. So
we don't know if febuxostat was causing
cardiovascular events or simply not preventing them
as allopurinol was.

Also, with the large number of events right
after stopping the drug, it is possible febuxostat
was cardioprotective, but then, again, there was
this rebound in cardiovascular events right after
discontinuation.

DR. SUAREZ-ALMAZOR: Dr. Chung?

DR. CHUNG: In terms of comments about these
being confirmatory information, there is
inconsistency, I think, across trials over time for
the CV death rate. I think if you look at, for
instance, the CONFIRMS trial, which was designed to
look at CV risk, there was not an increase in the
CV death rate. Also, in the CARES trial, as was
pointed out, the increase in death rate was not
associated with increases or imbalances in the
non-fatal CV events. I think these points are important to think about.

Also, in terms of the follow-up, or lack of follow-up in certain number of patients and whether that may have biased the outcome, I think it's worth reiterating the sponsor's analysis. Look and see what you have to assume to believe or to see the outcome actually change, and I think you have to see a much greater full difference in the post follow-up period that you didn't see. And in the patient population in the two groups that didn’t differ in terms of their baseline characteristics, I think this is highly unlikely. So I think those are also worth considering as well.

DR. SUAREZ-ALMAZOR: Dr. Curtis?

DR. CURTIS: As I think about contextualizing the findings and the strength of the findings, the B comment, and I think about how important is this -- Steve actually went back to PRECISION, where unlike this trial, I think the outcome ascertainment was, in fact, quite good.

You found hazard ratios from death for any
cause, when Celebrex was referent to naproxen, of 1.25, and that p-value was right around 0.05, and 1.28 for cardiovascular mortality, which favored Celebrex and was not favorable to naproxen. And non-fatal MI was higher in naproxen with a hazard ratio of 1.39, and that p-value was 0.04.

Then I have to think, well, if I have all-cause mortality, CV mortality, and MI rates in the 1.25, 28, and 39 range, and p-values very much in the range we're talking about, am I unhappy and feel uncomfortable ever prescribing ibuprofen or naproxen again; like if I'd just taken that out of what I would ever give to a patient? And I would say no.

So I guess even if one accepted that we have absolute truth with CV mortality, it's a difference of 4 per thousand person-years difference. Even if we were absolutely convinced that was God's truth, would that completely make this an unacceptable drug ever to give to a patient?

I guess drawing from what we learned from the PRECISION trial, I think that was helpful for
me to reflect on to contextualize the magnitude of what we're talking about, even if we did make the leap to say that we're convinced it's totally real. And that might be helpful, I guess at least for me as a prescriber, given other things that I still will feel comfortable using with some cautions in the ways that I think clinicians would apply to higher risk people, et cetera.

DR. SUAREZ-ALMAZOR: Yes. I'd like to follow-up a little bit on that, and Dr. Kulldorff gave some data that you calculated on the number needed to harm. I would like to get an understanding from the cardiologists, particularly the magnitude of this effect, what would you consider it might be?

DR. NISSEN: Well, I'm not a big fan of --

DR. SUAREZ-ALMAZOR: Dr. Nissen, for the record.

DR. NISSEN: Yes. I'm sorry. I'm not a big fan of this sort of analysis. I think what you were trying to say here is it's not trivial, and I would agree with that. I think it has to be
interpreted, and I'm going to talk more about this
later when I make some suggestions for what we
should do, that it is informative on understanding
the benefit-to-risk relationship, and that's why we
need to look at it.

I'm not going to comment on PRECISION.
Maybe I have a little bit different interpretation
than you do. But we were very conservative
interpreting the trial because we had a lot of
secondary endpoints, and we didn't have adjustments
for multiplicity and so on.

I did want to address one other issue here,
and that's this tipping-point analysis from the
sponsor. And I have to tell you that I get a
completely different result, and I think it's very
biased, this idea that you have 20-fold worse
outcomes in the missing patients in order to tip
the analysis. I don't think it's right. That's
why I asked FDA if they had a tipping-point
analysis on MACE because I would want it done by
independent statisticians.

Mike Gibson, I don't know if you have any
comments as well. You've done a lot of these sorts of analyses. But I just don't think that that's the correct interpretation, and I get a very different answer.

Now I did this back of the envelope here right here at the meeting, so I'm going to have to go back and sit down with my statisticians and do it a little differently. But it's not correct to say you have to have 20 times as many events in the febuxostat arm in order to tip the analysis. I think that's wrong.

DR. SUAREZ-ALMAZOR: Yes. I think that relates more to the missingness or the lack of follow-up, but I was thinking in terms of the magnitude of the deaths. One death may be one too many, but in terms of other cardiovascular trials, what does this mean as far as magnitude?

DR. NISSEN: If I could just add one final comment. For those of you that haven't read it, the Institute of Medicine report on missingness in trial data is an elegant description of the hazards of missing data and points out, really eloquently,
why missing data can bias trials and why there is no antidote; no tipping-point analysis substitutes, what you don't know, you don't know. And what we don't know here is many fold more than we would expect in a cardiovascular outcome trial.

Dr. Gibson does these trials as well. I've reviewed his trials for the New England Journal, and they typically have 99 percent ascertainment of the primary endpoint, and that's not what happened here.

DR. GIBSON: I would second the recommendation that the FDA look at the inflation, tipping point, and quan analysis of the missing data for the noninferiority of MACE.

DR. SUAREZ-ALMAZOR: Okay. Dr. Ranganath?

DR. RANGANATH: I'm speaking more from a rheumatologist standpoint. And if you're thinking about cardiovascular risk in a population who already has a pretty high cardiovascular risk to begin with, and kind of talking a little bit about what Dr. Miller and Dr. Curtis was hitting on those same points, we're comparing against allopurinol,
but are we comparing against -- that's the reason why I asked the prior question of looking at the data on people who have cardiovascular risk and gout, and comparing cardiovascular events between febuxostat and placebo and what that impact would have, because maybe it is reducing cardiovascular risk overall, but not in comparison to allopurinol.

I'm still grappling with the idea of how much risk are we willing to have, or how much death are we willing to -- like is there a standard, and how do we develop that? Maybe that's a different question, but I think that's an important question when we're thinking about this particular question.

To touch upon p-values, and I don't know for the statisticians in the room to be able to answer this, being married to a family of statisticians, from my understanding, a positive p-value is a positive p-value. It doesn't matter if it's 0.001 or it's 0.04; it means the same thing, in the sense that it's significant. I see this particular -- I'm taking the data from CARES as demonstrating that there is an increased risk of
cardiovascular mortality. Thank you. Happy to hear what other people --

DR. SUAREZ-ALMAZOR: Dr. McAdams?

DR. McADAMS-DEMARCO: Sure. I just want to point out one piece of research from patients without gout, that when you look at the association between serum urate level and the risk of all-cause in cardiovascular mortality, it's actually a U-shaped curve. I wonder how much of that could be explaining why we see better control and better lowering of urate levels in the febuxostat group, yet a higher risk of mortality, particularly cardiovascular mortality.

DR. SUAREZ-ALMAZOR: Okay. Any more questions, comments? Dr. Psaty?

DR. PSATY: I think that one of the questions was what is the risk difference for other therapies? And I think in a population receiving hypertension therapy or a primary prevention population receiving statin therapy, the number needed to prevent an event would be generally on the order of 1 in 200 to 1 in 300.
This is the obverse of that. It'd be about the same number of people to treat to increase a cardiovascular death. This is about the equivalent and opposite of what a preventative therapy would often do in a primary prevention population. I think that was your point earlier.

DR. SUAREZ-ALMAZOR: Okay. No more comments then?

(No response.)

DR. SUAREZ-ALMAZOR: I'll try to summarize what was said. I think, in general, the panel thinks that there is a signal that appears to be consistent, and this is on the basis of the CARES study but also the prior trials that had shown some risk for cardiovascular events and deaths.

There are also subgroup analyses in patients with risk factors that all go in the same direction, which would also support the presence of this signal. There is also a concern that the trial was not as robust and was -- as one might want, given that there were many losses to follow-up and therefore missing data, and that
leads to misclassification that goes towards the null and then can mask a true difference.

With respect to biological plausibility, there's not enough data that's known about how this could be happening. Perhaps it relates to the effect of uric acid in the sense that febuxostat may act more quickly in the lowering of uric acid, and possibly that could have an effect, and also the U-shaped curve that has been mentioned.

Finally, the subgroup analysis that showed consistent results with low aspirin and with patients with NSAIDs in opposite directions would suggest that perhaps there's an effect related to platelet aggregation.

Finally, there was a little bit of discussion in relation to magnitude of effect. The magnitude of the effect appears to be clinically significant, although possibly not very large, just clinically significant.

Any comments or add-ons to the summary?

(No response.)

DR. SUAREZ-ALMAZOR: Okay. We will move,
then, to question 2, discuss the benefits of 
febuxostat for the treatment or hyperuricemia in 
patients with gout.

Any clarifications with respect to the 
questions or can we move on to the discussion? 
Dr. Horonjeff?

DR. HORONJEFF: Yes. Jen Horonjeff. As I 
brought up before, I wish we had more data about 
other types of benefits because then we could have 
the cost benefit analysis from a patient 
perspective on whether or not even subgroups of the 
populations we're talking about may be able to 
tolerate this risk for other options.

I think that we hear this anecdotally and 
reading some of the comments that were submitted 
prior to the meeting, that this gives another 
option to patients that aren't able to tolerate the 
current treatment therapies, but I just really wish 
that we had more to go off of there.

All of that being said, I do think that 
there could be a benefit to give patients these 
therapies and have these conversations with their
clinicians, but I think it needs to be really clear what the risks are.

That doesn't give us a lot to go on, but I really wish that we had more data, and that would just be something to direct towards the FDA, that this would be really interesting to see how they weigh out, whether or not this allows them to participate in their life more because of other trade-offs.

That's just my way of pointing out that I'm disappointed that we don't have other things to factor into this analysis.

DR. SUAREZ-ALMAZOR: Dr. Nissen?

DR. NISSEN: Well, what makes this really an interesting and very difficult regulatory decision is the fact that this drug is effective for its primary indication. It's very good at lowering uric acid. It appears to prevent the sequelae of having a high urate level.

So I don't have any doubts about the efficacy of the therapy. Is it superior in most patients to allopurinol? I will leave that to the
rheumatologists. Obviously, the marketplace place has not dominated, although obviously it's branded, and the other drug is generic, which probably pharmacy benefit managers are probably telling our rheumatologists what they can and can't do.

But I do think it's efficacious, so I'm going to hold further comments about efficacy until we get to this question of risk-benefit, and I'm going to have a proposal for all of you to think about, about how do you deal with this increased risk of a morbid/mortal outcome versus a benefit on a non-mortal outcome. I think there is an approach, and I'll come back to it later when we get to that part of the discussion.

DR. SUAREZ-ALMAZOR: Dr. Oliver?

DR. OLIVER: Thank you. Just to follow on what Dr. Nissen was saying, that's what I'm grappling with after the last discussion as well, so it does appear that there is an increased cardiovascular risk with febuxostat. But weighing the pros and cons, primarily I see these patients in clinic as an adult rheumatologist, and it works.
You can make someone really happy, who has gout, if you can lower their uric acid. I have seen patients that have done very well on febuxostat who have been intolerant and had side effects to allopurinol as well, so it's a very difficult decision.

I agree with Dr. Horonjeff about patient outcomes. That would have been nice to see to show that there is more than just decreasing serum uric acid and anecdotal evidence from rheumatologists seeing patients in clinic, that we do see a benefit.

I think that one of the biggest barriers or one of the reasons that febuxostat does not have a larger marketplace is just what Dr. Nissen said. It's extremely difficult to get the medication approved, and usually there's a step added by the pharmacy managers that they have to fail allopurinol to begin with.

DR. SUAREZ-ALMAZOR: Dr. Cush?

DR. CUSH: The drug does work, and there is evidence that it may be even more effective at
lowering uric acid levels in achieving target. It achieved 70 percent in this trial, I guess, and some other trials it was even much lower. But that kind of target number doesn't really happen in real life. In real life, there's 9.2 million people with gout, and only a third of people on urate-lowering therapy, and we seldom ever get these kind of targets.

I'm going to make the comment that this drug works, and it may have a role, but what keeps getting missed is that it's always used when we can't use allopurinol. Yet, the vast majority of people who prescribe have no idea what they're doing with allopurinol, and misuse it, and misdose it. When you have so many people on 100 and staying on 100, that's a gigantic problem, and when you have rheumatologists who don't go above 300, that's a gigantic problem.

So when the reason to use the drug is because the renal doctor won't let it happen, well, we know that the whole issue of renal dosing has been gigantically overstated, and there's plenty of
literature to say you can use allopurinol safely as long as you monitor renal function, unless they have really, really severe chronic kidney disease.

Yes, people who have hypersensitivity might well go to this drug, this febuxostat as an alternative, but there are many instances, again, where the dosing and use of allopurinol is woefully bad, and I think this drug should fall in line behind allopurinol and should be mandated only after allopurinol use.

DR. SUAREZ-ALMAZOR: Dr. Felson?

DR. FELSON: I'll hold off other than to say that while the sponsor didn't do quality-of-life studies in gout, others have, and have shown that gout flares affect quite severely quality of life and decreasing the number of gout attacks and flares improves quality of life.

So I think even though it's not direct evidence here, I think it's fair to say that there will be effects on quality of life and other important patient outcomes.

DR. SUAREZ-ALMAZOR: Dr. Meisel?
DR. MEISEL: Steve Meisel. I just want to point out, this drug has been studied for a long time. It's been on the market for 10 years. It's been studied for quite a number of years before that. And yes, it does lower uric acid, and it does improve gout in all sorts of different measures. But there is not a single study out there that shows that it's any more effective in doing any of that, than allopurinol.

Yes, does it work, but does it work any differently? Yes, a slightly different mechanism of action, but does it work anymore effectively than allopurinol? The answer to that is no, so I think we need to keep that in mind.

Just to tack on one additional comment from my colleague over here, just because clinicians don't know to how use allopurinol properly, because they don't titrate it properly, doesn't make this drug more desirable. It means that we have to teach them how to use allopurinol differently. That's not an argument for this as a preferential agent. It's an argument for better treatment of
gout and understanding of the therapies that we have.

In terms of cost, just for frame of reference, in my organization a month of febuxostat is $307. A month of allopurinol is $8.10.

DR. SUAREZ-ALMAZOR: Dr. Horonjeff?

DR. HORONJEFF: I think it was in one of the FDA's presentations, the real-world evidence, that it was talked about better adherence on allopurinol, and to me, just intellectually looking at the various steps that one would have to take, I would have thought that would not be the case. But I would say that the dosing and the steps that one would have to take would favor in the opposite direction as a benefit for this therapeutic modality.

I had a little hard time getting around that. I don't know if they have any other thoughts around why that could be. I think the sample was a little small, so I'm not sure how much we can extrapolate that sort of adherence. But I would be curious about that because, otherwise, I would say
that would be a benefit to the febuxostat.

DR. SUAREZ-ALMAZOR: Dr. Curtis?

DR. CURTIS: Just to clarify, I don't personally consider that the Sentinel study was very informative to that point, and the Wright paper I think was a better study design.

People are not using febuxostat first line, by and large, but if you require a completely new, mostly naïve, for at least 6-month users, you're going to end up with these weird people in the febuxostat group, and I think that's what we learned from that.

I personally didn't actually find the adherence information, which, I agree, is kind of counterintuitive, very informative because it is this odd and highly, highly selected group, the way that they designed it.

I think the way that I would think would be rational is with a prevalent in the user design, like in the Circ [ph] paper that was published last year, and in fact, adherence was better in that. It wasn't leaps and bounds, but it was better on
febuxostat over allopurinol in probably as good of an observational study design as you could expect, trying to compare a drug that is mostly used second line to a drug that is almost always used first line as an XO inhibitor.

DR. SUAREZ-ALMAZOR: Dr. Nason?

DR. CURTIS: The adherence really does favor febuxostat when you use it in the way that we actually see happen in the real world, and we have that evidence.

DR. NASON: I actually have a question, more than any input to the clinicians around the table, which is we've been focusing really on the comparison of this to the other first-line drug, but it seems like as the conversation goes on and on, at least I am more thinking of it as a second-line drug. And yet I don't know anything about the comparison about how it might do compared to the other second-line drugs that are available.

So I was wondering if any clinicians who work with gout patients could just speak to that a little bit about if you did have someone who needed
another option, would you choose this over the other available second line and why?

    DR. SUAREZ-ALMAZOR: Dr. Cush?

    DR. CUSH: Well, it does get used, and I think most of us at the table do use allopurinol first. But as was sort of stated by the sponsor and the FDA, there's this range of drugs that we can use, and they all have some problem.

    Probenecid's got a real problem. Almost no one uses it. Pegloticase, many people are afraid to use, though it's gigantically effective. Then you're left with what other xanthine oxidase inhibitors you have other than -- so this is a good alternative to allopurinol. It seems to have a reasonable safety profile on a day-to-day basis, that you can have many patients on it without seeing either LFTs, or skin reactions, or cardiovascular events.

    Again, when you ask all doctors do you want another alternative, is there an unmet need, the answer is always yes. Would we be able to survive without this drug? Yes, we could. But I think it
really does play in the arsenal of a rheumatologist fairly well. The question is how good are they at getting to treat to target and how they use it, and what's their order of going through it.

Again, I think it's different than allopurinol, but at the same time, it, like allopurinol, seems to have a safety profile or a use that makes it easier.

One thing I didn't agree with the sponsor on was that you need to make multiple dose adjustments to get to the right dose of allopurinol. No, you don't. You use 100, and then you go to 300, and then maybe you go up to 450, 400, 6, and rarely go to 8. It's not that difficult. Yes, it might be one step less with febuxostat, from 40 to 80, but you're still making a judgment there, too, based on the clinical response and what their uric acid levels are doing.

DR. SUAREZ-ALMAZOR: Dr. Oliver?

DR. OLIVER: I do think there is an unmet need for urate-lowering medications. There certainly has been a role for febuxostat. Back to
something that Dr. Cush said, rheumatologists seem comfortable with titrating up allopurinol, but the majority of gout is diagnosed and treated by primary care physicians, and there seems to be, if they're able to get it, more use of febuxostat possibly in that group because of the dosing simplicity.

DR. SUAREZ-ALMAZOR: Dr. Curtis?

DR. CURTIS: I would extend what Dr. Cush said, to say that I think for a lot of patients, there would be no second-line drug. Pegloticase is not just a drug that inspires fear in many people who use it; it's dangerous and would be completely off limits to a lot of practitioners.

So that's not really a second-line agent for a whole lot of gout patients. I mean, you can kill people on that therapy, so you need to use that very carefully because of the hypersensitivity associated with that biologic, and that's not really a long-term medicine that you're going to use.

We've already heard lesinurad is no longer
going to be available in this country in about three weeks. You can't give probenecid to people with severely compromised kidney disease. So I think in truth, if allopurinol is not effective, or tolerated, or has some safety issues, there might not be a second-line therapy for a great swath of gout patients that have failed that.

One can look at fairly complicated and sometimes risky desensitization protocols for allopurinol that we used to use before we had any other agents, and those are generally bad and quite risky options. Sometimes people get put in the hospital while they're watched for that.

I guess to have very few second-line or subsequent-line options, we may end up finding ourselves having to go back to some of that, and I'm not sure that that really does patients good in terms of the safety perspective of trying to desensitize somebody to a drug that they're known to have an allergy to, even in a hospitalized setting.

DR. SUAREZ-ALMAZOR: Mr. Weiner?
MR. WEINER: Listening to this discussion as a patient is like listening to my nephrologist and cardiologist talk to each other; which is more important? What should be treated the most?

I have kidney disease, I have diabetes, I have heart issues, and so forth. In business, I do risk analysis as you do here. But the interesting thing in my business is, in risk analysis, the plausible outcome is never cardiovascular death.

DR. SUAREZ-ALMAZOR: Dr. Cush?

DR. CUSH: I wanted to add one more perspective on consideration of this data, specifically, to go forward to the next question. And that is we're talking about this CARES trial, which is impressive in its length and the numbers and the outcomes, and how we interpret it, but it is different than the trials that were done before, the APEX, and the FACT, and the CONFIRMS.

The age is older here. They actually have less males, 95 versus 84. They have less African Americans. The GFRs are different. The aspirin use is very different, 18 versus 48 percent. Tophi
might be different here compared to CONFIRMS.

The idea is that we're talking about very severe patients on a very severe end of the spectrum, which we have a few people of in our clinics in rheumatology. The vast majority of people are what Dr. Edwards said earlier, quirky people who don't come back, and you're struggling to get them managed, and get their uric acids down, and yet we have to make a prescribing rule for use for this drug that actually applies to everyone when we're considering, again, the tip of the iceberg, the worst-case scenario.

DR. SUAREZ-ALMAZOR: Dr. Scher on the phone?

DR. SCHER: Yes, can you hear me better now?

DR. SUAREZ-ALMAZOR: Yes.

DR. SCHER: Okay. I just wanted to add, we don't [indiscernible] see a lot of patients with gout, and fundamentally the question is, in a renally-impaired patient, we don't have an alternative. The alternative will be NSAIDs, and the NSAIDs are not drugs that we're able to use. Then the [inaudible - audio feedback] at high
doses.

So I would argue that we do not have an alternative, as it is, and I would consider that is an important fact with the risk-benefit analysis.

DR. SUAREZ-ALMAZOR: Okay. Thanks

Any other comments?

(No response.)

DR. SUAREZ-ALMAZOR: I will summarize. I think that, in general, the panel considered that febuxostat is an efficacious drug for gout. It's not clear that it's better than allopurinol. One of the concerns is that allopurinol is usually not well used by practitioners because it's used at lower dosages and not really following what's recommended by guidelines.

It was also mentioned that market data related to the use cannot really be translated into effectiveness data because the use of febuxostat may be restricted by insurance approval, and it doesn't really reflect real-world effectiveness per se.

There was a concern that there are no
adequate patient-reported outcomes in the trial, so it will be difficult for patients to make a trade-off between mortality risks and the benefits from treatment; although, from indirect data, we know that gouty arthritis affects quality of life in a very significant way.

It was also mentioned that there aren't really any other second-line drugs, at least to lower uric acid, that work within the spectrum or this class of mechanism.

Finally, it was also mentioned that this drug will be used by primary care physicians, and it could possibly be a little easier to titrate, although not the entire panel agreed with that.

Any additional comments?

(No response.)

DR. SUAREZ-ALMAZOR: No?

Okay. Let's take a 10-minute break only, and then we will come back for questions 3 and 4, and the voting.

(Whereupon, at 3:22 p.m. a recess was taken.)
DR. SUAREZ-ALMAZOR: We will be discussing question number 3 now. Given the results of the CARES study, discuss whether the benefit-risk profile of febuxostat for the treatment of hyperuricemia in patients with gout has changed. Address the following in your discussion:

a) discuss any patient populations in which the benefits outweigh the risks of the use of febuxostat; and b) discuss any patient populations in which the benefits do not outweigh the risks of the use of febuxostat.

Any questions or comments about the question per se?

(No response.)

DR. SUAREZ-ALMAZOR: Okay. Dr. Felson?

DR. FELSON: David Felson. Well, one could make the argument, I guess, based on the CARES, the unusually severe disease of the CARES trial population, as compared to other gout populations that were presented in the Sentinel database, et cetera, that the CARES group, the CARES-type patient, would be at higher risk -- higher absolute
risk, let's use that term as the appropriate one -- and that one might discourage use of febuxostat in that population but not in the broader population.

I want to raise that question, and I want to say that I'm not sure that would be the right -- the answer to the question is I don't think we should differentiate, and let me mention why.

I think the good news about the CARES study is it selected people at high risk of cardiovascular events to try to get enough events over a few years, and that was good. The bad news about studies like that is there's a collider selection bias that develops as a consequence of that.

What that means is that everybody in the study is at high risk of cardiovascular events, whether they get exposed to febuxostat, which might increase that risk or not. Therefore, it's another source of bias, one that Steve Nissen didn't mention, which biases toward the null. They might
have found an effect on MACE events, too, had they not had the problem with collider selection bias.

What it suggests is that the effect they would probably find would frankly be a larger relative risk in a population that wasn’t at risk of cardiovascular events. So I think we probably shouldn't differentiate between different people at risk.

I'm also mindful of the fact, and Jeff Curtis brought this up earlier, what we're doing with non-steroidals and whether we are -- we don't have any guidelines there, but many of us are practicing in a way, because we realize there are cardiovascular risks with some of these drugs, that are differentiating the patients that we give certain drugs.

I'm not sure whether that ought to enter into the discussion, but I think, by and large, my view of this is that there's a clear-cut benefit of febuxostat as an alternative when allopurinol, for a variety of reasons, does not work, or either is not effective, or is toxic. But I'm not sure that
we should differentiate types of patient populations where we choose here.

DR. SUAREZ-ALMAZOR: Dr. Nissen?

DR. NISSEN: I do think the understanding of the benefit-risk has changed as a result of CARES. For me, there are patient populations in which the benefits outweigh the risk, and I can name them. People that have had a serious skin reaction with allopurinol clearly belong in that category. People that are at very high risk for such reactions by HLA-type would be also in that category, and people who have high uric acid and high disease burden who absolutely don't tolerate allopurinol.

For everybody else, for the general population with gout, I would say the answer is, those people that benefit do not outweigh the risk. I think you have to have one of those categories where your likelihood of having harm from allopurinol is sufficiently high, or if allopurinol, for whatever reason, can't be taken.

How big that population is remains to be
discussed, but that's how I would frame this, based upon, now, the new information that we have from the CARES trial.

DR. SUAREZ-ALMAZOR: Sorry. Just to understand a little better your comment, you would never use in this other population?

DR. NISSEN: I'm convinced, based upon the fact that efficacy with respect to preventing gout events is not differential between the drugs, the fact that allopurinol can be given in higher doses to achieve efficacy, that as long as allopurinol is well tolerated, it doesn't have the signal for excess morbid/mortal events that febuxostat has, and therefore would be the preferred choice.

But we need a safety net. We need the safety net because there are these patients -- if you've had a Stevens-Johnson syndrome, and you've got a really high uric acid and a lot of disease burden, we need an alternative. And I'm convinced from comments from our colleagues in rheumatology here that the other available backup agents are just not effective or not available. So we've got
to have a backup, and I think that this is the appropriate backup.

DR. SUAREZ-ALMAZOR: Dr. Psaty?

DR. PSATY: Bruce Psaty. They did select high-risk patients in the CARES, but primarily to obtain higher numbers of events for the duration of follow-up. But in general, I think that the relative risk seen in primary and secondary prevention for most diseases are similar, and unless they're shown to be different, the number needed to treat may change, but the relative risk reduction tends to be the same.

That's certainly true for lipids and for hypertension. It may not be true for aspirin now with some of the recent trials. But I think we need to assume that the relative risk increase would be similar in other populations, and that's really kind of a conservative approach.

I agree with others who've stated that this drug should be available. If I had a patient with HLA-B5801, I would not want to start allopurinol in that person. If I had a person who could not
tolerate allopurinol and really needed urate-lowering, it's important to have this drug. But I think it's a very limited population in which the benefits are likely to exceed the risks.

DR. SUAREZ-ALMAZOR: Dr. Curtis?

DR. CURTIS: I think it's always fair to reframe the question a little bit. When we talk about risks of the use of febuxostat, I think we have to just ask ourselves, compared to what? I personally am not certain that there's almost any population where I feel like the risks of febuxostat would outweigh trying allopurinol. Maybe B5801 patients, the risks of reactions even in those people is high enough that I think they alone would probably give me pause, but maybe with only that exception. I can't see why anybody would start with this over allopurinol to try it.

I do agree that if people really are intolerant or have real safety issues, this would remain a good option, but I'm not sure why anyone would prefer that as first line outside of that genetic testing in that racial subpopulation that
has that polymorphism.

    I think that compared to allopurinol, there's not a lot of compelling rationale, in my own mind, based on the safety, but if the alternative is compared to nothing, then I think that compared to nothing, this is a helpful drug to have for the subgroup of people that really do have troubles with allopurinol.

    DR. SUAREZ-ALMAZOR: Dr. Ruha?

    DR. RUHA: Thank you. Michelle Ruha. I'm just trying to get a better understanding of this intolerance to allopurinol, aside from rash. Things like Stevens-Johnson, hypersensitivity syndrome, I'm told that if somebody had that to allopurinol, they were excluded from the CARES trial.

    First, do we know -- and maybe the rheumatologists can answer this -- that you can have hypersensitivity or Stevens-Johnson to allopurinol and then be put on febuxostat and do well? Has that occurred that anyone knows of or in any other trials? Then also, what is intolerance,
aside from rash? I just don't know and would like to better understand that.

DR. SUAREZ-ALMAZOR: Would anyone like to address that who's covered that before?

(No response.)

DR. RUHA: Do the FDA or the sponsor know?

DR. MEISEL: There are case reports of cross-reactivity between the two, where people had serious skin reactions to allopurinol, get put on febuxostat and react there as well. But whether that's -- it's not a hundred percent, but there are case reports where it does happen.

DR. RUHA: Well, that would almost be my assumption, which is sort of why I'm asking, is if you have a patient who had a serious hypersensitivity syndrome to allopurinol, or a really bad TEN or something, is that a patient that anyone goes and puts on febuxostat?

It sounds like that's exactly the population we want it for, where if you listen to our discussion, yet, it isn't clear to me that, really, anybody would do that or that it's been show it's
okay.

DR. NEUNER: This is Rosemarie Neuner. Last year, we relabeled the serious skin reactions as a warnings and precaution. When we added it to labeling of this, we used the sponsor's proposed language, and one of the comments was, "Many of these patients have reported similar skin reactions to allopurinol," and that was based on postmarketing case reports.

Patients with a history of serious skin reactions, or even minor skin reactions, were prohibited from entering even the pivotal phase 3 trials because of the risk of being randomized to allopurinol. So we don't have any data from randomized, controlled studies. All we have is postmarketing case reports.

DR. RUHA: Okay. It sounds like it's probably not necessarily an option if you have that type of reaction to allopurinol. So then that brings me back to a lot of people are using the word "intolerance." Is that GI? What is intolerance?
DR. RANGANATH: I wonder whether we might be confusing the term "intolerance" with failure or lack of efficacy for that particular patient, where they don't want to titrate up. They would rather not do allopurinol because it's taken them so long to be able to ramp up with a particular physician, though, in our hands, it may not be that way. I wonder if there is a confusion of terms.

MS. KNAPP: Is it okay if we address this?

DR. SUAREZ-ALMAZOR: Okay. One minute.

DR. KNAPP: Yes, please. Dr. Affinito?

DR. AFFINITO: I'll answer the question about cross-reactivity, and again, the label was changed. The genesis of that label change was 55 reports of serious skin reaction, and they were serious skin reactions. They were Stevens-Johnson's intense.

There were 55 reports for febuxostat, 11 of which had prior reactions to allopurinol. So just taking this notion of cross-reactivity a bit further -- we'll put the slide up if we can -- this is a Taiwanese study, and again, that population
you would expect would be at the highest risk for severe cutaneous reactions.

What they did is they looked at new users of febuxostat and allopurinol, and again saw a relatively low rate of hypersensitivity reactions. But I would direct your attention to those patients who had a serious cutaneous adverse reaction, and they had that to allopurinol, and then subsequently were given febuxostat and did not have a similar reaction, nor was there laboratory evidence of cross-reactivity with T cell activation.

You wouldn't expect that there would be cross-reactivity in the true sense. These are chemically distinct molecules, and this Taiwanese study supports it because these patients, who are the HLA-B type that is most feared, had a reaction to allopurinol, subsequently got febuxostat, and did not have that reaction.

DR. SUAREZ-ALMAZOR: Thank you. Dr. Liang?

DR. LIANG: Matt Liang, Boston. I would answer yes to the first part of discussion 3 question, but I would advise the FDA not to dwell
with A and B because I think these discussions of
cost benefit are extremely complicated, and if you
know anything about the science about decision
making under uncertainty, i.e., Tversky and
Kahneman, you realize that the framing of the
question drives the answer, and even that could be
open to question.

For instance, I haven't heard anything today
that would make me say there may not be a
possibility of a class effect between allopurinol
and Uloric vis-à-vis cardiovascular risk, since
most of the more stronger data, I believe, doesn't
have a comparison or a placebo. But there are so
many factors, and I think too -- and I did this for
a living in my early career, publisher on cost
benefit analysis.

I realize that this reductionist approach is
an oversimplification, and that the real purpose is
to have a dialogue with a person that you know and
a professional who can answer your questions. But
frame it in terms of the issues that are bothering
you as a patient, or you as a clinician with some
experience, about the real way that you would try
to think out loud about the problem, rather than
just make an artificial promulgation that these are
the populations where the benefits outweigh the
risk.

DR. SUAREZ-ALMAZOR: Okay. Dr. Scher on the
phone? We had a little bit of difficulty
understanding before, so maybe speak a little
slower and closer to the phone.

DR. SCHER: How's this? Better?

DR. SUAREZ-ALMAZOR: Well, start talking and
we'll let you know. Thanks.

DR. SCHER: Apologies then. I'll make my
comments brief. The first one related to the
question of intolerance, it's a fairly well
tolerated medication. Other than the skin rash,
there are a few patients that do get nausea or
diarrhea. Perhaps one aspect of allopurinol that
provides intolerance is a gouty attack when you
initiate the drug, but other than that, it is
fairly well-tolerated medication.

In terms of risk-benefit analysis, I would
somewhat disagree. I think patients that are at high risk for cardiovascular events and have other cardiovascular disease risk factors that are not under control, that would be a population in which the benefit would not outweigh the risk.

In terms of those patients that will be seeing some benefit, I would say, again, chronic kidney impairment, liver impairment, and those that truly are intolerant or have failed to control their gout with allopurinol.

DR. SUAREZ-ALMAZOR: Let me clarify because I'm not sure I understood. Did you say that the patients with cardiovascular disease are a population where benefit does not outweigh risks, or that you did not agree with that statement that someone made?

DR. SCHER: No, I think it's the contrary. [Indiscernible - audio gap] and individuals with uncontrolled cardiovascular disease would be a population in which the risk outweighed the benefit.

DR. SUAREZ-ALMAZOR: Okay. Thank you.
Dr. Kulldorff?

DR. KULLDORFF: Thank you. When it comes to our discretion to try again, death I think is one of the most serious ones, but it's also one of the more invisible ones because a physician -- if a patient has a rash or some other adverse events to allopurinol, for example, they will come back to the doctor and want some other medication that doesn't have those side effects. But a patient who has cardiovascular death will not come back to the physicians to request another medication.

What I question is we have a patient who has an adverse reaction to one medication, who maybe is very sensitive to medications. Should we then dare to put them on a different medication, which is similar, but which has an even more serious adverse reaction, or is that too risky? We don't have any data from today that's specific to this population. They could maybe have the same risk for cardiovascular death as [indiscernible], or they might be higher; we don't know.

So, I'm pondering as a non-physician whether
one should -- if one has a patient who has an adverse reaction to one medication, to put it on another one for which there are adverse reactions is even more serious, but more invisible because we don't see those patients again coming back to us.

DR. SUAREZ-ALMAZOR: We haven't talked at all about kidney disease, and this is typically used in patients with advanced chronic disease. Does the panel have any comments about whether that would be a population where it would be appropriate to start treatment with?

Dr. Oliver?

DR. OLIVER: As others have said, there is an algorithm to use allopurinol in those with chronic kidney disease. There have been some very nice studies by Stamp and the New Zealand group. What I see in practice is that it's the nephrologists and primary care physicians who are most comfortable with febuxostat and the indication for its use in chronic kidney disease.

Just as others have said, I will use allopurinol in practice in those with CKD, but it
gets taken off by the nephrologist the next time
they go. So there seems to be at least some bias
with other specialties.

DR. SUAREZ-ALMAZOR: Any more comments?

(No response.)

DR. SUAREZ-ALMAZOR: Okay. I will summarize
the panel's response to question 3. In general,
febuxostat is felt to be more of a second-line
drug, and it would only be used as a first-line
drug in those patients that are known to be at high
risk for hypersensitivity, for instance by HLA
typing, or if not, it would be used preferably on
those who have shown some sort of intolerance,
rash, or signs of hypersensitivity, and also,
perhaps GI disturbance. For the rest, it wouldn't
be appropriate, in general, as first-line
treatment.

There was a concern about its use in
patients with cardiovascular disease or with high
risk of cardiovascular disease, given the results
of the CARES study. Perhaps an analogy can be made
with what has happened with NSAIDs.
Then, we also talked a little bit about whether this could be a class effect, so it could be also an effect that allopurinol has as well. This has not been or there's not enough data to really pursue that any further, given that the studies that we have been referring to were not placebo controlled.

Any comments from the panel or add-ons? Dr. Nason?

DR. NASON: I guess I would just take that a step further and say it would be lovely to see placebo-controlled data in that context that we're talking about because there really isn't any. I don't know how that works as far as FDA and on market versus off market, but I guess I would add that it would be very useful to see both efficacy and safety in people who had already failed the allopurinol, if that's the set of people that we think this might still be useful in.

DR. SUAREZ-ALMAZOR: To see placebo controlled?

DR. NASON: Yes, because once they
failed -- yes, placebo controlled.

DR. SUAREZ-ALMAZOR: Yes, that would be probably difficult to do as there is an indication to treat these patients, so I don't know that one could design a trial including placebo.

DR. NASON: Sorry. Treat them with what, though, if they've already failed allopurinol? Am I saying it right?

DR. SUAREZ-ALMAZOR: Okay. I don't think one could have a trial with febuxostat, allopurinol, and placebo?

DR. NASON: I'm sorry if I wasn't clear. I meant of people who had already failed or had a hypersensitivity and could not take allopurinol, of those people, in that population, it would be useful to see a placebo-controlled trial since they don't have the option of allopurinol.

DR. SUAREZ-ALMAZOR: Okay.

DR. NISSEN: If I could just maybe comment a second. I'm not a rheumatologist, but I would think there would not be equipoise to do such a trial given the effects of the disease, that nobody
would want to enroll such a patient.

DR. OLIVER: It's not, but it's interesting that I think over 40 percent of patients that entered this study were not on urate-lowering therapy to begin with.

DR. NASON: I'm sorry. I know we're trying to move on, but could you just clarify that a little bit more; there's not equipoise. I thought some of the questions that had come up like Dr. Ruha had said about if somebody had had a sensitivity or a bad skin reaction, would you put them on this, and no one seemed to really have an answer to that. I'm curious why you're saying there's not equipoise in people who have had a bad reaction to allopurinol.

DR. SUAREZ-ALMAZOR: There are other treatments as well, uricosuric agents, if febuxostat was not available. So I don't think that it would be adequate to just have them on a placebo or febuxostat because there are other treatments, which also have contraindications and so forth. Pegloticase was also mentioned.
No more comments?

(No response.)

DR. SUAREZ-ALMAZOR: Okay, we will move on to question 4. Discuss the following potential regulatory activities in response to the results of the CARES study: a) update existing warning regarding cardiovascular events in the febuxostat product label; b) addition of a boxed warning for cardiovascular death to the febuxostat product label; c) modify labeling to limit use of febuxostat to second-line therapy, for example, second-line therapy in patients who have failed allopurinol; d) withdrawal of febuxostat from the market.

Dr. Nissen?

DR. NISSEN: I spent a lot of time last night, in fact a little bit of a sleepless night, trying to figure out what can we do here. So I want to speak to the review division and to all of you.

It's pretty clear from the history of all of these kinds of problems that changes in labeling,
even boxed warnings, rarely result in a major change in the utilization of drugs. They may reduce it or may reduce the growth of a drug like this, but they're not going to make use go away.

I answered that I believe that there probably are some people for whom the benefit exceeds the risk. So what I grappled with was how do we come up with a regulatory regimen, which would keep the drug as a backup for those people that I think most of us would agree there are at least somebody out there who you want to -- you don't want to have one drug on the market for something because there's always somebody out there that just absolutely can't take the drug.

When we wrote the FDA Amendments Act, we put in the potential for a variety of REMS actions, and I believe there is a REMS action here that is warranted. When this has been done for some other drugs, by some other divisions of the FDA, where the drug is available but only from a centralized pharmacy, and only if the physician and the patient sign a document, an informed consent that says we
recognize that this drug probably increases the
risk of mortality, and we accept that risk.

What that does is it puts enough of a
barrier into the mass use of the drug, that you've
got to really want to give your patient the drug in
order to actually get it. This has been done
before. I think it's warranted here and would
probably reduce utilization sufficiently to at
least, to some extent, limit the risk to patients
of the drug, and it also is important because it
does enforce shared decision making because both
the physician and the patient have to read a
statement that would be worked up in the FDA and
the sponsor about what these risks are, and they
would then be asked whether they are willing to
accept the risk or not accept the risk.

So it's not one of these options here,
although it's kind of implied in the question, but
I would at least like the agency to consider this
as a potential regulatory action.

DR. SUAREZ-ALMAZOR: Dr. Cush?

DR. CUSH: I am in favor of change. I'm not
in favor of taking it off the market. I think Dr. Nissen's suggestion is a good one, but I also think that that suggestion, I would put that in the category of what we've seen with thalidomide, or now you want to reduce the use of this drug to specialized centers and specialized people in specialized situations, and I don't know that it bears that kind of restriction of what I might call critical, nor is it deadly where I'd want to take if off the market. I think it's serious. I would recommend that it be a boxed warning with mention of use of aspirin being a part of that, and as far as an indication, that the drug should be indicated only after the use of allopurinol or when allopurinol can't be used, which currently it can be used as first-line therapy.

DR. SUAREZ-ALMAZOR: Dr. Gibson?

DR. GIBSON: I know you're gathering our input today, but some more input you might want to consider as, again, a fifth option, would be to go the FAST study DSMB and ask them to take a look at
unblinded data to see what they're seeing with
respect to cardiovascular death in that study, to
give you greater confidence about any decision that
you're making today.

There is a historic precedent for this. In
some trials we've seen Hy's Law cases with drugs.
You're about to approve the drug, but you see some
Hy's Law cases. You go look at other big trials to
see if they're also seeing some Hy's Law cases in
an unblinded fashion.

So that might give you some more data to
give you greater confidence with the decision
you're making, but I would favor option A here,
describing in detail the findings that we've seen
today.

DR. SUAREZ-ALMAZOR: Dr. Felson?

DR. FELSON: Yes, David Felson. Let me make
a comment, and then I'd like to defer to the FDA
because Steve Nissen said something about the
inefficacy or ineffectiveness of various approaches
here, and I'd like to ask you to provide some
information about boxed warnings, and second-line
therapy, and how much you can institute second-line therapy protocols or policies, and give us a sense of the effectiveness of different options we might choose here.

But before we go there, I'm quite nervous about what Steve suggested. Let me just put it in context. The majority of patients with treatable gout, many of whom have disability, are currently not receiving long-term therapy in the United States. I don't really want to put more scary barriers in front of them.

I'm thinking of a parallel, which isn't a fatal side effect of a drug, but is a necessary drug that we use for osteoporosis, bisphosphonates, which have now scared everyone off because of atypical fractures that occur very infrequently, and the rates of bisphosphonate use have dropped tremendously, and the rates of fractures that used to be going down are now going back up in part because people aren't using these drugs because they're too scared of them.

I'm nervous that we don't go so far that we
have the same effect; that we have a drug here we're talking about, whose benefit for many patients with gout I think probably outweighs its risk. It's small but a noteworthy risk that we're identifying. We want to discourage the use of that drug initially for sure. We want to have people start on allopurinol, which we're believing now is equivalently effective and probably a more or less safer drug.

But we don't want to make it so hard for them to get febuxostat after allopurinol has failed, which it not infrequently does, to make it so that they're too scared, really, to take it and to reduce their disability. I think we have to be mindful of that.

Let me stop what I was saying, and then if I can ask the FDA to provide some information for us, a little more about these options. What works? What doesn't work? What choices do we have?

DR. SEYMOUR: I was hoping you'd forget about the first part of your question because I don't honestly know if I have an answer for you. I
am not aware of data, unless somebody else from the agency is, about the effectiveness of each of these different options that we have.

Labeling is certainly something that we want to maximize, and these are the different approaches that we, as the division, are putting forward -- there may be others -- to consider for maximizing labeling. But I don't have data, per se, unless others do, on the effectiveness of changing something from first to second line, adding boxed warnings --

DR. FELSON: Can we do that, change something from first to second -- isn't that something that the American College of Rheumatology does? Does the FDA do that?

DR. SEYMOUR: I think there are guidelines, and they can certainly recommend a different order of treatment and guidelines. But we can certainly have a limitation of use in our indication. We can add information to the indication statement of only after treatment with allopurinol. We can add those types of information to the indication statement
and the product label.

    DR. NIKOLOV: Maybe I can add. We certainly rely on the community's input and decisions regarding treatment guidelines. I think when we are talking about changing an indication that's usually in the setting of a safety concern, we're trying to use the tools that we have in the labeling to limit that use. Again, that's separate from the treatment guidelines, but we certainly would like to have them concordant.

    DR. MEISEL: Can I just follow-up on this? Steve Meisel. My experience with labeling and black box warnings is that, by and large, people don't pay a whole lot of attention to them. I have a hard time even with the opioid black box warnings and so on, with the long-actings, and for acute pain, and that sort of thing. But what it does do is it provides a basis for, say, third-party payers to ask for prior authorization and those kinds of things.

    By themselves, they have limited impact, but when they're in the labeling, and now whoever,
United Healthcare, or whoever who are in terms of a payer, and you see that, and you also know this drug's more expensive, you say, okay, well, if it's a second-line agent, has a black box warning, so it will be used after, that provides them the incentive and the basis by which they would require a prior authorization.

So it has that sort of an impact, but by itself, the labeling, my experience is that has very limited impact.

DR. SUAREZ-ALMAZOR: Is your question or comment related?

DR. PSATY: I'm an occasional consultant in the Sentinel initiative, and I've seen an analysis, I can't remember the drug name, where the black box warning had no effect. Use of the drug -- and I can't remember the drug's name right now, but I can and I will eventually. Use of drug dropped after the publication of the trial, but by the time the black box warning came on, the drug use had already dropped, and the black box did not appear to have any additional effect during a time trend analysis.
So I agree with Steve that the black box warning is likely to have limited effect. The effect you described may be important. I'm not sure I would go quite as far as Steve. I wouldn't recommend withdrawing febuxostat, but it clearly should be a second-line agent in a way that can be convincingly conveyed by the FDA.

DR. SUAREZ-ALMAZOR: Dr. Horonjeff?

DR. HORONJEFF: Jen Horonjeff. What's weighing through my head are several points. I think what you brought up about the insurance companies and how they leverage this information as a patient is very important to think about; even what Dr. Nissen had said about how we can make it really more challenging to get this medication.

Again, as a patient I think, oh my gosh, how hard can it be when you are trying to get a drug that is approved, it can just be so much of a headache. I want to make sure that those who need it do not have to jump through a thousand hoops to be able to access it, and get denied because of the labels are where it should be.
All that being said, I think the sentiment is that it shouldn't be used as first line, except in these people, so how do we balance that it should go to those people, without too much headache, that actually need it?

I would also like to point out, I just searched. It looks like the ACR's guidelines are being revised to be put out for gout in 2019-2020. So I do think it would be important to make sure that these kind of discussions are included in that.

One last point is around whether or not the sponsor should also be thinking about other kinds of patient education that should be put out in relationship to this. And I don't know exactly what that looks like, but are there ways that they can be providing more resources for patients to understand the risk in a way that is accessible to them, rather than in a product label that they probably aren't reading. Those are my thoughts.

DR. FELSON: Let me just comment. My next-door protégé is the leader of the ACR
guidelines effort, and my understanding is -- and
this is why I raised the ACR guidelines
issue -- that febuxostat and allopurinol are
regarded equivalently in those guidelines. I think
what will happen is we'll make some suggestions
here that will come out on some guidelines, and
then the ACR, which is an influential organization,
is going to come out with something very different
from what we're suggesting.

DR. SUAREZ-ALMAZOR: Dr. Liang?

DR. LIANG: Liang, Boston. The target
audience is the patient and the primary care
doctors, as we've indicated in terms of the
epidemiology of prescribers, and I can tell you
that primary care physicians do not adhere to
guidelines.

The one on gout is being hotly debated to
vary between ACR, the American College of
Rheumatology, and the American College of
Physicians, over the simple concept that
rheumatologists take as an article of faith, treat
to target, and they're in a pitch battle right now.
Hopefully, your colleague will be able to resolve it, but it just shows you that there's no one cure, and I think one of the axioms of health educators is that you have to create a Chinese menu and give them simple directives at the time to make a decision.

That includes everything we've talked about, realizing that not any one of them is completely effective. But the one that will probably be the most effective are the payers, and I think that's the critical fulcrum. Everything that we can do to align what we say with something they can discipline, I think would be effective.

But adding to Dr. Nissen's suggestion, we in rheumatology now have very wonderful postmarketing surveillance for anti-TNF agents in Europe because the government pays for them. A person getting it has to register and be followed in perpetuity.

Here's the way we collect real rare events, long-term events as condition of payment. You're a part of registry that is organized where the data's collected directly from the persons involved, not
from passive surveillance like Medscape and the
18 million patient-years that we heard about
earlier. This is real surveillance data. I think
if we could get to that point, I think we could
really improve the data on which we're basing
future iterations of what we're debating now.

DR. SUAREZ-ALMAZOR: Dr. Meisel?

DR. MEISEL: Steve Meisel. I go back to the
notion that had this CARES study been available
11 years ago, 10 years ago, the drug never would
have made it to the market. But it is on the
market, and I think it's clear that there is a
small subset of patients for whom there's benefit,
and withdrawing it from the market is too extreme.

At the same time, the data in the package
insert is going to be pretty useless, and the black
box warnings will be -- which I think goes -- B and
C are sort of the same thing. You would put C into
B, but that will have minimal impact.

The idea, though, of a REMS -- what Steve
described before is maybe a little extreme on that,
the idea of going to a specialty pharmacy and that
sort of thing, if you live out in the middle of No
Place, North Dakota and trying to deal with a
specialty pharmacy is probably a barrier too far.
But there are REMS programs that can be
administered at any doctor's office. You sign up
for it, and you're going to prescribe it, and the
patient's got to sign off, yes, I understand the
risks and this sort of thing, is probably enough.

If we allow the patient to understand what
the potential risks are and let them decide whether
or not to assume those risks or to say that's not
for me; I'm going to just live with the gout, I
think it's up to them.

We have to empower the patients to make
their own decisions in an informed basis on this,
and we can do that through an effective REMS
program, properly designed, but I wouldn't go so
far as to pull this drug into a specialty pharmacy.
I think that's a barrier too far.

Would decrease utilization? Would it
decrease the use of this drug in patients who would
otherwise benefit because they get scared? Yes,
but it's their decision. As long as they're well informed, they need to assume their own risks and balances on this, do I prefer the gout or do I prefer the risk of cardiovascular mortality? Which is more important to me? And we can't make that decision for them; they've got to make that decision for themselves.

DR. SUAREZ-ALMAZOR: Dr. Kulldorff?

DR. KULLDORFF: Thank you. I did a back of the envelope calculation here. It's my understanding that about 1.3 million prescriptions are made of this drug per year. I'm assuming that these prescriptions, let's say, are 3 months of length.

If we then have 278 people as a number needed to harm, that means that this drug has killed 1,119 people per year during the last few years. That's a very large number. Of course, there's uncertainty in this number because of the confidence intervals and so on, so it could be more or less. But I think we've established that this is a dangerous drug.
The group of people that could benefit potentially of a benefit-risk assessment are those who do not tolerate allopurinol, but there has been no study on those group of people, whether there is a benefit or a risk for them.

I think Dr. Nason's suggestion of doing a randomized trial for that, and I can't tell if the -- obviously, allopurinol cannot be comparator group, but whether it should placebo or one of the other second- or third-line drugs, I can't judge. But it could either. But I think if we're going to give this drug that we know is a dangerous drug to this small group of people, we should at least give them the benefit of having a solid evidence-based, randomized trial where this drug is compared to what the alternatives are.

I think that from the perspective of patients, there's a trust that if the drug is approved by FDA, it should actually not be a dangerous drug. I think just approving it will make people assume that it is not dangerous when, in fact, in this case, it is quite a serious drug.
So I think that there is, therefore, an argument to be made for actually withdrawing the drug from the market and encourage the sponsor to do a randomized, well-designed clinical trial to compare the benefit-risk for those who do not tolerate the allopurinol drug, as Dr. Nason has suggested.

I was very much taken by the comment by Dr. Ruha, asking what is the alternative, and there was basically no answer in the room. I think that was a great question to ask, and I was very taken aback that there was no response to it. Thank you very much.

DR. SUAREZ-ALMAZOR: Dr. McAdams?

DR. McADAMS-DEMARCO: Dr. McAdams-Demarco here. My question was really surrounding the percentage of patients that start febuxostat first-line therapy. We didn't get an answer on that, so I feel like we've not heard any evidence that patients are actually starting with febuxostat as the first-line therapy.

We keep debating this point about it being
second-line therapy when we have no evidence contrary to the fact that it's not being used already as second-line therapy. So the question is what can we do to prevent more deaths moving forward?

I just would like us to keep that in mind and to maybe even think about the types of studies that would be needed, the types of data sets that could be used for the appropriate pharmacoepidemiologic study to understand what type of impact we would be having on public health by labeling this second-line therapy.

DR. SUAREZ-ALMAZOR: Okay.

DR. WILKINS: Hi. My name is Jamie Wilkins. I'm the deputy director of the Division of Risk Management and the Office of Surveillance and Epidemiology. I wanted to make some clarifications as the REMS discussion continues to go around the table quite a bit.

In the postmarketing setting, the threshold to place a REMS on a product is that we would otherwise be considering taking the product off the
market without the REMS in place, so I want to make sure to make that clarification.

Additionally, REMS, although they may suppress the use of a product, that's not their intention. Their intention is to mitigate a risk. Here, we would be mitigating the risk of MACE and how would we actually measure that outcome here if the only program we will be putting together would be informative?

What I'm hearing, aside from Dr. Nissen, is that we're hearing that the panel would like to make sure that the benefit-risk conversation that should be otherwise happening between a prescriber and patient is actually going on.

So in the postmarketing setting, unless you're otherwise suggesting to withdraw the product from the market, that a REMS is not going to be put in place from a regulatory perspective to achieve that goal, where here, we will be attempting to mitigate the risk of MACE.

We don't really have authorities in place, at this point in time, as we were outlining in the
background package, to adequately measure the mitigation of that risk and/or monitor. Are we going to have patients have EKGs done? Are we going to have CT scans? It's such a broad term, that putting a REMS in place is very difficult to actually quantify and assess whether or not it's successful in the setting of MACE.

DR. MEISEL: I'm sorry. You could put it in a registry. That's something you could use. I sit on a number of these various committees, and there are REMS programs for all sorts of drugs where there's not an alternative. The only alternative is take the drug off the market; I don't think that's accurate.

There are lots of REMS out there for drugs that would otherwise stay in market. We're trying to reduce their risk.

DR. NISSEN: I think she was referring to a postmarketing REMS; am I correct?

DR. WILKINS: Correct, because many of those REMS may have been put in place at the time of approval.
DR. NISSEN: Just if I could clarify my proposal, I was really intending this REMS to be an alternative to withdrawal. I would favor withdrawal, except for the fact that I think there is a narrow group of people for whom the benefits outweigh the risks. So I was hoping you could craft a REMS that would allow those patients to continue to get the drug. It was intended as an alternative to withdrawal.

DR. WILKINS: And your suggestion, Dr. Nissen, would be a REMS that actually limits the patient population.

DR. NISSEN: Well, that requires a very clear, informed consent, signed by the patient, signed by the physician, that outlines the population in whom the drug is indicated.

Since I have the floor, could I just finish? I wanted to make at least one or two more comments. The issue about whether labeling can solve our problem for us, I lived through a couple of these. I was on the panel many years ago that put a warning on Vioxx, and after that warning went on,
10 million people after the warning went on got the drug. I remember the agency with Baycol had learned that giving gemfibrozil with Baycol, greatly increased the risk of rhabdomyolysis. And they warned, and they warned, and they warned, and they warned, and people kept getting the two drugs together, and eventually Baycol had to be withdrawn from the market.

So history has told us that we can't solve the problem with labeling. I wish my colleagues around the world, around the country, read labels, but the reality is a lot of doctors don't read labels and so on.

Then one final comment; relying upon the payers to solve the problem for us, there's an issue here, which is this drug isn't going to be branded forever. So what happens when the drug is no longer expensive, and the PBMs are no longer restricting use?

We have to plan this regulatory strategy for the long haul, for what's going to happen 5 and 10 years from now, and I don't know when the
exclusivity ends, but it will end at some point,
and then the PBMs are going to no longer be
involved in mitigating the risk.

DR. SUAREZ-ALMAZOR: Dr. Oliver?

DR. OLIVER: Most of my comments have just
been stated by others. I would argue that it's
already a second-line drug, as Dr. DeMarco said.
At the end of the day, if you want to participate
in patient-centered care, it's sitting down with
the patient, exploring and explaining the risks of
the drug, and weighing if their burden of disease
warrants the use of this drug.

DR. SUAREZ-ALMAZOR: Dr. Chung?

DR. CHUNG: I think one needs to consider
the public health consequences of overstating the
risks for a disease that's already, I think as
stated, undertreated and for which there are very
few acceptable options. [Indiscernible]
anticipated, the FAST study results will be coming,
and it seems premature to make dramatic changes in
light of still some remaining uncertainties and the
importance of febuxostat in the management of gout.
In terms of putting the sequence of use within the label, I think there are cases in which physicians may want to use febuxostat first, as had been stated by Dr. Liang and others. I think this is a very complicated decision, and it's really unique for each patient. The change of the label may limit the patients who may appropriately need it.

Perhaps the appropriate setting for the communication and education would be between the physician and the patient, with the guidance of professional societies such as ACR.

DR. SUAREZ-ALMAZOR: Okay.

DR. CUSH: I want some clarification. Are you saying that we cannot, as part of a REMS program, mandate an educational program?

DR. WILKINS: Jamie Wilkins, FDA. REMS can absolutely mandate an educational program, but we have to craft a program that's going to mitigate a risk, and we also have to assess any program that we put together. So we have to think about both ends of that spectrum, when we would put a program
together, to mitigate MACE in this case.

    If we're simply informing here, how is that
going to be measured to mitigate this risk of MACE,
when that benefit-risk discussion should be your
baseline practice between a patient and
practitioner?

    DR. CUSH: But if that's not happening
because they don't know enough, maybe they need to
know enough so that might could happen.

    DR. WILKINS: But you're saying the
prescriber doesn't know enough about it.

    DR. CUSH: Yes.

    DR. WILKINS: I mean, that's something we'd
have to take back and discuss. However, again,
assessing a program for MACE is generally, without
thinking about how to put together a proper
assessment for that, is going to lead to a program
that we're not able to find out if it's being
successful.

    DR. CUSH: But we heard from many people on
the panel that one of the major problems here is
education, because we're concerned about this small
risk of cardiovascular death, and that's what we're trying to ultimately affect. So again, I think it should be part of a REMS program or a postmarketing commitment.

DR. MEISEL: Steve Meisel again. I go back to the -- it may not be perfect, but you could establish a registry, so that if people are going to be prescribed this drug, they get enrolled in the registry and there's data monitored over a longer period of time. There are ways of getting to some data that could be maybe imperfect, but creative.

DR. WILKINS: And to the point about a registry, that would then impart likely a quite restrictive program where there would be mandatory patient enrollment into a REMS, and therefore, it would have to go through a restricted distribution pharmacy that's verifying that the patient and the prescriber are both enrolled. So it can't be built in a microcosm without a lot of this burdensome restrictive program.

I hear your suggestion, but just so that the
rest of the panel understands, to get to that registry, it would require patient enrollment, prescriber enrollment, and therefore, a pharmacy to be able to verify both of those requirements before the drug was dispensed.

DR. CUSH: To me, this is unlike the narcotic situation where education has become a big part of the REMS, and you're looking at the same outcome; death.

DR. SUAREZ-ALMAZOR: We're getting close to the vote. There's a couple of points on question 4 that were not discussed. Most of the discussion was around B, the boxed warning, or C, modifying labeling for second-line therapy. But there was really not a lot of discussion about A, update existing warning regarding cardiovascular events and what's already there, and about D, which is complete withdrawal of the drug from the market.

So before we move to the voting, does anyone have any comments about any of those?

DR. GIBSON: Again, I'd recommend A. I think it already is second-line therapy, and I
think it should be a discussion between physicians and patients.

DR. SUAREZ-ALMAZOR: Okay. So let me summarize. I think there are two overarching concepts that guided the discussion. One was the fact that most patients with gout are not treated adequately and that, perhaps, any strategy that results in additional undertreatment could end up being deleterious.

The other one is that the strategies or regulatory activities should consider the target, and that could be the patient, the PCP, the rheumatologist, and third-party payers. It was felt that warnings, such a boxed warning, don't have a lot of effect on physicians but might have effect on patients. And also on third-party payers, although there was a concern that once the drug becomes generic, that effect on third-party payers may not be sufficient.

A big concern was education of physicians and the fact that they are not really knowledgeable about some of these issues and having a REMS
program was one of the suggestions that was brought forward, but the FDA feels that that's very difficult to implement once a drug is out there being used. And that's something that usually happens at the beginning of approval when a registry is established. It would also require more centralization and more restriction in the use of the drug.

There were a couple other strategies that were brought up that were not in the list that we have here. One was doing an additional trial, again, in patients who did not tolerate allopurinol, comparing febuxostat with placebo. That was felt by some that it could be important. Others felt that that could be very difficult to do, and possibly unethical. It had been discussed before.

Also, having a surveillance system or a registry to try to continue to monitor the effect of this drug in the population at large was felt as something that could be important. Then, in general, most people felt that this is really a
second-line therapy, although, if I understood correctly, there were a couple of people that felt that in addition to the cases that we mentioned before of hypersensitivity or intolerance, that some physicians might want to use febuxostat as a first line, and perhaps there should be a shared decision mechanism with informed consent that would allow for this drug to be used initially, although, in general, I think the consensus was more along second-line use.

DR. NISSEN: If I could just add one additional comment. I gave my answer on the assumption that a REMS could be constructed, and I just wanted to make clear that my belief is that if a REMS can't be developed, then I would favor withdrawal of the drug. If we can't find a way to do this, in a way that protects patients from getting the drug inappropriately, then my answer to that question would have been different, and the answer would be to withdraw.

DR. SUAREZ-ALMAZOR: We have Dr. Scher on the phone, who has a comment as well. Go ahead.
DR. SCHER: Yes. I just don't know if there's any precedent for this and whether or not this will be controversial. But is there a way for restricting the prescription of these drugs to rheumatologists?

The idea behind that is not to increase the burden on ourselves, but rather make it a true second-line drug. That way we, in fact, will be able to titrate allopurinol to the degree we can, and then move forward to febuxostat if that strategy has failed. So I guess the question was to the FDA.

DR. SUAREZ-ALMAZOR: FDA?

DR. SEYMOUR: I don't know that we can restrict the drug to rheumatologists. That would be extremely restrictive, and I would imagine have to be under some kind of REMS, very restrictive REMS program.

DR. MEISEL: Steve Meisel. I would also suggest that in the big city, that might be okay. If you're in the middle of No Place, North Dakota, where there may not be a rheumatologist, those
kinds of barriers would be a bit too much of a barrier.

DR. NISSEN: There are some cardiovascular drugs where you require the physician to have training and certification in order to give the drug, like dofetilide is a great example, where there's a big risk of proarrhythmia. You've done some REMS where it isn't related to their specialty, but it's related to having to undergo mandatory training in order to be able to use the drug, and I assume that would be on the table.

DR. SUAREZ-ALMAZOR: We will take the three final comments of the people who have raised their names, and then we'll move on to the voting.

Dr. Warholak?

DR. WARHOLAK: I came into this meeting today thinking that I favored a black box warning and making sure that the drug was second line, but if those don't have any effect, I feel like it's really important to make sure that we enforce the conversation that the provider should be having with the patient, so that the patient knows this a
risk. It's up to them to assume that risk, and I think there is some people for whom this drug may be beneficial, but they should know what they're getting into.

So I have a hard time believing that we can't construct a REMS that would at least, at the very minimum, require the patient to sign a contract with the provider, so that they understand. There's probably people who are willing to take that risk and people who aren't. But it's really up to them because they pay the price. So whatever we need to do to make that happen, I think it needs to happen.

DR. NIKOLOV: This is Nikolay Nikolov. May I just add a comment here? First, it's certainly disappointing for us to hear that the clinicians don't read the labels and labels don't have an impact. We always thought that labeling is the main tool that we have to communicate to prescribers.

It sounds like the discussion now revolves more around the lack of impact of any labeling
changes, and I'm not really sure whether we have any data to support that statement, and we certainly want to be very careful about making major decisions based on no data that at least we can refer to.

Maybe one point of clarification on the calculations from Dr. Kulldorff, you threw in an interesting number of how many deaths this drug may have caused on the marketplace when these estimates are based on a different patient population. The number needed to harm was based on patient population with cardiovascular disease.

This is just a word of caution; maybe I'm wrong.

DR. KULLDORFF: That's very true. I used the same attributable risk for the whole population, and that may or may not be true. It could be higher; it could be lower.

DR. NIKOLOV: I certainly want to have more balanced discussion and think about the facts.

DR. SUAREZ-ALMAZOR: Dr. Felson?

DR. FELSON: I guess I'm finding myself in
an unusual spot because the last time we had an FDA meeting about a gout treatment, I basically led the charge to not approve it, and it was because it was canakinumab. It was a drug that could kill people, and I thought this was a morbid disease and not a fatal one. I'm finding myself on the opposite side of this fence this time.

I tried the bisphosphonate example. Let me try a different example with you and try to figure out how this agrees with that example, which is oral diclofenac, which is a drug that's far more dangerous and kills far more people than this drug does now or will.

It's a drug that's associated with a two-fold increase in myocardial infarction, including all MACE events, not just cardiovascular mortality.

Oral diclofenac was a very, very popular drug. The most popular non-steroidal in Europe, and one of the most popular in the States, until about 2007 or 2008, when the American Heart Association and the British Heart Association both
came out with statements. Elliott Antman wrote the one in the United States that said, "Stop using this because it's terribly dangerous," and ACR publicized that risk.

Now, I don't know that the FDA put a label on it, but the reason I'm bringing it up is wondering how we get a drug to be dealt with seriously that has dangerous side effects.

What happened to oral diclofenac use was that its use dropped like a stone over the next two to three years after that, both in the United States and in the UK, and I think that's probably good.

Now, if we were all to discuss whether oral diclofenac ought to be taken off the market, this is a situation where's 34 other competitive drugs, many of which are better and safer than diclofenac. I don't think any of us would have any trouble, frankly, removing it from the market because of all the alternatives.

In this case, we're dealing with a drug that's quite effective. I have patients on it.
They like it. I can't tell you that from a public health perspective that's a great -- I'm mean, I'm speaking as an anecdotal clinician and not as a public health person right now. But allopurinol is not the solution in many patients with gout, for a lot of reasons, and this is a very reasonable alternative for a disease that's often very disabling. I'd be, frankly, very nervous about removing that option from patients.

I'm distressed that we can't come up with Steve's middle ground approach, but I'm really scared of removing an effective drug from the market that's offered a lot of help to people. I'd like to do anything I can to make sure that patients are apprised of that risk, and that physicians, hopefully like they now occasionally do with oral diclofenac, say I'm not crazy about prescribing this drug because I know now that it's quite dangerous. But I'm not thrilled about the idea of removing a drug from the market that works for a lot of people.

DR. SUAREZ-ALMAZOR: Okay. We are wrapping
up, Dr. Cush. No vote? Okay.

Dr. McAdams, just one minute, because we have to get to the vote.

DR. McADAMS-DEMARCO: Yes, very quickly. There's not really been any discussion about the findings in which taking low-dose aspirin did not increase the risk associated with febuxostat.

Would that be something that would be worth including in the labeling, or is there any way that that could come in to help get past this stalemate?

DR. CURTIS: I just had something very quick. I'm a little bit disturbed, sort of picking up on Terry's comment, that people seem anxious about B or C based upon some anecdotes that maybe labeling isn't very effective. I don't feel like we spent any time talking about how effective FDA labeling is or boxed warning is on prescribing.

David, I think your example might be a counterpoint to others we've heard of, but I would be very nervous to say B and C are not acceptable, but maybe they otherwise would have been, based upon a couple anecdotes about what somebody thinks
is or isn't effective in terms of what the FDA labeling can do. That feels very unsubstantiated and vague.

So I guess I personally wasn't very dissuaded from labeling changes, given this somewhat vague, perhaps evidence or just some perceptions that maybe labeling doesn't help or change prescribing patterns. I'm not convinced that we have any certainty that that is true, and I think labeling is quite appropriate to illustrate warning.

DR. SUAREZ-ALMAZOR: Okay. We're going to move on then to question 5 and the voting. Based upon the available data, is there a patient population in which the benefit-risk profile for febuxostat is favorable for the treatment of hyperuricemia in patients with gout? Yes or no?

If you voted yes, describe the patient population with a favorable benefit-risk profile for use of febuxostat. Also describe any other recommendations, for example, labeling changes you may have for use of febuxostat in this population.
If you voted no, discuss your rationale, the impact of this recommendation, and any other recommendations you may have.

Does anyone have any clarifying questions about the question, per se, the voting question?

(No response.)

DR. SUAREZ-ALMAZOR: No? You have three buttons here: yes, no, and abstain, and then we'll go around after you've voted, and you can explain your vote briefly, as we are supposed to adjourn at 5:00.

DR. GIBSON: By favorable, do you mean relative or allopurinol or placebo?

DR. SUAREZ-ALMAZOR: FDA?

DR. GIBSON: It says favorable. Is that relative to allopurinol or placebo?

DR. NIKOLOV: This is Nikolay Nikolov. It's favorable with respect to the currently approved indication, which is the broader first-line therapy.

DR. SUAREZ-ALMAZOR: You can vote now.

(Voting.)
DR. SUAREZ-ALMAZOR: We are waiting for Dr. Scher's vote. Someone has to vote for him.

DR. WANG: For the record, we have 19 yes, and 2 noes, and one abstain.

DR. SUAREZ-ALMAZOR: We will start stating our vote from my left. State your name, what you voted, and the reasons for your vote, and any additional comments on labeling you may have.

DR. GIBSON: Looks like I'm first. I voted yes. Again, I think the p-value was fragile, a p of 0.03, not significant when you look on treatment; when you look at the 87 percent of people who had complete data, no significant increase in cardiovascular or all-cause mortality.

So I felt that option A was best, but I do think that consulting with the FAST Data Safety Monitoring Board to look at unblinded data from their ongoing trial would be something that's reasonable. I think this is a treatment that's already second line and is used in 4 percent of patients.

I would suggest a Dear Healthcare Provider
letter, and I would suggest that patients and
doctors make informed choices. I don't know that
it's the job of the FDA to enforce those
conversations; that's what physicians should be
doing. Part of the conversation should be, or
could be, that if you're on aspirin, that would
minimize the risk.

DR. HABEL: Laurie Habel. I also voted yes.
I think that the benefits outweigh the risk in
patients who fail allopurinol or are intolerant, or
at an increased risk for hypersensitivity.

I think that I would recommend that there be
changes in the labeling to include the CARES
results, even though they are not definitive. And
I don't know whether that should be a boxed warning
or some other labeling that actually would result
in more restrictive use and encourage it as a
second-line therapy.

I like the idea of a letter or some sort of
material that doctors can use with patients; that
actually risk is so hard to communicate, that can
improve risk communication with patients, so that
they really can make an informed decision. I would hope that we could encourage professional societies to also recommend this drug as a second-line therapy.

I am concerned about barriers that would make the drug too difficult for patients who really need the drug. It's such a disabling disease that I would think that would be unfortunate if that was the result.

DR. RANGANATH: I'm Venna Ranganath. I voted yes, and I do think that there is a specific niche for patients who need to use febuxostat, where allopurinol may not either be tolerated or efficacious.

I do think that we do need to update the existed warning for cardiovascular events using the CARES data. I definitely think that -- well, as a rheumatologist, I think we already use febuxostat as a second-line agent and perhaps the American College of Rheumatology. I know that the EULAR update did use allopurinol as a first-line agent, but I wouldn't be opposed to see.
I'm a little concerned about B in that it may be difficult for me to convince the patient who needs febuxostat due to this label warning. I do have a lot of conversations with the patients, and I do think many of my colleagues in rheumatology do. I would be opposed to D, withdrawing the drug from the market.

DR. OLIVER: Alyce Oliver. I voted yes. I do think there is a need for this drug in a certain patient population who's been intolerant to allopurinol or where the drug has had no efficacy. I favor modifying the labeling, and there should be consideration for adding aspirin use.

Certainly, there needs to be more physician education so that there is an appropriate discussion of the benefit and risk that is made between the physician and the patient. How best to do that, I've heard a lot of suggestions. I think that's the FDA's hardest part.

DR. KULLDORFF: I voted no. I think that there's evidence that the drug causes death in some people. I think that there's no benefit-risk scale
for people who can't take the allopurinol. For
those who don't benefit from allopurinol or are
sensitive to it, there has been no study to
actually show that there is a benefit or there is
more benefit than risk in that group, so I think we
basically don't know.

I think that the future of this drug should
be, for the moment, to withdraw it from the market,
and then encourage to have a proper clinical trial
to study the drug among those who do not tolerate
allopurinol, to do a randomized trial.

DR. CURTIS: Jeff Curtis. I voted yes. I
would favor strengthening the warning. I think
that it's reasonable to mention the NSAID and the
aspirin potential interaction. At worst, the rate
difference is 4 per 1,000. That's not
inconsequential, but that's also in the highest
risk patient population one could possibly find,
which are those in the CARES trial, and we learned
that the generalizability of that high-risk group
is, in fact, not even very good to a gout
population. So I guess if that's the worst of it,
then I think stronger labeling, but not to impose a severely restrictive REMS nor to pull the drug from the market.

I think we mostly have evidence that this is a second-line therapy. I think it would be reasonable to change the indication, and my only carveout would be those with the B5801 polymorphism.

DR. GRIFFIN: I voted yes. I believe that there's a very small group of people who could benefit from this, but probably a lot fewer than are taking it now. I think there should be some ways to mitigate that risk. I think there can be monitoring of whether people are using this drug as first-line therapy. Marie Griffin.

DR. NISSEN: Steve Nissen. I voted no, and I want to be clear why. I wanted to vote yes, and I could vote yes, but I believe that patients need to be informed of these risks. I think the idea of an informed consent is critical.

So I was discouraged that FDA OSE doesn't think that a REMS can be constructed here. If a
REMS could be constructed that would ensure that
the patients who are truly intolerant to
allopurinol are the ones that get febuxostat, then
I would be okay with keeping the drug on the
market. But in the absence of that, I do not think
that warning labels work, and I think there's
actually quite ample literature to suggest that the
effect of even boxed warnings on utilization of
drugs, this far into the market, is very limited.

So we might see a leveling off of the growth
of the product or maybe a slight decline, but I
think you'd still have very large numbers of people
getting the drug. So unless a REMS can be
constructed that informs patients and allows them
to make an informed choice, then I do not think the
drug should be available.

I would love to get to yes, and I would
challenge the agency to come up with a REMS that
you can do, that would protect patients, so that
large numbers of people for whom the drug is
inappropriate don't get the drug. I've been very
discouraged by the efficacy of warning labels and
even boxed warnings in the past, and I think it would be particularly true here, where you have so many primary care physicians, so many people out there treating gout, that the efficacy -- I mean, busy primary care practitioners just don't read the label, and we kind of know that from the medical literature.

DR. RUHA: Michelle Ruha. I voted yes. I also agree I would favor a REMS for informed consent for patients so they really understood the potential risks and the results of the CARES. But if there wasn't a REMS, I'm a little bit more optimistic. I'd love to see the data from the FDA sometimes about effective boxed warnings and the label changes, but I would like to see it labeled as a second-line agent for people who can't take allopurinol. I'd also maybe favor a recommendation to take it with aspirin and boxed warning.

DR. CUSH: Jack Cush. I voted yes. I voted yes because I'd like to see the drug continue to be used but used with greater intelligence and with restriction. I would recommend strong, if not
radical, changes to the label, including a boxed warning. I don't think the problem is that people don't read boxed warnings. I think the problem is that people don't read the package insert until they have a question about something inconsequential, and they go and read three lines and they're done, so that's another problem. But I think there has to be a strong educational commitment by the manufacturer to right this wrong.

DR. MEISEL: Steve Meisel. I voted yes, and I'll just point out that I've been to a number of these meetings, and I would suggest the agency go to question writing 101 school because this question is really not getting at the answer here.

The yes is that the drug is favorable in a very limited population, and that is patients who need uric acid reduction, who can't tolerate, who have adverse effects to allopurinol, and to whom those adverse effects wouldn't translate to this particular drug. It has nothing to do with efficacy. There's nothing to suggest that patients for which allopurinol is ineffective would respond
to this drug as long as allopurinol is used correctly. I think that's a clarification there. It's only those who are intolerant, and for those who are informed.

Now, how do you make it informed? The only way to require the inform is through a REMS-type of program that we talked about. And I frankly reject the notion that the FDA is powerless to put a REMS in because if the alternative is to withdraw this drug from the market, I think there are many people here today who voted yes because they believe the drug ought to be available for this limited population. But we know the risks, and if you're giving us the choice of take it off the market or do nothing, or we'll just put in a black box warning, well maybe we take it off the market.

So there's got to be a middle ground here of some sort of a REMS with an informed consent type of arrangement, and let the patients make that choice. I believe that very strongly.

DR. SUAREZ-ALMAZOR: Maria Suarez-Almazor. I voted yes. I think gout is a disabling disease,
and there are very few options to treat it. I would recommend changing the labeling to second-line treatment, after failing allopurinol, either because of adverse events or efficacy. An exception would be those patients who are known to have risk for hypersensitivity through prior testing or family history.

I would recommend a boxed warning for cardiovascular death, but given that is primarily based on the CARES study, I think it should be for patients with pre-existing cardiovascular disease. I would also favor having in the label that there is an increased risk after discontinuation during the first 30 days, as well as interactions with NSAID and aspirin.

Dr. Scher?

DR. SCHER: Jose Scher. I voted yes. I agree with Dr. Cush and Dr. Suarez. I would add a warning box of CV death right to the label, modify to make it a second-line therapy, and I would take a step further and recommend the evolution of a cardiologist by the time someone decides to stop
febuxostat.

REMS is a good idea. I would recommend that as well, and somehow restricting the use of febuxostat, either through training or other mechanisms that the FDA has available, would be my choice.

DR. WARHOLAK: This is Terry Warholak, and I voted yes. I do believe that there's a very small subset of patients for whom this medication is very important, and it should be remaining for those patients, and it should be an option. I do think there should be a black box warning. I think that it should make sure in the label that's it second-line therapy.

But I also do think that it behooves everybody to make sure -- the sponsor and the FDA to make sure that the providers know about this, especially primary care providers, and to make sure that they have that conversation with patients. I'd be in favor of a REMS or a consent.

I think in the essence of patient-centered care, it should be the patient's decision, and
there's got to be a way to convey that to patients so that they understand that it's not too scary, and that gives them the option as well.

So I implore the sponsor to work with the FDA to come up with some standardized language that can be used, even in the absence of a REMS.

But the other thing that I think is really important, we've had a lot of discussion about whether a black box warning is effective or labeling changes. I think it's really difficult for us to make these recommendations if we don't really know.

So I think that it would be really important for the FDA next time to gather some information so that we have some statistics on impact of what we might do, so that we can ensure that whatever recommendations we're making will actually have the intended result.

DR. SUAREZ-ALMAZOR: Okay. Dr. Miller?

DR. MILLER: Thank you. I voted yes. I think this is a drug that we definitely need to have on the market. Gout is under treated, as has
been mentioned, and this is a drug that will help certain people.

Good point about the overall risk, that the risk would be about -- the number needed to harm is about 250 in a high-risk population, much less than that in an average-risk population, so I'm really against REMS or things that restrict use of the drug too much. I'm fine with any kind of labeling change but keep it on the market and keep it available.

DR. HORONJEFF: Jennifer Horonjeff. I voted yes. I agree with the sentiment going around. I want to make sure that the patients that need it have access to it. I believe second-line therapy is appropriate unless it creates more barriers for those particular patients to get it.

That may have to do with the payers putting on extra restrictions, but in general, I think that that is appropriate. I think adding a black box warning is also appropriate. Whether or not people are looking at that, it doesn't hurt to put it on there, I don't believe.
If in the context of having other trials, I would certainly encourage, if anything else goes forward, to include other patient-reported outcomes and other things that we can collect in order to weigh out the correct cost benefit analysis.

I'm throwing this out there. I'm not sure where this may lie, but something that comes to mind would be whether or not we could restrict any sort of direct-to-consumer marketing for something like this, that has more adverse effects.

MR. WEINER: Gene Weiner. I voted yes. I've experienced a number of debilitating bouts with gout, and they were really terrible. I was fortunate enough that allopurinol worked for me. But in thinking about this and listening to Dr. Edwards presentation, and the second line of defense, I would think that those that could not be helped, as I was, would need another approach, and I thought this would be an alternative for them.

DR. NASON: Martha Nason. I voted yes. I think I agree with pretty much everyone around this table, including the people who voted no, as so
often happens. There's maybe not that much of a difference between the noes and the yeses. I think we all have some consensus, as do I, that this should be a second-line therapy for people who cannot tolerate or for some reason cannot take allopurinol.

The only thing I would add, I guess, is it just seems to fit with the other -- to me, as a non-clinician, it seems to fit with the other second and third-line therapies, and so I am, I guess, optimistic that there is a way to educate people.

Just given that when I asked questions of my colleagues around the table about, well what would you do as a second-line therapy or if someone's failing if you didn't do this, the answer was, oh well, these other ones are scary and have all these side effects. So clearly, that information has gotten through. Those are still on the market. They have not been withdrawn, even though they may have negative effects.

So this seems to fit that paradigm to me.
that it could be, with proper education, a 
second-line therapy where people understand that 
there could be negatives and it should only be used 
in that way. So that's all.

DR. PSATY: Bruce Psaty. I attempted to 
vote yes, but it was inappropriately recorded as 
abstain. I think there's likely to be a group 
where the benefit exceeds the risk in those who are 
intolerant of allopurinol or failed allopurinol 
therapy. I think it's likely to be a small group. 

I would be cautious about advising the 
concomitant use of aspirin, since that's not 
terribly effective in primary prevention, so that 
would not be something that should go in the label. 
And I just wanted to clarify, my point about 
changes in use is that probably the changes in use 
of febuxostat occurred already with the publication 
of the trial. And by the time the black box label 
goes on, those changes will have occurred, and the 
black box tends to have little effect at that 
point.

I'm happy for you to include it. There is a
large literature suggesting not much effect on FDA label changes, so you could provide that. I am concerned about the risk here and would like to make sure patients are well informed, so a REMS or something like it, or a consent document would be desirable. Thank you.

DR. LIANG: Matt Liang, Boston. I recorded abstain because I didn't like the question. I didn't think it got at what we're trying to discuss today. I see a signal, and I think it's our moral duty to get it out to the physicians and to potential patients who are going to get this as a prescription.

I think the black label is far better than the drug insert, and it can be effective, I believe, if it's treated like a checklist where we tell people to take a time out and check the identification bracelet before you cut the wrong limb off kind of thing.

I think as Marie Griffin taught me once, it's no good for the primary care doctor who is actually making these decisions, more than that, to
tell them yet another thing they have to do, but without anything to substitute for the warning that this might increase cardiac events. And I think that would be an opportunity to talk about identifying and maximizing the management of known risk factors including, gout, hyperuricemia, and all the other ones that we know.

DR. McADAMS-DEMARCO: Mara McAdams-Demarco. I voted yes. I do, again, echo the concerns that have already been noted but feel that there is a clear benefit that outweighs the risk for those patients who have already failed or are intolerant of allopurinol.

I would also recommend a boxed warning stating that this is a second-line therapy. I think that should be clearly noted in the boxed labeling, so that hopefully the recommendations will carry over to the ACR.

I do also encourage OSE to develop ways to deal with REMS with postmarketing safety studies. With the introduction of FDAAA, we're going to be seeing more and more trials coming out that are
postmarketing, and if they really only are stuck in a binary world where it's either to remove the drug from market or to make a labeling change, there really aren't going to be enough options on the table with new information coming in.

DR. FELSON: Hi. This is David Felson, and I voted yes for the patients who will need this. I must ask the FDA to -- because we were basically at C with respect to figuring out which of the options you offered us might actually work. We're hearing anecdotes that this doesn't work, and we're hearing from Bruce there's a variety of studies that say it doesn't work.

It would helpful for the FDA to present the actual data to us as to what might work and what might not work, with respect to encouraging discussions between physicians and patients affecting use. And if there are experiments going on that are trying out new ways of doing this, new ways of labeling, new ways of black box warnings, it would be helpful for us to hear about that, too, so we might make suggestions as to -- I mean, it's
clear that this is an issue that the FDA is facing, not just here, and it would be helpful for us, in advising you and thinking through things with you, to be informed about all of what is known.

DR. SUAREZ-ALMAZOR: Dr. Psaty and Dr. Liang, it seems there was a little bit of a mix-up with your votes, so if each of you could state your name and what you voted, again, into the microphone.

DR. PSATY: Bruce Psaty. I voted yes.
DR. LIANG: Matt Liang, abstain.
DR. SUAREZ-ALMAZOR: Okay. Thank you.

Before we adjourn, are there any last comments from the FDA?

DR. NIKOLOV: This is Nikolay Nikolov. First of all, I would really like to thank the committee for a very, very productive discussion today. I think we got a lot out of this, and I think we have a lot to think through and work on. I think this was an extremely helpful feedback that we received. We're looking for more meetings for the next advisory committees with you.
Adjournment

DR. SUAREZ-ALMAZOR: Please take all your personal belongings with you, as anything that's left on the table will be disposed of. Also, remember to drop off your name badge at the registration desk for recycling, and we will now adjourn the meeting. Thank you very much.

(Whereupon, at 5:15 p.m., the meeting was adjourned.)