U.S. FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

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ARTHRITIS ADVISORY COMMITTEE (AAC) MEETING

ARCOXIA™ (ETORICOXIB)

(NDA 21-389 and NDA 21-772)

- - -

THURSDAY, APRIL 12, 2007

8:30 A.M. to 4:05 P.M.

- - -

GAITHERSBURG HILTON

620 PERRY PARKWAY

GRAND BALLROOM

GAITHERSBURG, MARYLAND

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P R O C E E D I N G S

(8:30 A.M.)

CALL TO ORDER

CHAIRMAN TURK: (Acting Chair) My name is Dennis Turk. I'm the acting chair for the Arthritis Advisory Committee for the Food and Drug Administration. There are a couple of things that I want to orient you to as we get started on this meeting. This meeting is an FDA/AAC-convened meeting to discuss a new application NDA 21-772 Arcoxia™ (Etoricoxib). Merck & Company has proposed this as a treatment for the signs and symptoms of osteoarthritis.

I have to make an official statement for the record. Today's meeting will have a lot of discussion which will result in recommendations at the end of the day from the Committee for the Food and Drug Administration.

We are aware that members of the media are anxious to speak with the members of the Committee and the FDA about these proceedings. However, both the committee members and the FDA must refrain from

discussing the details of this meeting with the media until its conclusion.

At that time the FDA will hold a press briefing for members of the credentialed media to discuss the recommendations from the Committee and to take any questions that they may have.

A couple of other orientation questions, for those of you that have cell phones, please either turn them off or mute them so that they will not interfere with the presentations.

For the members of the panel, you will notice that there are microphones in front of you. When you want to speak, you should try to make sure that Johanna Clifford, sitting on my right, catches your eye. She will try to record you, roughly, in the order that she sees you.

When you're speaking, turn on your microphone. When you're finished speaking, please turn off your microphone. That is to keep down the amount of noise that is going to be going on. So for those, that's some information.

We're going to have a number of

presentations, which we're going to go through very shortly to review the agenda; however, the way that we're going to try to structure things to make sure we accomplish as much as we can in the time available, is to hold questions until after all of the speakers have had an opportunity to present.

However, if you have a clarifying question, that is, not something that is specifically challenging or asking for additional information but rather just to clarify something that has been presented, we will take those questions after the presentations.

Although, we're going to try to take people in the order of the questions that they have, I'm going to try to keep us on certain topics and certain targets. So if in fact questions are our of order, I may ask people to hold that question until we get to that particular area so that in fact we can keep all of the questions related at the same point in time. Hopefully, that's clear to everybody.

INTRODUCTION OF COMMITTEE

CHAIRMAN TURK: What I would like to do now

is to begin having the Committee introduce themselves. If we could start on the far right, my far right or my far left, Dr. Jenkins.

DR. JENKINS: Good morning. I'm John Jenkins. I'm the director of the Office of New Drugs in the Center for Drug Evaluation and Research of FDA.

DR. MEYER: I'm Dr. Robert Meyer. I'm the director of the Office of Drug Evaluation, too, in the Office of New Drugs at the Center for Drugs at FDA.

DR. RAPPAPORT: I'm Bob Rappaport. I'm the division director for the Division of Anesthesia, Analgesia and Rheumatology Drug Products in CDER, FDA.

DR. HERTZ: Good morning. I'm Sharon Hertz, deputy director for the Division of Anesthesia, Analgesia and Rheumatology Products.

DR. SHIBUYA: Bob Shibuya, medical officer, Division of Anesthesia, Analgesia and Rheumatology Products.

DR. MORRIS: Lou Morris, Lou Morris & Associates.

DR. GARDNER: Jacqueline Gardner, professor of pharmacy, University of Washington.

DR. HENNESSY: Good morning. I am Sean Hennessy. I do pharmacoepidemiology research at the University of Pennsylvania.

DR. CRAWFORD: Good morning. Stephanie Crawford, University of Illinois at Chicago, College of Pharmacy, very happy to arrive after our little spring snowstorm yesterday.

DR. R. CANNON: I am Richard Cannon. I am the head of the Section of Cardiology, and I am clinical director for the Division of Intramural Research for the National Heart, Lung and Blood Institute.

DR. LEVIN: Arthur Levin, director of the Center for Medical Consumers and the consumer representative on the Drug Safety & Risk Management Advisory Committee.

DR. BOULWARE: I'm Dennis Boulware, a professor of medicine and a rheumatologist at the University of Alabama at Birmingham.

DR. STINE: Hi. I'm Bob Stine. I'm from the Department of Statistics at the University of Pennsylvania.

DR. TURK: I am Dennis Turk. I am John and Emma Bonica Professor of Anesthesiology and Pain Research at the University of Washington.

MS. CLIFFORD: Good morning. Johanna Clifford, Designated Federal Official to the Arthritis Advisory Committee.

DR. SAAG: Good morning. Ken Saag, professor of medicine and epidemiology at the University of Alabama at Birmingham.

DR. DAVIS: I am John Davis, associate professor of medicine, University of California, San Francisco.

DR. SANDBORG: I'm Christy Sandborg, professor of pediatrics and rheumatology at Stanford University.

MS. ARONSON: Good morning. I am Diane Aronson, consumer representative, president of the Road Back Foundation. I have as a consumer rep worked with the NIH, the FTC, and the CDC previously in the field of infertility. I do have rheumatoid arthritis.

DR. FRIES: Jim Fries, professor of medicine and epidemiologist and rheumatologist at Stanford.

DR. DAY: Ruth Day, director of the Medical Cognition Laboratory at Duke University.

MS. SOLANCHE: Good morning. I am Martha Solanche from New York City. I am the patient representative.

DR. FELSON: Good morning. I am David Felson. I am professor of medicine and epidemiology and chief of clinical epidemiology at Boston University.

DR. GINZLER: Good morning. I am Ellen Ginzler, professor of medicine and chief of rheumatology at State University of New York, Downstate Medical Center in Brooklyn.

DR. LEVINE: Good morning. I am Bob Levine, professor of medicine, State University of New York at Upstate Medical University in Syracuse and a former member of the Gastrointestinal Advisory Committee recently, from 2001 to 2005.

DR. PASRICHA: Good morning. I am Jay Pasricha, professor of medicine and gastroenterology at the University of Texas Medical Branch, Galveston, Texas.

DR. O'NEIL: I am Kathleen O'Neil. I am an associate professor of pediatrics in the Division of Rheumatology at the Oklahoma University College of Medicine.

DR. McLESKEY: I am Charlie McLeskey, anesthesiologist by training. I am the acting industry rep.

CHAIRMAN TURK: Thank you all. Let me say something because I've noticed some people observing. When you want to speak, if you push this on, there is a little red light to the right. You don't have to see if you're lit up on the side; so just push the button, and if you see the red light, you're ready to go.

Thank you all for being here. What I want to do now is to just go over very quickly what the agenda is going to be for the day to orient you to how things are going to proceed.

We will begin with, the call to order has already occurred, we will then hear from Johanna Clifford who will go over the "Conflict of Interest Statement."

There will be opening remarks by Dr. Rappaport. We will then have a presentation from the FDA about the history of cardiovascular findings as they relate to the nonsteroidal antiinflammatory drug studies.

We will then have presentations by the sponsor, Merck & Company. We will then have presentations by the FDA. As I suggested, we are going to try and hold questions after those presentations, unless there is a clarifying point.

We are going to have an opportunity for there to be an open public hearing, which we have I believe four people, for groups, who have requested to speak. There will be lunch. There will be breaks in between I didn't mention.

At that point, after lunch, we will begin questions from the Committee to the presenters, and then we have some specific questions that have been posed to the Committee by the Food & Drug Administration. We will go over those, and we will come to some discussions and recommendations. That will lead to the close of the meeting at which point I

believe the FDA will be having a public briefing.

That is the orientation of how we are going to go today. Please bear with me if I can't see your name from the angle I'm sitting at, I've got a sheet to try, but if I either can't see it or I mispronounce it. We've got Levine and we've got Levin (chuckling). I'll have a lot of fun with their names. You will catch me in all of my errors along the way.

I would like to begin with asking Dr. Rappaport to provide us with some opening remarks.

MS. CLIFFORD: Actually, I have to go first.

CHAIRMAN TURK: Oh, I'm already off.

MS. CLIFFORD: That's okay.

CHAIRMAN TURK: Johanna Clifford is going to read the "Conflict of Interest Statement," and then we will go to Dr. Rappaport.

CONFLICT OF INTEREST STATEMENT

MS. CLIFFORD: The following announcement addresses the issue of conflict of interest and is made a part of the record to preclude even the appearance of such at this meeting.

The matter coming before the Arthritis Drug

Advisory Committee is a particular matter involving specific parties based on the submitted agenda and all financial interests reported by the Committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest, with the following exceptions.

In accordance with 18 U.S.C. 208(b)(3), full waivers have been granted to the following participants: Dr. Dennis Turk has been granted a waiver for his unrelated advisory board activities for a competitor, which he receives less than $10,001 per year.

Dr. Kenneth Saag has been granted a waiver for his unrelated consulting for two competing firms for which he receives less than $10,001 per year from each firm. Dr. Saag has also been granted a waiver for his unrelated speakers bureau activities for the sponsor, for which he receives between $10,001 and $50,000 per year and for his unrelated advisory board activities for the sponsor, for which he receives less

than $10,001 per year.

In addition, Dr. Robert Levine has been granted waivers under 18 U.S.C. 208(b)(3) and 21 U.S.C. 355(n)(4) of the Food and Drug Modernization Act for ownership of stock in the sponsor valued between $25,001 to $50,000.

Waiver documents are available at FDA's dockets webpage. Specific instructions as to how to access the webpage are available outside today's meeting room at the FDA information table.

In addition, copies of all of the waivers can be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30 of the Parkland Building. We would also like to note that Dr. Charles McLeskey has been invited to participate as a non-voting industry representative acting on behalf of the regulated industry.

Dr. McLeskey's role on this Committee is to represent industry interests in general and not any one particular company. Dr. McLeskey is employed by ZARS Parma.

In the event that the discussions involve

any other products or firms not already on the agenda for which an FDA has a participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they wish to comment upon.

Thank you.

CHAIRMAN TURK: Now we will have opening comments and opening remarks by Dr. Rappaport, who is the director of the Division of Arthritis, Analgesia and Rheumatology Products at the Food and Drug Administration.

OPENING REMARKS

DR. RAPPAPORT: Good morning. Dr. Turk, members of the Committee and invited guests, thank you for our willingness to participate in this meeting of the Arthritis Advisory Committee. The primary purpose of today's meeting to ask for your advice to inform our decision making on Merck's new drug application

for Arcoxia.

This application is the first NDA for a COX-2 selective nonsteroidal antiinflammatory drug product to have been submitted to the Agency since the withdrawals of Vioxx® and Bextra from the market.

As you are well aware, since the withdrawal of Vioxx in September of 2004, there has been increased scrutiny of the safety of the COX-2 selective products and indeed all of the NSAID. Large quantities of data have been reviewed by the Agency, pharmaceutical companies and academics.

While there are still many unanswered questions regarding the cardiovascular and gastrointestinal toxicities of these products, there is enough evidence such that the Agency has been able to define the requirements for the approval of any new products in this class.

In their memo signed on April 6, 2005, Dr. John Jenkins, director of the Office of New Drugs, and Dr. Paul Seidman, who at that time was the director of the Office of Pharmacoepidemiology and Statistical Science, concluded that the three approved

COX-2 selective NSAID were associated with an increased risk of serious adverse cardiovascular events compared to placebo but that the available data did not permit a rank ordering of these drugs with regard to cardiovascular risks.

They added that long-term placebo-controlled clinical trial data were not available to adequately assess the potential for many of the nonelective NSAID to increase the risk of serious cardiovascular events. However, what data did exist confirmed some level of cardiovascular risk for the nonelective NSAID as well.

Absent the availability of additional long-term controlled clinical trial data, the data were best interpreted as being consistent with a class effect of an increased risk of serious adverse cardiovascular events for all NSAID whether they were relatively COX-2 selective or not.

Drs. Jenkins and Seidman also concluded that controlled clinical trial data were not available to rigorously evaluate whether certain patients derived greater relief of pain and inflammation from specific NSAID compared to others or responded uniquely to one

NSAID after failing to respond to another.

In addition, they stated that the overall benefit of COX-2 selective drugs in reducing the risk of serious gastrointestinal bleeding remained uncertain as were the comparative effectiveness of COX-2 selective NSAID and other strategies for reducing the risk of GI bleeding following chronic NSAID use, for example, the concomitant use of a nonelective NSAID and a protein pump inhibitor.

Even taking into account this framework, there are a number of questions regarding the data that have been submitted in support of the Arcoxia application that we would very much like the Committee to help us address.

While this new COX-2 selective NSAID may provide some additional benefits compared to some of the currently marked nonelective NSAID products, it may also have some increased associated risks. Determining exactly how to weigh these benefits and risks in our assessment of the products' approvability is challenging.

In order for you to have as full an

understanding of the data in the Arcoxia application, we will begin today with presentations starting with Dr. Sharon Hertz, one of our deputy directors, who will review our current understanding of the cardiovascular toxicity of the coxibs and other NSAID drugs, then Drs. Wang, Cannon and Curtis representing Merck will present the applicant's perspective on the place of this product and what place it might fill in the rheumatologic armamentarium and their analysis of the data submitted in their application.

These speakers will be followed by Dr. Robert Shibuya, the primary clinical reviewer for the application who will present the Agency's analyses and interpretations of the data.

Finally, we have invited Dr. David Graham, a clinical epidemiologist in the Office of Surveillance and Epidemiology at the Agency, who has a considerable interest in the NSAID issue to provide you with his own perspective on the data available from epidemiological studies of the NSAID toxicities.

This afternoon, we will hear from members of the community during the open public hearing portion

of this meeting. That session will be followed by our asking you to address the discussion points submitted by the Agency and then to answer what might be considered to be a particularly challenging question, whether or not you believe that the risk/benefit balance of Arcoxia is adequate to support the product's approval.

Your deliberations and recommendations will play an important role in our decision-making process. I would like to thank you for taking time from your other extensive responsibilities to participate in this process.

CHAIRMAN TURK: Thank you, Dr. Rappaport.

The next presentation will be by Dr. Sharon Hertz. She is deputy director of the Division of Arthritis, Analgesia, and Rheumatological Products. Dr. Hertz is going to be specifically commenting on the history of cardiovascular findings from the NSAID studies.

Let me just say this to all speakers while Dr. Hertz gets prepared. To the best of your possibility, when you have been designated a certain

amount of time to speak, please try to stick to that as much as you possibly can so we can move things along.

Dr. Hertz.

HISTORY OF CARDIOVASCULAR FINDINGS FROM NSAID STUDIES

(PowerPoint™ slide presentation.)

DR. HERTZ: Thank you.

Good morning. I'm going to review the cardiovascular findings from the large outcome studies from the available COX-2 programs that we have gotten so far and briefly review our prior conclusions, which you have already heard to some extent from Dr. Rappaport.

A little déjà vu here. We were here a few years ago. February of '05 was our first Joint Advisory Committee with the Arthritis and Drug Safety Committees where we heard data presented on rofecoxib, celecoxib, lumiracoxib, and the early data on etoricoxib.

I'm going to review now each of the available COX-2 selective products and the data that

we have so far. Rofecoxib was initially approved in 1999 with an initial safety database of approximately 5,000 subjects with more than 700 with one year of exposure at the 2 doses proposed for chronic dosing. There was no clear cardiovascular signal at that time. There were a small number of events, but there was no dose response.

The VIGOR study was a large outcome study looking at serious GI events as well as cardiovascular events. This was a study of a higher than proposed dose for chronic dosing, 50 milligrams, compared to naproxen and enrolled approximately 8,000 patients with rheumatoid arthritis. Aspirin use was not permitted, so patients who required aspirin use were not permitted.

The median exposure was nine months, and cardiovascular risk was identified for patients who had received rofecoxib as compared to naproxen with an overall relative risk of 2.3 and specifically for MI a relative risk of 5.

You can see the number of events wasn't great, but it was a fairly consistent signal. The

incidence appeared to increase over time, and these results were also taken to AC in 2001.

We had additional data coming in from other Vioxx studies. There were three placebo-controlled studies in Alzheimer's disease ranging from 15 to 24 months in duration, enrolling approximately 2,800 patients total. Here again we saw no consistent cardiovascular signal.

Then, we heard about the results from APPROVe, a study evaluating the effects of rofecoxib on reducing the occurrence of adenomatous polyps. This was a randomized, placebo-controlled, double-blind study, 3 years on drug, with a year of additional followup. The dose was 25 milligrams of rofecoxib, and it was placebo-controlled and it enrolled almost 2,600 patients.

In September of 2004, the company informed us that there was a cardiovascular signal against placebo for all events of relative risk of 1.8; for MI, 2.5 with a similar rate of 1.8 for ischemic CVA. Shortly after that, the company withdrew Vioxx from the market.

Here is just a review of the actual data. I don't seem to have a pointer. Yes, here's the mouse.

You can see that overall the number of events according to the APTC definition. It's a slightly modified APTC, that is, the "Antiplatelet Trialists' Collaboration." For our purposes, it is predominantly cardiovascular death, MI, and stroke, both ischemic and hemorrhagic.

You can see that these are a sizeable number of events, 59 and 34 for the two treatment groups. You can see that there was still a difference in the nonaspirin users and much less of a difference, so a clear effect but not a clear effect, with concurrent aspirin use.

For Celebrex®, Celebrex was initially approved as a celecoxib in 1998. This initial database was a total of about 9,600 patients. Again, there was no cardiovascular signal seen with the initial application.

The large GI outcome study for celecoxib was CLASS, which was an active-control study of one year duration that enrolled approximately 8,000 patients.

This was a little different than VIGOR. It enrolled patients with OA and RA. Aspirin use was permitted, if indicated. It was a fairly high dose of celecoxib, 400 milligrams, twice daily. This is an approved dose but not for OA or RA, It's twice that highest approved dose.

There was no apparent cardiovascular signal as compared to ibuprofen or diclofenac, so also a different comparator in contrast to naproxen. Here is the number of myocardial infarctions from the CLASS study. You can see that here the diclofenac actually looks the best out of all three treatment groups, but the numbers are fairly small.

In terms of the rate per hundred patient years, it's about the same between celecoxib and ibuprofen. The numbers get very small when we look at the patients based on aspirin use, but here we see almost a large effect in the aspirin users in contrast to VIGOR but still a little -- well, not much of a signal for the nonaspirin users.

We then heard about the results of the APC trial. Again, this was a placebo-controlled trial

evaluating celecoxib and its ability to reduce the incidence of sporadic colorectal adenomas. There were two doses of celecoxib in this study and placebo. It was also a three-year study.

In December of 2004, the study was halted due to a cardiovascular signal for celecoxib compared to placebo, and the closest definition that we had to the APTC was the death from cardiovascular causes, MI, or stroke. We can see that for the lower dose in the study, 200 twice a day, the relative risk was 2.5 compared to 3.4 for the higher dose.

This is taken from the Advisory Committee presentation of Dr. Houck. I just took some of the extra rows out of the table, just so you can see how the numbers compared across their different outcomes. Here is the hazard ratio for those same outcomes. This is a Kaplan-Meyer estimate showing that there appears to be separation in the curves around 12 months.

At the same time there was another study looking at the ability of celecoxib to prevent colon adenomas. This was preSAP. There was only one dose

of celecoxib. This was 400 milligrams once daily compared to placebo. These results didn't seem to have the same signal as the APC trial.

There has been some speculation if it was different dosing parameters, once a day versus twice a day, that might have had some effect there. I just did sort of an unofficial calculation just to try and get at the number of actual MIs. If you just look at MIs alone, there does appear to be perhaps something there, but it is very small numbers.

There was one more study ongoing at the time, and this was the ADAPT study. It was an Alzheimer's prevention study. This study was comparing celecoxib, 200 milligrams, twice a day; a fairly low dose of naproxen; and placebo. This study was halted in the wake of the APC and preSAP trials being halted.

The data is less well formed. The study was less far along than the colon adenoma prevention studies. From what we can see, it didn't appear that there was a risk for celecoxib compared to placebo, and there has been some question about whether there

was a risk associated with naproxen.

TARGET is a large outcome study for a product for a product, lumiracoxib. This was a 52-week, a one-year study, enrolling 18,000 patients. The design of target consisted of two substudies, one in which lumiracoxib was compared to naproxen and the other compared to ibuprofen. Aspirin use was permitted.

What we see here is that lumiracoxib seems to have a greater risk as compared to naproxen and about the same or slightly less risk as compared to ibuprofen. If we look a MIs and the rate per 100 patient years, that follows the APTC outcome.

But what has been curious, and I'm still not sure what the answer is, is that the two lumiracoxib groups in the substudies were quite different. I still don't know what that means.

This is the Kaplan-Meyer estimate from that. The red curves are the two lumiracoxib groups and the two blue curves are the naproxen and ibuprofen comparators.

At the 2005 Advisory Committee we had a

review of the epidemiologic studies. The one extremely consistent finding is that there is cardiovascular risk clearly associated with the highest dose of rofecoxib. We saw somewhat variable findings of risk associated with other selective and nonelective NSAID. We will hear more about the epidemiologic studies and results with Dr. Graham's presentation today.

As Dr. Rappaport mentioned, in 2005, following the Advisory Committee, the Agency issued a Decisional Memo, it's always available online, where basically we said that the three approved COX-2 selective NSAID are associated with an increased risk for cardiovascular events.

I didn't review the data for valdecoxib because there were no large outcome studies, and the shorter-term studies are a slightly different type of study and not necessarily related to our conversation today.

Based on the data from these long-term trials, it's unclear that there is any difference in risk that we can tell based on a comparison from COX-2

selective and nonelective studies.

We are missing long-term, large outcome studies for most of the currently approved nonelective NSAID. We have the data available mostly because they have been using newer studies as comparators.

Following the Advisory Committee and our Decisional Memo, we took regulatory actions. Based on our decision and our thinking, we changed the label for all prescription NSAID; we issued a class medication guide for all prescription NSAID; and the warnings were also revised for the over-the-counter NSAID.

Just to be sure, we issued an information request for the sponsors for the approved NSAID to go back and take a look at the available data to see if there is any information that we could glean from their databases.

When we reviewed the data that came in, what we found was that the sample size, even with pooling across studies, was quite small. There were a very small number of events. The events weren't adjudicated. The duration of treatment was generally

too short.

That is my presentation.

CHAIRMAN TURK: Thank you, Dr. Hertz.

If there are any clarifying questions that people have that they would like to ask of Dr. Hertz?

Dr. Boulware.

DR. BOULWARE: Yes. Could you please clarify Slide 16 and 17 for me when you showed the hierarchical cardiovascular incidents as well as hazard ratio? That was death from all cardiovascular causes and then nonfatal: MI, stroke, congestive heart failure.

DR. HERTZ: Sir, which slide? Which slide number?

DR. BOULWARE: Sixteen. As you progress down on the rows, you have death from cardiovascular causes. Is that nonfatal MI? Nonfatal stroke? Nonfatal--?

DR. HERTZ: Yes. Yes, being added in.

DR. BOULWARE: Okay.

CHAIRMAN TURK: Any other questions?

(No verbal response.)

CHAIRMAN TURK: Thank you, Dr. Hertz for staying on time.

Next, we will have presentations from the sponsor. Introducing the sponsor will be Dr. Peter Kim, who is the president of Merck Research Laboratories.

SPONSOR PRESENTATION: MERCK COMPANY, INC.

OVERVIEW

DR. KIM: Thank you very much.

Good morning, Mr. Chairman, Advisory Committee members, FDA staff, ladies, and gentlemen. My name is Peter Kim, and I am president of Merck Research Laboratories. Osteoarthritis continues to be an underserved conditions with physicians and patients calling for additional treatment options.

The physicians and scientists at Merck Research Laboratories developed etoricoxib in order to provide them with just that, another option to treat the symptoms of osteoarthritis.

Etoricoxib has been approved in 63 countries outside the U.S. with the first approval occurring in 2002. All medicine comes with benefits and risks.

The same is true of the currently available treatment options for the symptoms of OA.

For NSAID, while they are often highly effective for managing the symptoms of OA, their labels currently include warnings regarding both gastrointestinal and cardiovascular risks.

It is only through well-controlled clinical trials that the unique benefits and risks of individual agents, including these GI and cardiovascular risks, can be defined.

We initiated the MEDAL Program for etoricoxib in 2002. The MEDAL Program is the largest and longest controlled-clinical trial specifically designed to assess the cardiovascular safety of a treatment in patients with arthritis.

Over 34,000 patients were enrolled in these trials with over 17,000 patients receiving etoricoxib for a mean duration of treatment of 18 months, yielding over 26,000 patient-years of exposure to etoricoxib.

Indeed, for the COX-2 selective inhibitor class of drugs, the MEDAL Program alone has

practically doubled the total amount of data from controlled clinical trials comparing COX-2 selective inhibitors to nonelective NSAID.

Collectively, the clinical data from the MEDAL Program in conjunction with the data from our other clinical trials comprehensively characterizes the safety and efficacy profile of etoricoxib and reflects Merck's longstanding commitment to patient safety and to rigorous scientific investigation.

We are Merck believe that etoricoxib represents a valuable treatment option for patients with osteoarthritis. We would like to emphasize that there is more long-term safety data from controlled clinical trials in terms of patient years of treatment for etoricoxib than for any other NSAID including traditional NSAID and COX-2 selective inhibitors.

We hope you will conclude that patients in this country should also have access to this treatment option. We look forward to the scientific discussion of the extensive data provided to you as preparation for this meeting.

Thank you very much for your attention. I

will now turn the podium over to Dr. Scott Korn.

INTRODUCTION

DR. KORN: Good morning. My name is Scott Korn and I am executive director of regulatory affairs at Merck Research Laboratories. It is a privilege to be with you today to discuss Arcoxia, Merck's trademark for etoricoxib, which we are proposing for the symptomatic treatment of osteoarthritis at a dose of 30 and 60 milligrams.

The efficacy and safety data support our proposal that Arcoxia at doses of both 30 and 60 milligrams be indicated for the relief of the signs and symptoms of osteoarthritis, with 30 milligrams as the initial recommended dose.

The presentation you will hear today is a comprehensive summary based on our extensive clinical database for etoricoxib. The MEDAL Program alone includes over 26,000 patient-years of exposure to etoricoxib.

The detailed summary of the clinical data has been provided to you in your briefing document. Due to time constraints, today's presentation will

focus on key topics and conclusions.

Patients with osteoarthritis want and deserve additional treatment options. We believe the data for etoricoxib indicate it would be a valuable treatment for many of these patients and would help meet the need for additional treatment options.

The extensive clinical program has demonstrated that etoricoxib has a favorable benefit-to-risk profile in patients for whom NSAID Class therapy is indicated.

Etoricoxib provides effective pain relief and improved physical function without the liabilities associated with narcotic agents. Etoricoxib has improved GI safety and tolerability compared to traditional NSAID even in those patients who are taking a proton-pump inhibitor. The thrombotic cardiovascular safety profile of etoricoxib has been well characterized and is consistent with that of non-naproxen NSAID.

Following my introduction, Dr. Grant Cannon, professor of medicine in the Division of Rheumatology at the University of Utah will briefly speak to the

need for new options for patients with osteoarthritis.

Dr. Sean Curtis, executive director of clinical research at MRL, will then present the clinical overview of the efficacy and safety data for etoricoxib.

With us today as consultants are five cardiology, gastroenterology, rheumatology, and epidemiology experts. They will be available to the Committee to address any clinical or scientific questions during the meeting. They are Drs. Chris Cannon, Mark Hochberg, Richard Hunt, Loren Laine, and Samy Suissa. Drs. Cannon and Lane were the co-chairs of the MEDAL Steering Committee.

Now to begin the discussion on the treatment of osteoarthritis, I would like to turn the podium over to Dr. Grant Cannon.

UNMET MEDICAL NEED IN OA

DR. G. CANNON: Thank you, Dr. Korn.

(PowerPoint presentation in progress.)

DR. R. CANNON: Osteoarthritis is the most common musculoskeletal disease in the United States. While the prevalence of this disease and the estimates

thereof depend on the population tested, the anatomical sites evaluated, and the methods utilized, an estimate of the prevalence of symptomatic osteoarthritis is 12.1 percent of the general population or over 21 million patients. We all know that our population is aging and that there is a projected increase in osteoarthritis with this aging population.

Osteoarthritis is associated with significant pain, progressive disability, a decrease in quality of life, and significant medical costs. Using standard methods the decrease in function and quality of life in patients with osteoarthritis, and particularly severe osteoarthritis, has been similar to that seen in patients with congestive heart failure and advanced lung disease.

As a practicing rheumatologist, I want to emphasize the critical need for new and effective therapy with appropriate risk benefit profiles for the treatment of patients with this disabling and devastating problem.

The management guidelines for the treatment

of osteoarthritis have been developed by the American College of Rheumatology or "ACR." These guidelines recommend treatments that have been proven effective in either reducing pain and/or improving function in patients with this disease.

The guidelines emphasize the use of nonpharmacologic and pharmacologic therapies. The specific agents are listed in this table. Medications providing pain relief are the base of therapy. Acetaminophen is frequently used; however, traditional nonsteroidal antiinflammatory agents, or NSAID, with or without gastroprotective agents and selective COX-2 inhibitors are the most commonly employed medications and the foundations of therapy.

Pure analgesic medications such as tramadol and opioids have been recommended for patients that are intolerant or unable to respond to traditional therapies.

The large number and type of recommendations highlight the fact that no therapy is either universally effective or a universally well-tolerated modality for the treatment of patients and that each

option has its own risk/benefit ratio.

While these agents and modalities have been proven effective in comparison to control groups, they are rarely effective in completing relieving pain and restoring clinical function.

These facts support the importance of having many effective treatment options for the treatment of osteoarthritis in approaching this difficult clinical problem. We need to expand the number of options available for the treatment of osteoarthritis so that we as physicians can effectively treat our patients with this disease.

The ACR Guidelines provide evidence-based practices to follow. Patient-specific management is needed because of the variation in patient response to different agents. This assessment involves the assessment of risk for adverse events, particularly gastrointestinal toxicity with NSAID and patient preferences.

This assessment requires the patient and the physician to balance the potential benefits against the possible limitations and risks with treatment.

For example, while acetaminophen may be effective in osteoarthritis patients, data suggests that in some patients, particularly those with more severe osteoarthritis, NSAID and selective COX-2 inhibitors may provide greater pain relief.

Many patients with NSAID are at risk for severe gastrointestinal toxicity, yet less than half of the individuals at risk for this toxicity and complication receive the gastroprotective therapy.

Data have clearly demonstrated that while these agents can reduce GI risk when taken regularly as prescribed, failed adherence is a significant limitation to prevention of gastrointestinal complications.

Despite the availability of effective therapies, there are currently many unmet needs and levels of high dissatisfaction. In one survey, 73 percent of general practitioners and 63 percent of their patients with osteoarthritis were dissatisfied with their treatment options.

Dissatisfaction is demonstrated by the frequent switching of nonsteroidal antiinflammatory

agents with 53 percent of patients switching to a second nonsteroidal antiinflammatory drug within 60 days of the initial treatment.

Lack of efficacy is the most common reason for changing NSAID and adverse events such as GI intolerance is the second leading cause. Studies on persistence of therapy have demonstrated that switching is less common with selective COX-2 inhibitors.

This shifting between treatments is eventually needed to find the most effective therapy and best tolerated agent for each patient. It demonstrates the critical, significant, and unmet need for developing new and effective therapies for osteoarthritis. Because no single therapy has been demonstrated to be the most beneficial for osteoarthritis patients or universally well tolerated, the development of new therapies for the treatment of this disease is an imperative.

In conclusion, osteoarthritis is a serious, prevalent, and disabling disease that is a growing problem in our population. With the aging population,

this problem is expected to increase. While current therapy provides some relief to osteoarthritis patients, significant dissatisfaction persists.

The addition of new agents even with similar mechanisms of action has the potential to provide additional relief for may osteoarthritis patients including those who have not had a sufficient response to current agents.

As the Committee hears the information, I hope that this review will be considered in the context of the challenge that I face with my physician colleagues and particularly our patients in finding effective therapies for osteoarthritis.

Thank you.

DR. CURTIS: Thank you, Dr. Cannon.

EFFICACY & SAFETY REVIEW

(PowerPoint presentation in progress.)

DR. CURTIS: Good morning, members of the Advisory Committee, FDA, ladies and gentlemen. My presentation will begin with a review of the efficacy data in osteoarthritis with etoricoxib followed by a review of the safety data. We will begin with

reviewing the thrombotic cardiovascular safety, move on to a review of upper-GI safety, and then on to renovascular safety.

Within each of these categories, data will be presented sequentially from the Etoricoxib Development Program and from the MEDAL Program. An overview of our proposed approach to post-approval activities will then follow, and I will concluded with a summary.

As Dr. Korn mentioned, this presentation should be viewed as a summary with detailed information provided in the briefing document.

The focus of my presentation will be on the following points: the efficacy demonstrated with etoricoxib in patients with osteoarthritis is comparable to fully efficacious doses of comparator NSAID.

From the perspective diclofenac of thrombotic cardiovascular safety, naproxen has shown lower rates of thrombotic cardiovascular events as compared to etoricoxib, whereas etoricoxib and diclofenac have shown a comparable rate of thrombotic

events. These results are, in fact, consistent with what's been observed in prior randomized clinical trials of COX-2 selective versus traditional NSAID.

The GI safety and tolerability profile of etoricoxib has been favorably differentiated from traditional NSAID. We have shown for the first time, based on clinical GI outcomes in the MEDAL Program, a treatment benefit versus traditional NSAID in the setting of patients on a proton-pump inhibitor.

The renovascular effects of etoricoxib, specifically the effects on blood pressure, are dose-related and at doses of 30 and 60 milligrams, once daily, occur at an instance between that observed with traditional NSAID, specifically naproxen and ibuprofen.

The overall benefit to risk for etoricoxib is favorable a doses of 30 and 60 milligrams once daily in patients for whom NSAID therapy is required. This conclusion is based on an extensive clinical development program totaling approximately 60,000 patient-years at risk and includes of course the MEDAL Program, the long-term cardiovascular

outcomes program.

I will now begin with a review of the efficacy data. The efficacy of etoricoxib was established in seven clinical trials. One-dose ranging study and six Phase III protocols. There was one set of replicate studies evaluating etoricoxib, 60 milligrams, and two sets of replicate studies comparing etoricoxib, 30 milligrams.

All of these studies utilized standard methodology and were of standard design, all were randomized double-blind and contained a placebo and/or an active comparator group, and all studies evaluated patients with osteoarthritis of either the knee and/or hip and used validated endpoints covering important domains of pain and function as well as including global assessments of both response to therapy and disease activity by both patients and the study investigators.

I will present representative data from these studies using the WOMAC pain subscale, one of the primary endpoints. Results from the dose-ranging studies are presented first, patients who are seen for

an initial screening visit, denoted by "S" on the "X" axis, and then washed out from their prestudy NSAID. Those patients who met the flare criteria were then randomized, denoted by "R" on the "X" axis to either to either placebo or etoricoxib in doses ranging from 5 to 90 milligrams. The mean change from randomization for the WOMAC pain subscale is plotted by visit for each treatment group. The randomization visit is set at zero.

A more negative on-treatment value here represents a greater treatment response. All etoricoxib doses provided significant efficacy versus placebo. The 60-milligram dose, denoted here by the yellow square, was the minimal dose to provide maximal efficacy. No additional efficacy was obtained with the 90-milligram dose.

The 30-milligram dose, denoted by the yellow inverted triangle, also provided significant treatment effects, achieving a clinically meaningful effect versus placebo for two of three co-primary endpoints; although, it was statistically significantly less efficacious than the 60-milligram dose.

Based on these results, both the 30- and the 60-milligram dose were taken forward into Phase III studies. One set of replicate Phase III studies evaluated etoricoxib in comparison to naproxen over 52 weeks with an initial 12-week placebo-control arm as well.

Using the same graphical display as for the dose ranging study, results for one of the two studies are displayed here on this slide. On the left, results over the initial 12 weeks demonstrate efficacy with etoricoxib: superior to placebo and comparable to naproxen, 1,000 milligrams total daily dose.

On the right, results over the entire 52-week treatment period, demonstrates the maintenance of treatment effect over the entire duration of the study. Similar results were observed for the other endpoints and in the replicate study.

There were two sets of replicate Phase III studies evaluating etoricoxib, 30 milligrams, as I mentioned. One set of 12-week studies comparing etoricoxib, 30 milligrams, to placebo and to ibuprofen, 800 milligrams three times a day; and one

set of 26-week studies comparing 30 milligrams to celecoxib, 200 milligrams once daily over 26 weeks with inclusion of a placebo arm over the initial 12 weeks.

This slide shows results for one of the two studies versus ibuprofen on the left and versus celecoxib on the right. In these studies etoricoxib provided significantly greater efficacy than placebo with treatment effects comparable to both ibuprofen and celecoxib.

In the celecoxib studies, maintenance of this treatment benefit was observed over the entire 26-week period. Thus, to summarize the efficacy data with etoricoxib in the symptomatic management of osteoarthritis, 30 milligrams of etoricoxib once daily provides efficacy superior to placebo and comparable to both ibuprofen at 2,400 milligrams total daily dose and celecoxib, 200 milligrams once daily.

We observed clinically important improvements across all domains including pain and function and results for the global assessments by both the patients and physicians were consistent with

these results.

In a study which directly compared 30 milligrams and 60 milligrams once daily, 60 milligrams provided greater efficacy compared to 30 milligrams. In separate studies, 60 milligrams once daily, as reviewed, was comparable to naproxen, 1,000 milligrams.

I will now begin reviewing the safety data. As we are all aware, in 2005 the FDA issued a memo on the cardiovascular effects of NSAID in which they concluded, as summarized by Drs. Rappaport and Hertz earlier today, pending the availability of additional data from long-term clinical trials, the available data are best interpreted as being consistent with the class effect of an increased risk of serious adverse cardiovascular events for COX-2 selective and nonelective NSAID.

While the Agency recognized there was some evidence that naproxen may not share the same degree of risk, an NSAID template for members, all members, of the NSAID class which included a boxed warning for both gastrointestinal and GI risk was developed.

In 2006, a meta-analysis of all randomized clinical trials data was published by Dr. Baigent and his colleagues at Oxford University. This meta-analysis was notable for the fact that Dr. Baigent accrued all available randomized clinical trials data from the literature and directly from sponsors to ensure that all data, both published and unpublished, were included in his evaluation.

For the analysis, trials-level data were included from studies of at least four weeks of duration which compare directly a COX-2 inhibitor either to placebo or to a traditional NSAID.

The COX-2 inhibitors evaluated included rofecoxib, celecoxib, etoricoxib, lumiracoxib and valdecoxib, and the traditional NSAID evaluated were naproxen, diclofenac, and ibuprofen.

In this analysis, the endpoints included vascular events, MI, stroke, and vascular deaths. All data from the original etoricoxib development program which met Dr. Baigent's criteria as well as data from one of the MEDAL Program studies, the EDGE study, were included were included in this meta-analysis.

The key findings from the meta-analysis are as follows. In comparison of all COX-2 selective inhibitors to placebo, an overall relative risk of 1.42 was observed. There was no evidence of heterogeneity among the individual COX-2 selective inhibitors as evidenced by this "P" value of 1.0. The results were largely accounted for by an increased risk of myocardial infarction.

The other key finding from the meta-analysis was that naproxen had a lower rate of events combined as compared to the COX-2 inhibitors whereas ibuprofen and diclofenac showed similar rates as compared to the COX-2 selective inhibitors. The test for heterogeneity between naproxen and non-naproxen NSAID was statistically significant at a "P" value of 0.001.

Although there are limitations to this meta-analysis, it represents the most comprehensive evaluation of the highest level of evidence, namely, randomized clinical trials data.

Notably, these results are consistent with the FDA's conclusions from 2005, which stated that the available data supported a class effect for increased

cardiovascular risk for COX-2 selective and the nonelective NSAID.

The purpose of beginning my presentation with a review of Dr. Baigent's analysis is twofold. Number one, to ensure that the etoricoxib thrombotic cardiovascular safety data are viewed within this contemporary perspective of NSAID cardiovascular safety; and, secondly, the organization of the clinical development program for etoricoxib lends itself to be reviewed as two complimentary programs which follow the organization of the meta-analysis and the findings of the meta-analysis.

First, the Etoricoxib Development Program which supports the comparison of etoricoxib to naproxen for the important safety domains of upper-GI and thrombotic cardiovascular safety.

Secondly, the MEDAL Program, an event-driven, cardiovascular outcomes program consisting of three studies which compared etoricoxib to diclofenac.

The dates listed next to each program represent the range of the years that the study

included in these programs took place, just for clarification. Thank you.

Let's begin with the Etoricoxib Development Program, which I will now describe in more detail. It is defined by 18 studies of at least 4 weeks in duration, which directly compared etoricoxib to placebo and/or an NSAID in over 10,000 patients.

This included 11 studies in patients with osteoarthritis, 3 additional studies in patients with rheumatoid arthritis, as well as 3 studies in patients with chronic low-back pain, and one study in ankylosing spondylitis patients.

The majority of the data from this grouping of studies are from studies which use naproxen as the active comparator, 63 percent based on patient-years at risk. Thus, this data supports a comparison of etoricoxib directly to naproxen.

Thrombotic cardiovascular safety from the development program was assessed through a prospective analysis of adjudicated patient level data. Comparisons of etoricoxib were made either to placebo or NSAID comparators using data from the studies that

contained the treatments being compared.

The etoricoxib group consists of doses pooled from 30 to 120 milligrams and for the comparison to traditional NSAID, etoricoxib was compared to naproxen separate from diclofenac and ibuprofen based on the fact that naproxen is distinct pharmacodynamically from diclofenac and ibuprofen based on antiplatelet effects.

Furthermore, this approach is consistent with the FDA's guidance to evaluate agents in comparison to naproxen. The endpoint specified as primary for this assessment was a composite endpoint of all thrombotic cardiovascular events confirmed by the Adjudication Committee and includes cardiac, cerebrovascular, and peripheral vascular events and is referred to collectively as a confirmed thrombotic endpoint.

The antiplatelet trialist collaboration endpoint, or "APTC" endpoint, of myocardial infarction, stroke, and vascular death was also evaluated.

This slide provides more detailed

information about the size and duration in each of the three thrombotic cardiovascular safety datasets.

The naproxen-controlled dataset on the right is the largest of the three based on total patient-years at risk and also the one with the longest duration, 11 to 12 months median duration. The other two datasets are more limited both in size and duration, particularly the placebo-controlled dataset, which is on the left here.

The mean dose of etoricoxib in these three datasets range from 72 milligrams per day up to 89 milligrams per day in the naproxen-controlled dataset.

Results of the pooled thrombotic cardiovascular analysis are displayed here. Let me take a moment to explain the data display. The relative risk of a thrombotic event for etoricoxib in comparison to either placebo, non-naproxen NSAID, or naproxen are displayed here as inverted triangles which represent the point estimate of the relative risk, the size of which is proportional to the sample size, which is displayed here in this column.

Also, provided in the far right-hand column are the number of patients with events in each of these datasets. A corresponding 95 percent confidence interval around the point estimate is provided as well.

Results here are displayed for the primary endpoint I mentioned, confirmed thrombotic events. The data comparing etoricoxib to placebo are very limited in amount and duration and no conclusions can be made.

The data comparing etoricoxib to non-naproxen NSAID, which again is a combination of diclofenac and ibuprofen, are also limited. As you see, the relative risk is numerically less than one with a ninety-five percent confidence interval which includes one.

When comparing etoricoxib to naproxen here, the relative risk is greater than one, indicating a difference favoring naproxen. Results using the APTC endpoint were consistent with these results. For the comparison of a naproxen using the APTC, the difference between etoricoxib and naproxen was

statistically significant.

I would now like to come back to the MEDAL Program, which I briefly introduced a few moments ago, beginning with a summary of the major design features. Beginning in 2002, as Dr. Kim mentioned, we worked in close collaboration with a steering committee comprised of experts in a range of medical disciplines to design a clinical trials program.

The program objective was to compare the thrombotic cardiovascular safety of etoricoxib to that of a traditional NSAID in arthritis patients. In order to achieve the greatest degree of precision possible for that comparison, a single active comparator was chosen.

A placebo rather than an active comparator was not considered reasonable in a long-term trial of symptomatic arthritis patients. The primary program hypothesis was that etoricoxib would demonstrate noninferior thrombotic cardiovascular safety to the traditional NSAID comparator, which was diclofenac, which I will discuss momentarily.

The primary endpoint was thrombotic

cardiovascular events as confirmed by the Adjudication Committee through blinded expert adjudication. Secondary endpoints included the APTC endpoint and arterial-only events.

The program was endpoint driven, which means the duration would be determined by the time necessary to accumulate the predetermined number of thrombotic events, which was prespecified to be at least 635.

For the hypothesis of noninferiority, it was specified that etoricoxib be noninferior to diclofenac if the upper bound of the 95 percent confidence interval for the hazard ratio was no greater than 1.30.

The per-protocol population was used for the primary analysis, but additional analytical approaches including an intention-to-treat analysis were performed to assess for consistency of the results.

Before reviewing the results, I would like to comment on the active comparator that we in collaboration with the steering committee chose. As previously stated, we chose a single active comparator and decided upon diclofenac for the following reasons.

Diclofenac is an effective NSAID in the active management of both osteoarthritis and rheumatoid arthritis and is the most widely prescribed NSAID on a worldwide basis, thus it provides a clinically relevant comparison.

Secondly, diclofenac does not interfere with the antiplatelet effects of aspirin. Although the clinical consequences of this interaction have never been definitively proven, we expect that least 25 percent of the MEDAL Program patients to be on low-dose aspirin.

For those patients on low-dose aspirin for cardiovascular prophylaxis, we chose to avoid any ethical issues for those patients as well as potential issues in interpreting the study results when the study was completed.

Thirdly, diclofenac is a COX-1 and COX-2 inhibiting NSAID and thus can be viewed within a spectrum of traditional COX-1 and COX-2 inhibiting NSAID.

Two other comparators were considered but ultimately ruled out, first of all, naproxen. The

Etoricoxib Development Program had already collected a meaningful amount of safety data versus naproxen. Those data provided evidence of a decreased cardiovascular risk and an increased GI risk for naproxen in comparison to etoricoxib.

It was thus felt that it would be important to generate complimentary data versus an NSAID other than naproxen in order to provide additional information about the relative thrombotic risk of etoricoxib.

Ibuprofen was also considered, but concerns over the use of ibuprofen were based on the emerging data that strongly suggested that ibuprofen interfered with aspirins antiplatelet effects, which in fact has resulted in an FDA statement in 2006 regarding the potential for this effect, in addition, concerns about ibuprofen as an active comparator in a long-term trial or its effectiveness and its tolerability over the long-term.

In support of the fact that diclofenac does inhibit COX-1, results from a double-blind, four-period crossover study in sixteen healthy

subjects are shown here.

In each treatment period, subjects were administered one of four treatments: either placebo; diclofenac, 75 milligrams, twice daily; etoricoxib, 90 milligrams, once daily; or celecoxib, 200 milligrams, twice daily. COX-1 enzyme activity was assessed ex vivo by measuring serum thromboxane levels in clotting whole blood.

Shown here is the percent inhibition of serum thromboxane over a 24-hour dosing interval on the seventh day of treatment. As you see, diclofenac, in blue, inhibited COX-1 achieving maximal inhibition of serum thromboxane B2 levels of approximately 90 percent. As expected, neither etoricoxib or celecoxib had any appreciable effect on COX-1 activity.

As previously described, the MEDAL Program consists of three studies. A total of 34,701 patients were enrolled in the program, approximately three-quarters of whom had osteoarthritis.

The average duration of therapy was 18 months, with some patients achieving a duration of

therapy of approximately three and a half years. Details for the three component studies -- the EDGE, the Edge II studies, and the MEDAL study -- are tabulated here in columns on the right.

Thrombotic cardiovascular safety results for the MEDAL Program are displayed on this slide as the cumulative instance of confirmed thrombotic events in the per-protocol or primary population for this noninferiority trial.

The cumulative instance with etoricoxib compared to diclofenac satisfied the proportional hazards assumption, indicating a confidence hazard ratio over time.

As you see here, the relative risk of etoricoxib to diclofenac was 0.95. The upper bound of the confidence interval is 1.11, which was less than the prespecified, noninferiority bound of 1.30, which indicates that the primary hypothesis for the program was satisfied.

Although the primary analysis was per-protocol, as I mentioned, other analytical approaches were used to assess for consistency, these

included: intention to treat analyses, which considered events in patients up through 14 days following the discontinuation of study therapy or for 28 days following the discontinuation of study therapy for all randomized patients, as well as one which considered all events up through the end of study through for all randomized patients.

We made extensive efforts to follow up on all patients, however, in order to ensure that we collected all potential thrombotic events. However, patients' therapy and medical conditions in this, to support this ITT analysis, were not collected.

I want to just review again for a moment what this 95 percent confidence interval really means. What this tells you is that with 95 percent confidence interval, the true value for the relative risk lies between these bounds. It could be as high as this (indicating) value; it could be as low as this value.

As you see for the primary endpoint of confirmed thrombotic events, the results were very consistent across these four analytical approaches. As you see here for the additional secondary endpoints

of confirmed arterial events and confirmed APTC events, the results are in fact quite consistent, again, with the primary endpoint in showing consistent results, which met the noninferiority bound for all these analyses.

Summarized here are rates of nonfatal and fatal myocardial infarction and ischemic strokes. As you see, rates of nonfatal MIs, nonfatal ischemic strokes, and fatal ischemic strokes were similar between etoricoxib and diclofenac. Rates for fatal myocardial infarctions were low but numerically higher on diclofenac.

Results of the MEDAL Program thrombotic cardiovascular event analyses are displayed here on this slide for a subset of the prespecified subgroups. No significant treatment by subgroup interactions were noted for age, gender, or ethnic group nor was a significant interaction observed for OA versus RA or, importantly, dose within the OA patients, 60 versus 90 milligrams.

Additional subgroups are listed here and include an assessment of the relative thrombotic

cardiovascular risk for etoricoxib to diclofenac across patients with different cardiac risk factors and in the presence of baseline cardiovascular disease. Again, no significant treatment by subgroup interactions were observed among these subgroups, either.

In summary, the MEDAL Program demonstrates comparable thrombotic cardiovascular safety for etoricoxib and diclofenac. Notably, this result is consistent with the conclusions drawn by the FDA in 2005, when they stated the available data supported a class effect for increased cardiovascular risk for both COX-2 selective and nonelective NSAID, pending the availability of additional data from long-term controlled clinical trials.

When arriving at their conclusions in 2005, the Agency took into consideration data from both randomized clinical trials and observational studies, indicating that in their memo, that data from well-controlled observational studies have not provided consistent assessments of risk between COX-2 selective and nonelective NSAID.

In addition to being consistent with the FDA conclusions, the MEDAL results are in fact consistent with the 2006 meta-analysis by Dr. Baigent of all randomized clinical trials data in which no difference was observed in the rates of vascular events between COX-2 selective inhibitors and diclofenac or ibuprofen.

Additional observational data including data on the cardiovascular safety profile of diclofenac have been published since 2005. The observational data do not clearly establish the magnitude of the cardiovascular risk with diclofenac.

Numerous studies have compared diclofenac to nonuse of NSAID and have formed the basis for two published meta-analysis including one by McGettigan, et al.

In the McGettigan, et al., analysis, a relative risk of 1.4 was observed for diclofenac. The estimates of cardiovascular risk from the individual studies in this meta-analysis are variable, ranging from 0.8 to 1.6, with significant between study heterogeneity observed.

Data from one large study in which a relative risk of 1.02 was observed for diclofenac versus remote use of NSAID was not included in the meta-analysis.

In two studies which compared diclofenac versus other NSAID using myocardial infarction as the endpoint, the results are variable. In one study, the relative risk was 0.59 for diclofenac versus other NSAID, and in the other study the result was 1.33.

We feel for all the reasons cited including the data we had against naproxen, concerns about aspirin interactions, that as an NSAID comparator for the MEDAL Program diclofenac was the right choice in 2002 and remains a scientifically valid and appropriate choice even today.

To summarize the thrombotic cardiovascular safety data for etoricoxib from all randomized clinical trials, the relative risks are presented here together from the Etoricoxib Development Program, which again provides comparison of etoricoxib to naproxen versus non-naproxen, as well as from the MEDAL Program for the comparison of etoricoxib to

diclofenac.

As this display highlights, a difference between etoricoxib and naproxen is observed whereas etoricoxib and diclofenac are comparable in terms of thrombotic cardiovascular risk.

Although not depicted here, I would like to mention the limited data from published epidemiologic studies of the association of etoricoxib with thrombotic cardiovascular risk.

The three published studies which compared etoricoxib to nonuse of NSAID were summarized in the briefing document we provided. The number of cases with etoricoxib in these studies are small, resulting in wide confidence intervals around the point estimates.

The result of these studies needs to be interpreted in light of the small number of events in the analysis and in the context of the large amount of randomized clinical trials data just summarized for etoricoxib, specifically from MEDAL in which no difference was observed between etoricoxib and diclofenac in a clinical trials program specifically

designed to assess cardiovascular risks in arthritis patients who require NSAID therapy.

I would now like to summarize all cause mortality. For both the Etoricoxib Development Program and the MEDAL Program, rates per hundred patient-years by treatment group are displayed, along with the number of patients who died in each of these treatment groups.

In the Etoricoxib Development Program, on the left, the number of cases is small and the confidence intervals around the rates for all treatment groups are wide and broadly overlapping.

In the MEDAL Program, where there is a substantially larger amount of data, the estimates are more precise and the rates are similar for both treatment groups.

I will now summarize the GI safety data. The GI Safety Program was specifically designed to evaluate the entire GI tract, ranging from an assessment of the biochemical impact of etoricoxib on gastromucosal prostaglandin synthesis to an evaluation of upper-GI events.

The term "upper-GI clinical events" refers collectively to upper-GI bleeding, perforations, obstructions, and ulcers diagnosed upon clinical workup during the course of one of the trials. All workups for these potential events were initiated by the investigator for cause based on clinical signs and symptoms.

There were no scheduled or predetermined GI evaluations in our trials with the exception of the two surveillance endoscopy studies. All of these potential events were subject to blinded, expert adjudication using objective prespecified criteria in order to be confirmed.

For both the Etoricoxib Development Program and the MEDAL Program, analysis of upper-GI clinical events were prespecified. For the Etoricoxib Development Program, data from the same 18 studies which formed the basis for the thrombotic cardiovascular analysis were pooled at the patient-level data for an analysis of upper-GI events.

The primary assessment was a comparison of etoricoxib at doses of 30 to 120 milligrams pooled

versus combined traditional NSAID. But, as we reviewed previously, the majority of the NSAID group consisted of naproxen, so an assessment in comparison to naproxen individually was supportable.

The limited amount of data versus diclofenac and ibuprofen from the Development Program precluded analyses of these comparators separately. For the MEDAL Program, the data were pooled across the three MEDAL Program studies for an assessment of upper-GI safety.

Since the MEDAL Program included patients at increased GI and increased cardiovascular risk, appropriate use of low-dose aspirin and GI co-therapy was advocated as per current clinical guidelines. This resulted in approximately a third of the patients in the MEDAL Program using low-dose aspirin regularly and approximately 40 percent of patients using a proton-pump inhibitor regularly, defined here as a use of at least 75 percent of the time during the course of study therapy.

For both programs, the primary endpoint was overall upper-GI clinical events as confirmed by

expert adjudication. Evaluation of the subset of complicated upper-GI events was also undertaken. All events which occurred up through 14 days following last dose or study therapy were included in these analyses.

As illustrated here, the endpoint of overall upper-GI clinical events included: perforations, obstructions, bleeds, and ulcers. As mentioned previously, all upper-GI events were diagnosed based on clinical evaluation of signs and symptoms which developed in a patient during the course of a trial.

All evaluations were done for cause and were not, for example, performed as part of routine endoscopic surveillance. Therefore, all events including the ulcers were clinically manifested and represent true clinical events and were adjudicated in order to be confirmed. The subset of complicated events includes the perforations, the obstruction and the complicated bleeds.

Information regarding the size and the duration in the combined NSAID analysis and in the analysis of naproxen separately are summarized here.

The primary comparison involved approximately 7,000 patients and 6,700 patient-years. The comparison of etoricoxib to naproxen included approximately two-thirds of that total exposure.

Summarized here are results for the pooled upper-GI event analysis from the Etoricoxib Development Program. The relative risk for etoricoxib as compared to traditional NSAID for an overall upper-GI clinical event is plotted here as a point estimate with a corresponding 95 percent confidence interval.

For the primary assessment of overall upper-GI clinical events with etoricoxib compared to NSAID, an approximate 50 percent risk reduction was observed for favoring etoricoxib. The magnitude of the risk reduction for complicated events was similar.

Results for the comparison of etoricoxib to naproxen were consistent with the results for the primary analysis and for both overall and complicated events.

Displayed here are results for the MEDAL Program upper-GI event analysis. The cumulative incidence of overall upper-GI clinical events by

treatment group are presented on the left; and for the subset of complicated events, on the right.

For overall events, a statistically significant risk reduction of approximately 30 percent was observed, favoring etoricoxib. For complicated events there was no significant difference observed between etoricoxib and diclofenac.

The specific type of upper-GI events observed in the MEDAL Program analysis are tabulated here by treatment group, etoricoxib and diclofenac. The risk reduction observed in overall events was due to a lower rate of ulcers, as indicated here on the bottom row.

Although the term "uncomplicated" is used for the purposes of event categorization, the diagnosis of an uncomplicated, symptomatic ulcer is clinically meaningful.

In clinical practice, it will typically mandate additional followup with the potential for additional testing and the associated healthcare costs.

Furthermore, NSAID therapy should in this

setting ideally be discontinued; but if required, would require GI co-therapy typically with a proton-pump inhibitor or misoprostol.

Subgroup analyses were performed to evaluate the effect of aspirin and proton pump-inhibitor therapy on upper-GI events in the MEDAL Program. For these analyses, use of aspirin and proton-pump inhibitor at baseline or prerandomization as well as postrandomization were evaluated.

To be considered a regular aspirin user or a regular proton-pump inhibitor user postrandomization, patients were required to have taken that therapy concomitantly for at least 75 percent of the time on study therapy for the analysis shown here.

The results of this analysis for overall upper-GI clinical events are presented here. The results were, in fact, consistent for both prerandomization and postrandomization definitions. No significant treatment by subgroup interactions were noted in these analyses, indicating that the treatment effects observed were maintained with regular use of these agents.

To summarize the upper-GI event analysis for the two programs, a significant reduction in overall events was observed for the comparison of etoricoxib to naproxen, with a similar magnitude of reduction observed for the complicated events, versus naproxen; and in the MEDAL Program, a significant reduction in overall upper-GI clinical events was observed in comparison to diclofenac for overall events but not for the complicated events.

The reduction in ulcers with etoricoxib is maintained in patients treated with proton-pump inhibitors and is also observed with regular low-dose aspirin use.

In addition to the analyses of upper-GI safety just presented, an evaluation of analyses of GI tolerability were also prespecified in both programs. For the Etoricoxib Development Program, five endpoints including the use of GI co-therapy and patient discontinuations for different groupings of GI symptoms were specified, of which two representative endpoints will be shown, new use of gastroprotective agents and patient discontinuation for NSAID type

adverse events.

Data from two studies, the two surveillance endoscopy studies, were not included in this analysis because gastroprotective agent use was not allowed in those two studies. The primary assessment was etoricoxib, again doses from 30 to 120 milligrams pooled, versus the traditional NSAID combined.

For the MEDAL Program, the GI tolerability endpoints included patient discontinuations for clinical GI adverse events and patient discontinuations for hepatic adverse events.

Comparisons were made of etoricoxib to diclofenac based on each individual MEDAL Program study as well as based on the pooled MEDAL Program data, which is presented on the next slide.

As shown here, for the two representative endpoints from the development program as well as for the two MEDAL Program endpoints, a consistent risk reduction favoring etoricoxib was observed.

I would now like to review the renovascular safety data. As discussed earlier in the presentation, of the 18 studies comprising the

Etoricoxib Development Program, 11 studies evaluated osteoarthritis patients exclusively. These studies were used to evaluate renovascular safety in the target osteoarthritis population.

Data from these studies are organized into three groupings or populations: a placebo-controlled population, a six-month population, and the one-year population.

For the OA Development Program data, I will focus on blood pressure measures and on the incidence of hypertension, edema, and congestive heart failure adverse events.

For the MEDAL Program, renovascular data are presented for the MEDAL study by the three cohorts as defined in the briefing document. The OA 60 milligram cohort, the OA 90 milligram cohort, and the rheumatoid arthritis cohort.

Since only adverse events resulting in discontinuation are considered serious in the MEDAL study, I will present the incident of hypertension and edema-adverse events resulting in discontinuation.

For congestive heart failure, the incidence

of congestive heart failure requiring hospitalization, as confirmed by the Adjudication Committee, will be presented.

Beginning with blood pressure with the OA Development Program, plotted here for the placebo-controlled population are mean changes from baseline in systolic blood pressure. The values are presented as differences from placebo using the placebo value from the corresponding studies.

For example, patients treated with etoricoxib, 30 milligrams, which is again the yellow inverted triangle, had increases from baseline ranging from approximately 1 millimeter of mercury up to about 2-1/2 millimeters of mercury, systolic.

As you can appreciated, there is evidence of a dose response across the etoricoxib dose range, with 120 milligrams achieving the largest difference from placebo.

For the same OA placebo-controlled population, I am now displaying on the right the values for the active comparators: naproxen, ibuprofen, and celecoxib.

The values are presented the same way as for the etoricoxib groups as mean changes from baseline and different from placebo. Naproxen and celecoxib in this dataset were not associated with any meaningful increases from baseline and systolic blood pressure. Ibuprofen here did result in an increase in systolic blood pressure of approximately 4 millimeters of mercury.

Now, to present the OA placebo-controlled population as a whole, the 30- and the 60-milligram groups are now displayed with the active comparator NSAID.

As you can appreciate visually, the mean increase is observed with 30 and 60 milligrams of etoricoxib were between the effects observed with naproxen and ibuprofen, two NSAID approved of course for the symptomatic management of osteoarthritis.

I would now like to present the data on hypertension adverse events. This bar graph here on the bottom half of the slide displays the incidence of hypertension adverse events in each active treatment group in the OA placebo-controlled population.

For each active treatment group, which is displayed in color, with etoricoxib 30 and 60-milligram in yellow, the placebo value from the corresponding studies is provided adjacently in white.

On the top half of the slide, the incidences for the active treatments are also provided but expressed as differences from the corresponding placebo with a 95 percent confidence interval.

For example, here with ibuprofen, it has an incidence of 6.3 percent and a corresponding placebo value of 2.5 percent, resulting in a difference of 3.8 percent as shown here on the top.

For etoricoxib, the mean differences from placebo varied but across the dose range were generally greater than placebo, showing an increase. The effects observed with 30 and 60 milligrams of etoricoxib lie between the effects observed with naproxen and ibuprofen.

These results based on adverse event reports from the study investigators are, in fact, consistent with the objective blood pressure measures reviewed on the previous slide.

Using the same presentation as on the previous slide, the incidence of edema adverse events in the OA placebo-controlled population are displayed here.

On the bottom, again, the incidence of edema adverse events in each active treatment group and the corresponding placebo value; and on the top, expressed as differences from placebo, with 95 percent confidence intervals.

Here for edema adverse events, the incidence appears generally similar for all active treatment groups. Here, again using the same presentation format, we have the incidence of congestive heart failure adverse events in the OA placebo-controlled population.

As you can see in the bar graph on the bottom half, the instance of congestive heart failure is low in this grouping of study for all the active treatments. On the top, expressed as a difference from placebo, similar in all the active treatment groups.

I would now like to summarize the

renovascular safety data from the MEDAL study, beginning with blood pressure. For the two MEDAL study OA cohorts, 60 milligrams on the left and 90 milligrams on the right, mean change from baseline in systolic blood pressure is plotted for each treatment group.

In the 60-milligram OA cohort, mean increases were observed with both etoricoxib, in yellow, and diclofenac, in blue, with approximately 1.6 millimeter greater mean increase observed with etoricoxib over the course of the study.

In the 90-milligram OA cohort, the observed mean difference between etoricoxib, here in orange, and diclofenac, again here in blue, was greater. It was an approximately 2.3 millimeters mean in difference.

These findings are consistent with a dose response in blood pressure from 60 to 90 milligrams of etoricoxib. Although not shown here, results were similar to this for the rheumatoid arthritis cohort. Again, the dose in the rheumatoid arthritis cohort was the 90-milligram dose.

Consistent with the display of renovascular adverse event data from the OA Development Program, the bar graph displayed here presents the incidence of patient discontinuations for hypertension adverse events, here on the left; patient discontinuations for edema adverse events, here in the middle; and the incidence of confirmed congestive heart failure requiring hospitalization, here on the right for each of the three cohorts.

In the 60-milligram cohort, again depicted in the yellow for etoricoxib 60 for these three different endpoints, etoricoxib was associated with a significantly higher incidence of patient discontinuations for hypertension adverse events, again, expressed as a between treatment group difference here.

In a similar incidence to diclofenac for patient discontinuations for edema adverse events, for congestive heart failure the incidence was low in both treatment groups, 0.3 percent or 19 cases on etoricoxib, 60 milligrams, and 0.2 percent or 14 cases in patients on diclofenac.

In the 90-milligram cohorts, both the OA and the RA, etoricoxib was associated with a higher incidence compared to diclofenac for these all three endpoints, again, consistent with a dose response from 60 to 90 milligrams.

To summarize the renovascular data for etoricoxib focusing on 30 and 60 milligrams, the doses for which we are seeking approval, the effects on blood pressure with etoricoxib based on blood pressure measures and on adverse events as reported by its study investigators, based on as I mentioned both the objective measures of blood pressure and adverse event reporting, are dose-related across the dose range.

The specific effects of 30 and 60 milligrams lie between the effects observed with naproxen and ibuprofen. In the instance of edema, focusing on adverse event incidences, is similar to comparator of traditional NSAID.

Thirdly, the incidence of congestive heart failure for etoricoxib 30 and 60 milligrams is low and similar to comparator NSAID.

This concludes the presentation of clinical

data. I would now like to provide an overview of our proposed postapproval activities. The product label is the basis for risk communication. As such, it must effectively communicate important prescribing information.

The NSAID class template, which was provided to you in the Agency's briefing document, is the basis for the proposed etoricoxib label. I would like to take a moment to review the warning sections beginning with the boxed cardiovascular and gastrointestinal risk statements.

These are clear statements about the fact that the use of NSAID may cause serious cardiovascular and/or gastrointestinal events. Also, included is a specific contraindication for the use in the treatment of perioperative pain in the setting of coronary artery bypass grafting.

The proposed etoricoxib label would also carry the NSAID class warnings language for hypertension, congestive heart failure and edema. The warning language for hypertension is very clear, that NSAID, including etoricoxib, can lead to either onset

of new hypertension or exacerbation or worsening of preexisting hypertension. Blood pressure should be monitored very closely both following the initiation of therapy and throughout the course of treatment.

For the patient, an NSAID class medication guide has been developed and is distributed to patients each time an NSAID product is dispensed.

With this label in place and serving as the basis for risk communication, the following actions are proposed as part of our postapproval activities: spontaneous adverse event reporting including continuing to send expedited, serious cardiovascular events to the Agency, submitting periodic safety update reports, and initiation of a pregnancy registry, which is a Merck standard for all marketed products in patient populations which include women of childbearing potential.

Additional postapproval activities would include: a comprehensive education plan for physicians and patients to heighten awareness of the benefits and the risks of NSAID including etoricoxib, physician awareness of NSAID attributes will be tested in

support of our educational plan, and drug utilization studies will be performed to inform these educational efforts as well.

The key objectives of these studies will be to understand the characteristics of patients prescribed etoricoxib and understand usage of the product including: dose, duration, and dose titration.

We have no plans for broadcast direct-to-consumer television advertising at this time. This will only be considered after physicians are aware of key product attributes. We look forward to further discussion of these activities with the FDA.

I will now conclude my presentation with a summary. The information presented supports a favorable benefit-to-risk profile for etoricoxib in patients for whom NSAID therapy is required.

The efficacy of etoricoxib, 30 milligrams, we've shown is comparable to comparator NSAID and consistently showed clinically important improvements across multiple domains including pain and physical function.

In a study which directly compared 30 milligrams to 60 milligrams, 60 milligrams demonstrated a greater treatment effect, indicating that in some patients 60 milligrams will provide additional benefit. The availability of two doses would provide flexibility based on clinical judgment in order to satisfy and meet patient needs, which can be variable.

The GI safety and tolerability that has been established for etoricoxib differentiates it favorably from the traditional NSAID. We know one of the most common reasons patients stop NSAID therapy is due to the development of GI symptoms. Therefore, providing an additional choice with an improved safety and tolerability profile for patients on NSAID therapy is an important contribution.

Etoricoxib has shown a benefit in overall upper-GI events versus naproxen, as we showed, and a consistent risk reduction in complicated events versus naproxen; as we reviewed the MEDAL Program data versus diclofenac and symptomatic ulcers, which importantly was maintained in patients on proton-pump inhibitors;

