DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF
THE ARTHRITIS ADVISORY COMMITTEE AND
THE DRUG SAFETY AND RISK MANAGEMENT
ADVISORY COMMITTEE

VOLUME I

Wednesday, February 16, 2005

8:00 a.m.

Hilton Gaithersburg
620 Perry Parkway
Gaithersburg, Maryland

P A R T I C I P A N T S

Alastair J.J. Wood, M.D., Chair

Arthritis Advisory Committee:

Allan Gibofsky, M.D., J.D.
Joan M. Bathon, M.D.
Dennis W. Boulware, M.D.
John J. Cush, M.D.
Gary Stuart Hoffman, M.D.
Norman T. Ilowite, M.D.
Susan M. Manzi, M.D., M.P.H.

Drug Safety and Risk Management Advisory Committee:

Peter A. Gross, M.D.
Stephanie Y. Crawford, Ph.D., M.P.H.
Ruth S. Day, Ph.D.
Curt D. Furberg, M.D., Ph.D.
Jacqueline S. Gardner, Ph.D., M.P.H.
Eric S. Holmboe, M.D.
Arthur A. Levin, M.P.H., Consumer Representative
Louis A. Morris, Ph.D.
Richard Platt, M.D., M.Sc.
Robyn S. Shapiro, J.D.
Annette Stemhagen, Dr.PH. Industry Representative

FDA Consultants (Voting):

Steven Abramson, M.D.
Ralph B. D'Agostino, Ph.D.
Robert H. Dworkin, Ph.D.
Janet Elashoff, Ph.D.
John T. Farrar, M.D.
Leona M. Malone, L.C.S.W., Patient Representative
Thomas Fleming, Ph.D.
Charles H. Hennekens, M.D.
Steven Nissen, M.D.
Emil Paganini, M.D., FACP, FRCP
Steven L. Shafer, M.D.
Alastair J.J. Wood, M.D., Chair

P A R T I C I P A N T S (Continued)

National Institutes of Health Participants (Voting):

Richard O. Cannon, III, M.D.
Michael J. Domanski, M.D.
Lawrence Friedman, M.D.
FDA Consultants (Non-Voting):

Byron Cryer, M.D. (Speaker and Discussant)
Milton Packer, M.D. (Speaker only)
Guest Speakers (Non-Voting):

Garret A. FitzGerald, M.D.
Ernest Hawk, M.D., M.P.H.
Bernard Levin, M.D.
Constantine Lyketsos, M.D., M.H.S.
FDA Participants:

Jonca Bull, M.D.
David Graham, M.D., M.P.H.
Brian Harvey, M.D.
Sharon Hertz, M.D.
John Jenkins, M.D., F.C.C.P.
Sandy Kweder, M.D.
Robert O'Neill, Ph.D.
Joel Schiffenbauer, M.D.
Paul Seligman, M.D.
Robert Temple, M.D.
Anne Trontell, M.D., M.P.H.
Lourdes Villalba, M.D.
James Witter, M.D., Ph.D.
Steven Galson, M.D.
Kimberly Littleton Topper, M.S., Executive Secretary

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order

DR. WOOD: Let's get started. For those of you who missed the memo, this is the committee to discuss the safety and efficacy of COX-2 inhibitors. It is worth perhaps just giving some thought to why we are here. We are here to evaluate the relative efficacy and risk of these drugs, and to decide whether the benefits from these drugs outweigh the risk, in contrast to whether the risks outweigh the benefits.

It is probably also worth just saying what we are not here for. We are not here to delegate blame or revisit the past. We are here to look into the future and determine what we should do in the future. It is important I think for everybody to remember that as we move through the discussions.

I guess the first thing to do is let people at this enormous table introduce themselves. Let's start down in this corner with John.

DR. JENKINS: Good morning. I am John

Jenkins. I am Director of the Office of New Drugs in the Center for Drug Evaluation at FDA.

DR. O'NEILL: I am Bob O'Neill. I am the Director of the Office of Biostatistics in CDER.

DR. BULL: Good morning. I am Jonca Bull, the Director of the Office of Drug Evaluation V, in the Office of New Drugs.

DR. GALSON: I am Steven Galson, the Acting Director of CDER.

DR. TRONTELL: Anne Trontell, Deputy Director of the Office of Drug Safety.

DR. SHAFER: Steve Shafer. I am not the director of anything. I am a Professor of Anesthesia at Stanford and Biopharmaceutical Science at UCSF.

DR. HENNEKENS: Charlie Hennekens at the University of Miami School of Medicine and Florida Atlantic University.

DR. FRIEDMAN: Larry Friedman, from the National Heart, Lung and Blood Institute.

DR. PAGANINI: Emil Paganini, a nephrologist out of the Cleveland Clinic.

MS. SHAPIRO: Robyn Shapiro, I direct the Center for of Bioethics of the Medical College of Wisconsin. I am a Professor of Bioethics there and

I chair the Health Law Practice Group at Michael, Best and Friedreich.

DR. CANNON: I am Richard Cannon. I am Clinical Director of the Division of Intramural Research, NHBLI, National Institutes of Health.

DR. MORRIS: Lou Morris, President, Lou Morris and Associates.

DR. D'AGOSTINO: Ralph D'Agostino, biostatistician from Boston University and the Framingham Study.

DR. ILOWITE: Norm Ilowite, Schneider Children's Hospital and Rheumatology at Albert Einstein College of Medicine.

MR. LEVIN: Arthur Levin, Director of the Center for Clinical Consumers and consumer representative on the Drug Safety Committee.

MS. MALONE: I am Leona Malone. I am a licensed clinical social worker and I am here as a patient representative for the Arthritis Committee,

and I have struggled with rheumatoid arthritis and osteoarthritis for 35 years.

DR. BATHON: Joan Bathon, Johns Hopkins University, Department of Medicine, Division of Rheumatology.

DR. CUSH: I am Jack Cush. I am a rheumatologist from Presbyterian Hospital, Dallas.

DR. GIBOFSKY: Allan Gibofsky, Professor of Medicine and Public Health, Cornell University; Adjunct Professor of Law at Fordham University; and I am Chair of the Arthritis Advisory Committee.

MS. TOPPER: Kimberly Topper, with the FDA. I am the Executive Secretary for the Committee.

DR. GROSS: I am Peter Gross. I am Professor of Medicine and Community Health in New Jersey Medical School; Chair of Medicine, Hackensack University Medical Center; and I chair the Drug Safety and Risk Management Advisory Committee.

DR. HOLMBOE: I am Eric Holmboe, Vice President for Evaluation Research at the American

Board of Internal Medicine.

DR. FARRAR: I am John Farrar. I am a neurologist and epidemiologist at the Center for Clinical Epidemiology and Biostatistics at the University of Pennsylvania.

DR. MANZI: I am Susan Manzi. I am a rheumatologist from the University of Pittsburgh Medical Center, and with an appointment in epidemiology at the Graduate School of Public Health.

DR. HOFFMAN: I am Gary Hoffman. I am Professor and Chairman of Rheumatic and Immunologic Diseases at the Cleveland Clinic.

DR. DWORKIN: Hi. I am Bob Dworkin. I am Professor of Anesthesiology and Neurology at the University of Rochester School of Medicine.

DR. BOULWARE: I am Dennis Boulware, Professor of Medicine, and rheumatologist at the University of Alabama at Birmingham, and member of the Arthritis Advisory Committee.

DR. DOMANSKI: I am Mike Domanski. I am a cardiologist. I head the Clinical Trials Group at

the National Heart, Lung and Blood Institute.

DR. FLEMING: Thomas Fleming, Chair of Biostatistics, University of Washington.

DR. FURBERG: Curt Furberg, Professor of Public Health Sciences, Wake Forest University. I am a member of the Drug Safety and Risk Management Advisory Committee.

DR. DAY: Ruth Day, Duke University, Director of the Medical Cognition Lab, and a member of the Drug Safety Committee.

DR. PLATT: I am Richard Platt. I am Professor and Chair of the Harvard Medical School, Harvard Pilgrim Healthcare Department, Ambulatory Care and Prevention. I am principal investigator of one of the HHRQ centers for education and research in therapeutics. I am a member of the Drug Safety Committee.

DR. GARDNER: I am Jacqueline Gardner, University of Washington School of Pharmacy and Pharmaceutical Outcomes Research Program. I am on the Drug Safety and Risk Management Committee.

DR. ELASHOFF: Janet Elashoff,

Biostatistics, Cedars-Sinai and UCLA.

DR. NISSEN: I am Steve Nissen. I am the Medical Director of Cleveland Clinic Cardiovascular Coordinating Center. I am a cardiologist, and I am the Chair of the Cardiorenal Advisory Panel for the FDA.

DR. ABRAMSON: Steve Abramson, I am Chairman of Rheumatology at NYU and the Hospital for Joint Diseases.

DR. CRYER: I am Byron Cryer. I am a gastroenterologist from the University of Texas Southwestern Medical School in Dallas, and the Dallas VA Medical Center. My role here today is as an FDA consultant to this group and as a member of the Gastrointestinal Drugs Advisory Committee.

DR. STEMHAGEN: I am Annette Stemhagen. I am an epidemiologist with Covance and I am the industry representative to the Drug Safety and Risk Management Committee.

DR. WOOD: I am Alastair Wood. I am the Associate Dean at Vanderbilt and Professor of Medicine and Professor of Pharmacology.

Now we will have the "reading of the lesson" from Kimberly Topper.

Conflict of Interest Statement

MS. TOPPER: The following announcement addresses the issue of conflict of interest with respect to this meeting, and is made part of the record to preclude even the appearance of such. Based on the agenda, it has been determined that the topics of today's meeting are issues of broad applicability and there are no products being approved. Unlike issues before a committee in which a particular product is discussed, issues of broader applicability include many industrial sponsors and academic institutions.

All special government employees have been screened for their financial interests as they may apply to the general topics at hand. To determine if any conflict of interests existed, the agency has reviewed the agenda and all relevant financial interests reported by the meeting participants. The Food and Drug Administration has granted general matters waivers to the special government

employees participating in the meeting who require a waiver under Title 18 United States Code, Section 208. A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

Because general topics impact so many entities, it is not practical to recite all potential conflicts of interest as they apply to each member, consultant and guest speaker. FDA acknowledges that there may be potential conflicts of interest but, because of the general nature of the discussions before the committee, these potential conflicts are mitigated.

Further, during today's session Dr. Bernard Levin will be presenting data on the prevention of colorectal sporadic adenomatous polyps trial, the PreSAP trial, a Pfizer-sponsored clinical trial. We would like to note for the record that Dr. Levin is attending this meeting as a consultant to Pfizer.

With respect to FDA's invited industry

representative, we would also like to disclose that Dr. Annette Stemhagen is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Stemhagen's role on this committee is to represent industry interests in general and not one particular company. Dr. Stemhagen is the Vice President of Strategic Development Services for Covance Periapproval Services, Inc.

In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participant's 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 product they may wish to comment upon. Thank you.

DR. WOOD: For those of you still standing, there are apparently seats in the overflow room. Let's go right on to the first

speaker, who is Steve Galson. Steve?

Welcome

DR. GALSON: Thank you. I want to welcome everyone and thanks in particular to our Chair, Dr. Alastair Wood, committee members, special guests, members of the public and FDA staff who have really done a tremendous job in putting together a particularly and unusually complex meeting.

We have some special guests today that I want to point out. We have representatives from the drug regulatory authorities of the member countries of the European Union and six separate countries--Canada, Japan, Singapore, Australia, Switzerland and Mexico, and I really want to welcome them. Thank you for being with us. We also have several guests from congressional staff offices and we are very pleased that they are with us as well to learn about this important issue.

There is really an unprecedented level of international attention to one of our advisory committees today, and we are very proud that this is taking place and we think it represents a new

level of collaboration and discussion around the world about an emerging public health issue.

Many millions of people all over the world are taking the products that we are discussing. Indeed, they depend on them for a range of conditions from the mild to the severe and life-threatening. We must keep the interests and health of these patients front and center in these deliberations.

I wouldn't be complete in this introduction if I didn't acknowledge the controversy surrounding these products, particularly over the last year. I want to emphasize that we are anxious to hear all points of views from the advisory committee and, of course, from agency staff. It goes without saying that all FDA staff are free to make any presentation without fear of any retaliation. I don't want anyone sitting around this table to be shy.

Also, we look forward to hearing a wide range of views from the more than 50 members of the public who are going to be making brief statements

later in the meeting. I want to remind the public that all members of this committee have been carefully screened for conflicts of interest and we have used the same standards in this process that we have used for other committees and similar meetings.

A few comments about the challenging risk/benefit balance that the agency must achieve in making its regulatory decisions: Although you have all heard strong opinions in the media and medical literature about safety issues related to the drugs we are discussing, our job and, indeed, your job is to assess any safety concerns when balanced by the benefit of these products. We cannot lose sight of the reduced morbidity, pain and suffering achieved by the products that are under discussion and the real impact on people that changes in the regulatory status may entail.

You will be assessing the risk/benefit balance of these products this week in the midst of a changing information environment and this represents a particular challenge. We are aware of

at least a half dozen ongoing meta-analyses and huge population-based studies, in addition to several of the studies you will hear about this week for which data analysis continues as we speak. Although we have a full three days, the time really isn't long enough to hear details about every single ongoing, or incomplete, or unreviewed study of which we are aware. Leaving them out of the agenda has absolutely nothing to do with wanting to keep information from you and everything to do with allowing you to focus so that you have time to get to our critical advisory questions.

We must be very cautious about interpreting data for regulatory decision-making that has not been thoroughly vetted and peer reviewed, and even more cautious about interpreting data of preliminary studies that are not even complete. You will be hearing about some data in these categories and I would remind you to exercise caution in their interpretation.

As scientists, we have all seen examples of ongoing studies whose findings have changed as

analysis is in the final stages, or examples where inadvertent errors have led to misclassification in epidemiologic studies, or when data that comes in at the end of the data gathering stage influences results. In today's 24-hour news environment, it is difficult to not react to these incomplete reports but we must go back to the basics of relying on sound science and use the peer review system to strengthen findings before utilizing them to make regulatory decisions.

Lastly on the risk/benefit balance, as you members know but it is sometimes difficult for us to convey to the public, our job at FDA and your job in the advisory group is to balance risks and benefits on a population basis for the nation as a whole. This is very different from the risk/benefit assessment physicians do with individual patients where specific risks of the medications, family history, a patient's risk tolerance and other factors must be taken into consideration. A drug may, based on the weight of evidence, have a positive benefit/risk balance for

the population leading to approval, yet, cause grievous harm in a specific subset of individuals. We say over and over again that all drugs have risks, but when a person you know suffers an adverse event the faulty assumption is sometimes made that we must have made a mistake in the approval.

I would also like to mention an unusual feature of many of the data from the trials you will be hearing over the next few days. The data on safety of these drugs is, as I have mentioned, unusually complex and represents the fact that clinical trial methodology to look at cardiovascular effects as adverse events has changed dramatically. When discussions began about cardiovascular safety of NSAIDs there was no standard methodology by which cardiovascular adverse events were confirmed or categorized. Analyses vary by trial. Confirmatory processes vary by trial. Only after the VIGOR trial did the methods of establishing confirmatory processes and standardization become better established. Of

course, in population-based cohorts and case control studies case reporting and confirmation is both rudimentary and completely inconsistent between studies.

In addition, as you know already, unlike drugs designed to treat cardiovascular disease, these trials have not been designed to do a full cardiovascular assessment. So, major pieces of information that you might like to have are simply not available. So, in many ways we are forced to compare apples to oranges in these trials and studies, and when you are not doing that you are trying to draw conclusions based on insufficient information, making your task even harder.

In spite of all the ambiguity, work in progress, changing standards and questions, we ask you for the miraculous job of crystal clarity in your responses to our questions. We know this is tough on such challenging scientific and controversial issues, and we are enormously grateful to you because we know that you all are up to this challenge. The agency will act rapidly

within the next few weeks to act on the recommendations you communicate to us over the next few days.

I would like to quickly go to the agenda. Today through midday tomorrow you will hear from sponsor companies, FDA staff and NIH researchers about data on both approved and unapproved COX-2 selective and non-selective products. Tomorrow afternoon we have 54 members of the public registered to speak. On Friday you will hear about important methodological issues in interpretation of these studies, and then we will move on to the questions.

Again, thank you and on behalf of the FDA I wish you the very best of luck on this important endeavor. Thanks, Dr. Wood.

DR. WOOD: Thanks a lot. Two additional people have joined the cast of thousands that we have at the table, and perhaps it would be worth having them introduce themselves. Bob, you go first.

DR. TEMPLE: I am Bob Temple. I am

Director of the Office of Medical Policy.

DR. WOOD: Stephanie?

DR. CRAWFORD: Thank you, Mr. Chair. Stephanie Crawford--good morning--University of Illinois at Chicago, College of Pharmacy; member of the Drug Safety and Risk Management Advisory Committee.

DR. SELIGMAN: Good morning. This is Paul Seligman. I am the Director of the Office of Pharmacoepidemiology and Statistical Science.

DR. WOOD: Is there anyone else I didn't notice arrive? No? Then, let's move on to the next speaker. Jonca?

Regulatory History

DR. BULL: Good morning. Again, I would like to extend a warm welcome to the members of the committee and to extend and acknowledge a particular thanks to our staff at FDA, specifically Dr. Villalba, Dr. Witter, Dr. Schiffenbauer from our team, our statistical staff, and colleagues in the Office of Drug Safety who have put in countless hours in preparation for this meeting.

The NSAID class is one that probably everybody in this room has a product in their medicine cabinet that is a member. It is a large

class of marketed products for both OTC and prescription indication use. It is a wide range of products with varying risk/benefit profiles. Their approved indications are for short-term use such as dysmenorrhea and acute pain; chronic use for osteoarthritis, rheumatoid arthritis, familial adenomatous polyposis in the example of Celebrex. So, clearly, we have drugs that for everyone, from the young female with cramps to the senior citizen with arthritic pain, have importance and clearly there is a need for them in the marketplace. There are other proposed uses that are known to be under investigation, and you will hear about studies in the setting of Alzheimer's disease, as well as sporadic polyp prevention.

I would like to briefly review some of the regulatory history for these products, going back to December of 1986 when there was a public advisory committee meeting that discussed the GI

paragraph and databases were discussed at that time.

This was followed in 1995 where revisions for the NSAID class label were discussed, as well as a subsequent advisory committee in 1998 when the new science of the COX-2s were discussed and their potential enhanced safety for GI benefit.

In December of 1998 an advisory committee was held to discuss the data for Celebrex, followed in December of 1998 when that drug was approved first in this new class of products. In April of 1999 an advisory committee was held for Vioxx, followed by its approval in May of 1999. We held another advisory committee meeting in 2001 which discussed the large outcome studies which sponsors had undertaken to further evaluate how clinically meaningful the data from endoscopic studies was in order to further evaluate the enhanced GI safety claim.

This time line has several points I would like to bring to your attention. The first IND for these products came in 1994 so we are dealing with

a relatively short time line, given that this is year 2005, in drug development, marketing and an evolving picture for safety.

The products below the time line are the ones that have been approved, and I would like to bring your attention to those above the line, Arcoxia, Prexige, the IV formulation of Bextra which have not been approved in the United States due to insufficient safety data.

The COX-2 agents--are they different? In what way? When we look at risk to benefit, how do these agents differ from the traditional NSAIDs? Can a clinically meaningful benefit for GI safety and less risk, that is for CV risk, renal risk, hepatic risk, allergy--can that be characterized? What additional study is needed to better understand the science of COX-2 inhibition?

When we think in terms of labeling risk management, what risk management options are appropriate in this settings, ranging from potential withdrawal of the product to labeling changes?

Certainly there are lessons learned for drug development. I cite a quote at the end of an article by Dr. Temple and Marty Himmel, in JAMA in

May, 2002, and I think the statement is quite a relevant one to our deliberation, that no improvements in drug development can completely eliminate the risk of unexpected events.

Looking at large NDA databases is helpful but continued monitoring is essential to assess evolving risk profiles for new products. Certainly, the impact of aggressive marketing must be taken into account for these unknowns of drug safety.

Dr. Galson has already gone through the schedule for the meeting. I will just briefly allude to our framework for this deliberation. Following me, Dr. Byron Cryer will be discussing the gastrointestinal effects of the NSAIDs and COX-2 specific inhibitors; followed by Dr. Garret FitzGerald on mechanisms for cardiovascular risk from inhibition of COX-2s. This will be followed by a presentation by Merck and the FDA presentation

by Dr. Lourdes Villalba.

This afternoon you will hear from Pfizer and their review of cardiovascular safety and risk/benefit assessment of celecoxib, followed by the FDA presentation by Dr. James Witter. There will be a presentation then on the NIH-sponsored colon polyp prevention trials, with subsequent presentations by Pfizer on valdecoxib and parecoxib, and an FDA presentation on valdecoxib. This will be followed by Bayer and Roche discussing naproxen.

Tomorrow you will hear about the epidemiologic studies, followed in the afternoon by the open public hearing and committee discussion.

Day three in the morning will focus on the Alzheimer's prevention trials. The ADAPT trial will be discussed that morning by Dr. Constantine Lyketsos; followed by a presentation by Dr. Milton Packer on interpretation of cardiovascular events; a presentation by Dr. Robert Temple on clinical trial design and patient safety, future directions for COX-2 selective agents; and a presentation by

Dr. Robert O'Neill on issues in projecting increased risk of cardiovascular events to the exposed population. Dr. Sharon Hertz will then present a summary of the meeting presentations prior to the afternoon discussion of our questions.

Again, our thanks to the committee members for taking time from their extraordinarily busy schedules for this important meeting as we reach another milestone in the regulatory history of these products.

DR. WOOD: Thanks very much. Let's just go straight on to the next speaker, who is Dr. Byron Cryer who is going to talk on the GI effects. Dr. Cryer?

Gastrointestinal Effects of NSAIDs
and COX-2 Specific Inhibitors

DR. CRYER: Thank you. For the purposes of full disclosure, I would first like it to be noted that I have been invited to give this presentation by the Analgesic and Anti-Inflammatory Division of the FDA. I do have relationships with sponsors of products being mentioned in today's

presentation, however, I am not being paid for my participation in this meeting nor for my presentation today.

For those of you not familiar with me, I am a gastroenterologist and I am thrilled that the FDA has been begun this meeting with the focus on this subject because many of us have forgotten that the initial reason for the development of the class of the COX-2 specific inhibitors was entirely because of the gastrointestinal effects of the non-steroidal anti-inflammatory drugs and, for that reason, I think it is very appropriate that we have this review of the gastrointestinal effects of NSAIDs and what the data say from the GI perspective about the gastrointestinal effects of COX-2 specific inhibitors.

From the perspective of the NSAIDs risk, listed here are several of the known risks associated with the non-steroidal anti-inflammatory drugs, the gastrointestinal risks, the cardiorenal risks and the anti-platelet concerns. Among these, as the group knows, the adverse concerns of

greatest risk historically were the gastrointestinal effects that present with features such as ulcers, perforations, bleeding, obstruction strictures and many other interesting manifestations. Over the last several years, added to this list and a focus of this meeting are cardiovascular concerns of the non-steroidal anti-inflammatory drugs but my perspective are the issues listed at the top, the gastrointestinal effects.

When looking more extensively at what the specific gastrointestinal effects of NSAIDs are, we have learned that NSAIDs have effects throughout the GI tract. The upper gastrointestinal effects are the most pronounced but there are some very interesting effects that we see throughout the GI tract, such as in the small intestine and colon. In recent years we have had an increasing focus on lower gastrointestinal effects of NSAIDs, a very interesting phenomenon. Several have been assessed by endoscopic means but there has been a lot of discussion as to what are the clinically relevant

untoward major events that might happen in the lower gastrointestinal tract. While this is debated with respect to the prevalence of lower GI effects, these effects are likely somewhere in the range of 10-20 percent of total gastrointestinal effects that happen within the GI tract attributable to NSAIDs. Clearly, the major effects of NSAIDs in the GI tract are in the upper gastrointestinal tract, such as ulcers more commonly in the stomach and the duodenum, and concerns such as gastrointestinal bleeding, perforations and obstructions. So, that is really the focus upon which the strategies were developed to increase NSAID safety within the gastrointestinal tract.

With respect to the epidemiology of ulcer disease in general, some very interesting phenomena have been observed which have persisted into recent years. But the overall summary of the phenomenon that I would like to focus your attention to is that while in recent years the overall incidence of uncomplicated ulcers, both gastric and duodenal,

has been markedly declining in the U.S. and worldwide, very interestingly, the incidence of complications, specifically gastrointestinal bleeding, has not declined in similar proportions and, in fact, has persisted or increased. This phenomenon, in particular the bleeding, has been felt to be a manifestation of the effects of the non-steroidal anti-inflammatory drugs within the GI tract.

This problem presents itself clearly with respect to morbidity and, unfortunately, mortality and several hundreds of thousands of hospitalizations. The costs have been debated. The actual quantified amount of mortality in the U.S. is also a number that is debated. The 16,500 estimate is probably an overestimate. But the bottom line is that NSAIDs are clearly associated with morbidity, mortality and costs in this country as well as worldwide, and this is has been the issue that has led to the discussions of the need for increasing gastrointestinal safety for NSAIDs.

So, the various ways in which these

assessments have been done has ranged from studies which we have seen over the years that have been short-term evaluations of physiologic or pharmacologic effects on healthy volunteers to the more relevant studies of the gastrointestinal effects of these drugs in arthritis patients. These studies have ranged from long-term endoscopy studies to a fewer number but very important studies that have assessed clinical events such as symptomatic ulcers, GI bleeding, perforation and obstruction.

Over the years there has been extensive discussion as to the relevance of the endoscopy studies and how the endoscopic observations with NSAIDs might relate to the outcome studies. One of the criticisms of the endoscopic studies is that the endoscopic lesions are numerous. They are mostly only known from endoscopies that are done as a part of a scheduled study and they are asymptomatic. However, what we have learned from comparing the numerous endoscopic studies to observations that have been seen in the outcome

studies is that the relative proportions in terms of outcomes seen in endoscopic studies tend to be predictive of what one would expect to see in an outcome study. So, we have come full circle then in our understanding of the role of endoscopic studies and, at least in the gastroenterology community, we now feel that there is some substantial value in endoscopic studies and that they are predictive of what one might expect to see in outcome trials.

Now, with respect to what we see in these types of trials, when one looks endoscopically there is a range of findings in people who are taking high doses of NSAIDs. In greater than 90 percent, if one were to look, we would see this phenomenon of NSAID gastropathy, which is this constellation of erosions and hemorrhages but it is mostly asymptomatic, mostly not clinically relevant.

With respect to incidences of asymptomatic endoscopic ulcers, gastric ulcers happen two to three times more commonly than the duodenal ulcers,

with the ranges that are shown on the slide. Again, these lesions are mostly asymptomatic and don't progress in the majority of individuals to clinically untoward gastrointestinal events.

What these things look like--this is an endoscopic photograph of gastropathy demonstrating the constellation of hemorrhages and erosions that, again, are going to be mostly asymptomatic, ranging to a picture, shown here, of an endoscopic ulcer seen in the antrum of the stomach of an NSAID user.

The more clinically concerning endpoint, that being clinically significant ulcers, occurs with the non-selective NSAIDs on average about 2 percent, with a range of about 1-4 percent. This range and this mean are important numbers as benchmarks to remember because they will become relevant as we discuss some of the outcome studies that have been conducted with the COX-2 specific inhibitors.

Having reviewed what the risks are, I would now like to move the discussion to what our strategies have been to reduce the risk of the

gastrointestinal complications with NSAIDs. It is a simple strategy and most experts will recommend identifying the patient population who might be at risk and this is based upon identification of risk factors. Then, once having identified susceptible populations for risk, one employs strategies that would reduce risk, such as either the use of gastroprotective drugs or the use of safer NSAIDs, and the category of safer NSAIDs clearly involves the subclass of the COX-2 specific inhibitors.

With regard to identification of risk factors, a risk factor not commonly mentioned is the NSAIDs themselves. NSAIDs clearly provide risk for gastrointestinal effects. Shown here are various NSAIDs available by class and by prescription in the United States. As you can see, they have been divided into traditional NSAIDs, non-salicylates; aspirin related, salicylate-based compounds; and then COX-2 inhibitors which are currently available, in development or previously available in the U.S.

With regard to identifying patient

characteristics which may suggest risk, these have been extensively studied and they are listed here, things such as increasing age and the threshold age is widely debated but one category that has been suggested would be those greater than 65, let's say. Clearly history of GI ulceration; having had a complication; concomitant drugs such as corticosteroids or anticoagulants; cardiovascular disease, interestingly, such as CHF; and this issue of multiple NSAIDs all increase the risk.

Of this list that the group is very familiar with, the one that has probably not been as widely appreciated and one which has been highlighted from some of the outcome trials of the COX-2 specific inhibitors is this issue of multiple NSAIDs, and it is a risk factor that presents itself in the context of a patient profile, a patient who takes prescribed NSAIDs along with either low doses of aspirin of over-the-counter NSAIDs. Since we know that the risk for NSAID-related gastrointestinal events is related to dose, what one accomplishes in this group of

multiple NSAIDs is essentially to increase the overall dose of NSAIDs delivered.

With regard to the strategies after having identified the susceptible population, the first category essentially is that of co-therapeutic gastroprotection. As alluded to a minute ago, it would be desirable to use the lowest effective dose of an NSAID. Then really the two prevailing gastroprotective or co-therapy strategies that we have are the use of either misoprostol or proton pump inhibitors.

Several studies have been done in either of these categories. I will just highlight for purposes of discussion two outcome trials that I think nicely demonstrate the effectiveness of these strategies. With regard to misoprostol, the most widely quoted study was the outcome trial, the MUCOSA trial in which misoprostol was given to patients who were chronically taking NSAIDs over 6 months and were demonstrated to be associated with a 40 percent or less reduction in gastrointestinal complications.

From the perspective of the PPI outcome trials, there have been fewer evaluations but there have been, in fact, some evaluations for clinically

relevant outcomes for PPIs, this being one example of a trial which was actually not intended in its design to evaluate outcomes of a proton pump inhibitor in patients taking NSAIDs but, nevertheless, provided us with some insight into the potential effects from the perspective of gastrointestinal outcomes.

This was a trial that was designed with the question in mind of whether or not H. pylori eradication prior to starting an NSAID would be an effective therapy or not for the reduction potentially of NSAID-related bleeds. So, in this group of H. pylori infected NSAID users, half of them were treated for their H. pylori infections prior to being started on an NSAID and acted as a control. The other half were given a proton pump inhibitor. In this specific instance omeprazole.

What was observed, very interestingly, at the end of 6 months is that in this instance there

was a 76 percent reduction in the subsequent incidence of upper gastrointestinal bleeding in the group that had received the proton pump inhibitor approach.

From the perspective of the safer NSAIDs, this is a story that is also well known. Its focus today is really to look at specifically the COX-2 specific inhibitors shown on the far right. The concept has been widely discussed and is arguably somewhat simplistic, but for the sake of today's discussion, as the group knows, it is highlighted by the observation that there are 2 COX isoforms available, COX-2 and COX-1, and that COX-1 is the isoform which is primarily responsible for the protective prostaglandins in the stomach which typically protect against injury. Once inhibited by non-selective NSAIDs, the prostaglandin products produced by COX-1 lead to an increased susceptibility for injury. The concept at least for COX-2 specific NSAIDs in that they have limited inhibitory effects on COX-1 is that they would likely not inhibit prostaglandins, likely not be

associated with ulcers, and likely be associated with a reduction in clinically significant gastrointestinal untoward events with NSAIDs.

Having said that, there have been a few gastrointestinal outcome trials that have been designed to evaluation whether or not the COX-2 inhibitors would meet this objective or not. Shown here are two of the outcome trials with rofecoxib and celecoxib.

As the group knows, there has also recently been another completed outcome trial with lumiracoxib. In general, the outcome trials have compared COX-2 specific inhibitors at higher than usual therapeutic doses for osteoarthritis to non-selective NSAIDs and evaluated the clinically significant events on average over a year. The major difference of importance between the outcome trials with celecoxib and rofecoxib was the inclusion or exclusion of low doses of aspirin. We know that low doses of aspirin are ulcerogenic. In the CLASS trial 21 percent of patients took low doses of aspirin, 325 mg/day or less, and none of

the patients in the rofecoxib experience were taking low doses of aspirin.

The principal gastrointestinal observations from the CLASS trial are, as shown here in this figure, taken from the publication in the JAMA, which represents the 6-month data point from this year-long trial. In the top panel are all the patients who were evaluated in the trial who were taking either celecoxib or one of the non-selective NSAIDs, ibuprofen or diclofenac. As you note, there was a numeric but not statistically significant reduction in ulcer complications in the overall group, remembering that 21 percent of the patients in the CLASS trial were taking low doses of aspirin and that some of the ulcer effects were related to the effects of aspirin.

So, to get a better concept of the effects of a COX inhibitor compared to non-selective NSAIDs, the middle panel looks exclusively at the patients in this 6-month evaluation of the CLASS trial who were not taking aspirin, just celecoxib, ibuprofen or diclofenac. As you observe in this

middle panel, there were statistically significant reductions associated for GI outcomes with celecoxib when compared to traditional NSAIDs in the absence of aspirin at 6 months.

However, for those of you who were here four years ago this month at the long-term safety evaluations of the FDA, the entire CLASS trial data set was evaluated with respect to gastrointestinal complications. When compared to either ibuprofen or diclofenac alone or combined, with respect to complications there were not statistically significant gastrointestinal reductions in events associated, as you can see, with celecoxib.

With regard to the VIGOR trial, just to refresh the group's memory, this was clearly exclusively an evaluation of rofecoxib versus naproxen. There was no low dose aspirin. Their observations were straightforward in with respect to either primary or secondary event being confirmed upper GI events or complicated events. There was a statistically significant reduction associated with rofecoxib compared to naproxen.

As I have mentioned, there has also been a similar in design outcome study with lumiracoxib. The variable observations between these outcomes

trials have led to extensive debate in the medical and scientific communities as to why one might have observed differences with respect to gastrointestinal endpoints between the outcome trials of COX-2 specific inhibitors.

While I don't have time to get into the nuances and specifics of that debate, one point that I would like to bring to the group's attention that I do think is worthwhile reviewing is that, to the extent that there were differences between the observations in the outcome trials, these differences may have had more to do with differences in ulcerogenic effects with the traditional NSAID comparators such as naproxen, ibuprofen and diclofenac than they may have had to do with differences with respect to ulcerogenic effects between rofecoxib and celecoxib.

The point to be highlighted is that the non-selective NSAIDs differ with regard to their

ulcerogenic effects and that the delta, the difference observed between a COX-2 inhibitor and a non-selective NSAID will matter, and it will be based upon the choice of comparator being used. I am not here to speak about cardiovascular effects. Dr. Garret FitzGerald will talk about cardiovascular issues in the talk to follow. But I would like to point out that this concept of differences in COX-1 effects of non-selective NSAIDs is also applicable when we turn to a discussion of considerations of potential differences in cardiovascular observations between the trials of COX-2 inhibitors.

Having pointed out the data with the COX-2 specific inhibitors, I would like to mention that there are other potential approaches, and I would like to turn the discussion to a consideration, as shown on the bottom, of potentially older, safer NSAIDs that may be associated with gastrointestinal safety, agents such as the non-acetylated salicylates, nabumetone, diclofenac and etodolac.

I mention this because--these are not

gastrointestinal events, this is a reflection of in vitro evaluations of COX-1 versus COX-2 selectivity of various NSAIDs. On the left, in the green, are NSAIDs which have increasing in vitro COX-1 selectivity and are going in the negative direction; on the right, is increasing COX-2 selectivity. When one evaluates COX-2 selectivity in vitro, there is a group of NSAIDs which fall within this mid-range category of what I would call moderately COX-2 selective, and this COX-2 selectivity of agents such as meloxicam or etodolac may be predictive of what one might see in outcome trials.

Taking etodolac as an example, when it was evaluated with respect to gastrointestinal outcomes compared to a non-selective NSAID such as naproxen, shown in the upper panel, there was a statistically significant, greater than 50 percent, reduction in gastrointestinal outcomes associated with an agent such as etodolac. So, this leads me to conclude, over here in this group of category for COX-2 specific inhibitors, that there are agents which

have COX-2 selective activity which had not been widely appreciated historically.

Since aspirin was such and important phenomenon in outcome trials, I think it is relevant to review the gastrointestinal effects of low doses of aspirin. This has been looked at mostly from an epidemiologic perspective, and trials such as this have tended to show a dose-response relationship. Although not statistically significant in this case, clearly lower doses, at least numerically, of aspirin such as 75 mg were associated with a lower rate of clinically relevant gastrointestinal bleeding than higher doses such as 300 mg. In this instance, at least numerically from 75 to 300 mg, the odds ratio of clinically relevant upper gastrointestinal bleed doubled.

Because of the risk associated with very low doses of aspirin such as 75 mg, doses of aspirin that have been quite low, such as 10 mg, have been evaluated in human studies to assess the question of whether or not there would be any daily

orally administered dose of aspirin which would be without gastrointestinal effects.

When measured by use of an intermediate marker that would be of COX inhibition or measurement of gastrointestinal prostaglandins, daily doses of aspirin given out to 3 months, as low as 10 mg, were associated with as great of a reduction of gastrointestinal COX as seen with 320, and gastric ulcerations were observed with a dose of aspirin that was as low as 10 mg, suggesting that there is likely not a dose of aspirin that would be effective that would be daily administered that would be without gastrointestinal risk.

Another commonly asked question would be the potential benefit of an enteric coating or buffered preparation of aspirin. When assessed in this cohort from the Framingham trial of patients who were taking various formulations of low dose aspirin, as one sees that there was no appreciable reduction in gastrointestinal bleeding associated with either enteric coating of aspirin or buffered aspirin when compared to plain, non-enteric,

non-buffered aspirin preparations.

Coming back to the risk factor which I mentioned had been not widely appreciated, the risk factor of multiple NSAID use, that is, combining low dose aspirin with a non-selective NSAID or COX-2 specific inhibitor, I think it is valuable to appreciate for a moment the actual risk, numerical risk, contributed by the addition of aspirin to another prescribed NSAID.

From this population study in Denmark, it was apparent that when one combines the use of low dose aspirin and a non-selective NSAID the risk of having a clinically significant bleed, upper gastrointestinal bleed, more than doubled, such that several people would feel that the risk of a 6-fold increase in the combination of a non-selective NSAID plus aspirin is sufficiently high that this population of users would need to be further risk reduced.

These are data with non-selective NSAIDs. The data with respect to COX-2 specific inhibitors have come primarily from a few sources. In this

previous figure in which we saw earlier the 6-month data from the CLASS trial we stopped with the middle panel and had events in individuals taking celecoxib or non-selective NSAIDs in the absence of aspirin.

But when one looks at the bottom panel, rates of events, complications or symptomatic ulcers and ulcer complications in individuals who were taking one of these agents in the face of low doses of aspirin, it is clear that the use of low dose aspirin in the face of a COX-2 specific inhibitor markedly increased the rates of gastrointestinal events.

But a point that I would like you to focus your attention on is the actual incidence of events in the patients who were taking either aspirin in combination with a COX inhibitor or non-selective NSAID. You will remember that the problem that led to really the focus and development of classes of safer NSAIDs is an incidence of ulcer complications of 1-4 percent in the population that takes non-selective NSAIDs. When one looks at the

incidence of events that occurs annualized in patients who take aspirin, at least derived from the data in the CLASS trial, it is clear that the incidence that was observed of 2-6 percent is higher than the original problem.

So, I would like to summarize with respect to the effects of low dose aspirin that low dose aspirin clearly increases the risk and mitigates the potential gastrointestinal beneficial effects of a COX-2 specific inhibitor. These observations have been seen in other experiences with regard to the total lack of outcome data which I previously showed you, where we stopped on the top panel. When looking at the observations in patients taking low doses of aspirin, the beneficial effects of total lack disappear.

In endoscopic trials recently we have also seen this effect of aspirin in this trial over 12 weeks in which either aspirin was given alone or in combination with rofecoxib and compared to ibuprofen. Focusing on the rofecoxib plus aspirin comparison, rofecoxib plus aspirin users have a

similar, equivalent incidence of endoscopic ulcerations to non-selective NSAIDs such as ibuprofen. So, the short conceptual way of summarizing this is a COX-2 specific inhibitor plus aspirin equals the effects of a non-selective traditional NSAID.

The gastrointestinal discussion that we have had so far has pointed out some of the potential gastrointestinal effect benefits of a safer class of agents such as a COX-2 specific inhibitor. Clearly, the gastrointestinal benefit does not exist in the face of aspirin and what we have recently learned is that the gastrointestinal benefit derived from a class of safer agents in the GI tract might be mitigated by adverse events in other areas, and other areas for consideration for this week's meeting are potential cardiovascular effects.

Given the limitations of COX-2 specific inhibitors and low dose aspirin users or when there may be potential cardiovascular concerns, one question that we have been asked to address would

be in a potential world of no COX-2 specific inhibitors would we return to the problem of several gastrointestinal bleeds, hospitalizations or mortality?

Well, this brings us back to the question of what might be the other approaches to accomplish the objective of reductions in GI events. We have discussed some of the older, safer NSAIDs. There are NSAIDs in development such as nitric oxide NSAIDs or phosphatidylcholine NSAIDs, the effects of which we are unsure of now and they are currently being evaluated. But the other prevailing strategy to accomplish this objective would be the consideration of a non-selective NSAID plus co-therapy with either a proton pump inhibitor or misoprostol.

Data in support of the proton inhibitor approach have been looked at in several trials, one example of which is shown here, endoscopic ulceration in NSAID users receiving co-therapy with either placebo, a proton pump inhibitor or misoprostol. What the data pretty consistently say

is that proton pump inhibitors have similar ability to misoprostol to prevent recurrent ulceration in NSAID users.

Given that there are two prevailing approaches to accomplishing GI safety, either COX-2 specific inhibitor alone or a non-selective NSAID plus a PPI, an important question which has presented itself for evaluation has been how might these two approaches compare directly and this is an important question to consider when considering the alternatives to having a world potentially in which there might not be COX-2 specific inhibitors available. Could GI safety be accomplished?

Well, this question has been asked at least in two trials or similar design in which high risk NSAID users--high risk being defined as people who previously had a history of bleeding ulcers. Once the ulcers were healed, they were then placed on either of the combination of non-selective NSAID plus a proton pump inhibitor or a COX-2 specific inhibitor, and then were followed for 6 months for rates of recurrent gastrointestinal bleeding. The

results of one of these trials has been fully published in a peer reviewed journals, shown here.

The two endpoints being looked at--on the right are outcomes such as upper gastrointestinal bleeding; on the left are the results of endoscopic ulceration. Either of these endpoints tells us that the approach of a non-selective NSAID plus a PPI appears comparable to the COX-2 specific inhibitor approach for achieving the objective of reductions in GI safety. However, two important points that I would like to point out to the group are, one, we have endoscopy on the left and outcomes, GI bleeding, on the right. Again, the endoscopic ulcerations that are seen in the trials generally predict what one would see in an outcomes study but, more importantly, if one looks at the actual rates of events which occurred, on the right, 5 percent and 6 percent with either approach in a group of individuals at high risk, meaning they previously had a history of gastrointestinal bleed, it is clear that either approach, either NSAID plus PPI or COX-2 specific inhibitor, is

sufficiently adequate to reduce the rates of events back to a comfortable range. The rates of events seen here in a high risk population are similar to the initial problem for which these approaches were developed.

In conclusion I have several observations. The untoward gastrointestinal effects of NSAIDs, as we know, cause considerable morbidity, mortality and cost. Secondly, COX-2 specific inhibitors were developed principally to achieve a reduction in NSAID gastrointestinal toxicity. That was a very desirable objective to be reached. But very interestingly, as we just reviewed, this objective has been partially reached. It seems that the risk reduction may not be achieved to the extent that we would have liked in patients who are at high risk for gastrointestinal bleeding, and the reason this is important is that that is clinically the target group of interest for risk reduction.

Paradoxically, I did not mention that if one looks at subgroup analyses of outcome studies it appears that people who are at lower baseline

gastrointestinal risk do have a benefit from receiving a COX-2 specific inhibitor. However, the low risk group has a low prevalence of this problem of NSAID-related gastrointestinal events in the population.

So COX-2 inhibitors, it appears, have been widely used by patients who are not at high risk for GI effects, and we have reviewed over the last several minutes that there are some limitations with COX inhibitors. In my opinion, there is no great clinical need for COX-2 specific inhibitors in patients who are at baseline at low GI risk. It is also clear that there is no GI benefit in patients who are concurrently taking aspirin. We are here to discuss the possibility that cardiovascular concerns may exist for some groups of patients.

So, the strategies to reduce the gastrointestinal effects of NSAIDs should focus on patients at greatest risk. Just to reiterate, the patients at greatest risk may not be sufficiently risk reduced by either of the prevailing strategies

which we currently have available clinically. For such patients, COX-2 specific inhibitors may be an attractive option but it looks like the target group of interest may not have the anticipated benefit.

For patients who are taking low dose aspirin or, if cardiovascular concerns were to exist, we have been asked to consider that if there were a world without COX-2 specific inhibitors how might we accomplish this objective, and it is clear that there are other strategies available that may lead to a reduction in NSAID GI effects. Thank you very much.

DR. WOOD: Thank you very much. Byron, could you just stay there in case there are specific questions for you while the slides are up? I have one. Could you put up slide 4 again? That shows data through 1990.

DR. CRYER: Yes.

DR. WOOD: What surprised me is Jim Freis has updated that data through 2000, and that dramatically changes what that slide looks like.

In fact, he found a 67 percent decline since 1990 in complicated ulcers, the vast majority of which occurred actually before COX-2 specific inhibitors went on the market. So, I am interested, first of all, in why you chose to present 15-year old data when there is new data out there that contradicts that, and whether you would like to comment on his publications from which this data came as well.

DR. CRYER: Sure. It is correct that there are newer data available that have demonstrated a reduction in gastrointestinal bleeds on a population basis. On the other hand, it is also very true that this problem of gastrointestinal bleeding with NSAIDs continues to be a significant problem despite its more recent decline. But, more importantly, he also highlighted a very important observation which is that the declines in gastrointestinal bleeding that have been seen in populations preceded the introduction of COX-2 specific inhibitors, and there are some data sets to suggest, at least in the U.S., that hospitalizations for

gastrointestinal bleeding since the introduction of COX-2 specific inhibitors have not markedly declined compared to hospitalizations prior to their introduction.

DR. WOOD: Right. So, most of the 67 percent decline occurred before these drugs went to the market, and that 67 percent occurs from the points on your slide here.

DR. CRYER: Point well taken.

DR. WOOD: And one other point of clarification I guess, the data you showed from CLASS, was that data from the predefined endpoint of the study at 18 months or the 6-month analysis that was published?

DR. CRYER: Just for sake of review, I have pointed out both time-dependent endpoints. The endpoint that was published and shown here, in the JAMA, was the predefined 6-month data and the endpoints that are shown here represent an evaluation of the entire data set. There are clearly differences in the conclusions about the effects of celecoxib which varied by time and

varied by whether one evaluates the data at 6 months or evaluates the entire data set.

DR. WOOD: Just remind us, at 18 months what did the data set show?

DR. CRYER: At 13 months the data, with respect to complications, indicate that there was no statistically significant reduction in upper gastrointestinal complications associated with celecoxib, at a dose of 400 twice daily, when compared to either diclofenac or ibuprofen individually or when compared to both of them together. I will point out for the sake of fair balance that this data does include the 21 percent of individuals who were taking low doses of aspirin.

DR. WOOD: Other questions from the committee? Dr. Nissen?

DR. NISSEN: Yes, this 1-4 percent rate, I am interested in understanding the time-dependent hazard. If a patient is put on a non-selective NSAID and, let's say, for the first year has no GI events, is the risk in the second and third and

fourth years the same as it is in the first year? In other words, once you know that a patient is tolerating an NSAID are they no longer at high risk?

DR. CRYER: There are a few answers, sub-answers to that question. It is a complicated discussion. What is clear that risk persists, that even in the individual who did not develop a complication in year one, that individual continues to have risk in subsequent years--two, three, four, etc. There are data sets that suggest that the period of highest susceptibility, highest risk is within the first three months of administration. Having said that, there are other data sets to the contrary. This incidence of gastrointestinal events that are time-dependent in individuals has been difficult to assess primarily based upon a concept of selection of susceptible individuals. People drop out because of other reasons such as dyspepsia. So, it is difficult to get a firm estimate on that. But it is clear, in summary, that the risk after one year or after any period of

time is always persistent as long as the NSAID exposure is present.

DR. NISSEN: Two more quick questions. I didn't see any analysis of COX-2 plus low dose aspirin versus a non-selective NSAID plus low dose aspirin. The reason I am asking that is that, as a cardiologist, in my patients who are taking conventional NSAIDs, if they need aspirin for cardiovascular prophylaxis I give them aspirin. So, the question is are there any studies looking at NSAID plus aspirin versus COX-2 specific inhibitor plus aspirin?

DR. CRYER: Well, the CLASS trial addressed that question in a subpopulation of individuals which was under-powered statistically to give a definitive answer to that question. That is an ongoing debate within the medical communities. I will say, however, that while the debate continues what is clear is that with either approach COX-2 specific inhibitor plus aspirin or non-selective inhibitor plus aspirin the ensuing rates of gastrointestinal events are too high for

us to feel comfortable that we have risk-reduced those patients sufficiently.

DR. NISSEN: And a final question, symptoms of dyspepsia are obviously one of the issues as well, and I want to make sure I understand what fraction of the population, let's say an osteoarthritis population, simply cannot tolerate NSAIDs because of GI discomfort. Do we have data on that?

DR. CRYER: Sure. A couple of comments about dyspepsia which I didn't mention, NSAID dyspepsia is common. Its prevalence varies depending on how dyspepsia has been defined in trials, and because there have been variable definitions of dyspepsia, its reported rates have varied anywhere from 10-30 percent of NSAID users, but it is clearly more common than complications.

In the patient who has dyspepsia, the presence of dyspepsia is not predictive of the patient who might have risk. In most of these studies dyspepsia, in my way of thinking, is considered more of a nuisance issue that can be

controlled symptomatically with acid reduction rather than something that presents significant gastrointestinal concern.

DR. WOOD: Dr. Gibofsky?

DR. GIBOFSKY: You commented extensively on the upper GI risk but in your second slide you correctly pointed out that there are problems with traditional medications affecting the structures of the GI tract below the ligament of triads. Could you comment somewhat on the data comparing the effect of COX-2 specific inhibitors versus traditional non-steroidals with or without proton pump inhibitor protection on the lower GI tract?

DR. CRYER: There have been fewer data sets which have assessed the lower gastrointestinal events with NSAIDs. A few comments on the types of studies that have been done, there have been studies using pill endoscopy which have indicated that lesions, endoscopic ulcers and erosions occur in the lower gastrointestinal tract contributed to by non-selective NSAIDs, an effect which can be reduced by a COX-2 specific inhibitor, an effect

which is not reduced by the co-therapy approach of adding a PPI to a non-selective NSAID. I am speaking of the lower gastrointestinal effects.

Having said that, again similar to the endoscopic ulcer story, these endoscopically detected lesions in the lower gastrointestinal tract probably have very limited clinical relevance. When lower gastrointestinal clinically significant events have been assessed from the prospective trials, the one noted most commonly in the literature is an assessment of the VIGOR trial looking at the effects of rofecoxib compared to naproxen, in which case a 40-50 percent reduction was seen in lower gastrointestinal events with rofecoxib compared to naproxen, again to reiterate, a reduction which would not be expected to be observed with the proton pump inhibitor approach.

Having said that, in that assessment of the rofecoxib experience there was an inclusion in the definition of lower GI events of individuals who had had reductions in hemoglobin and hematocrit and who did not otherwise have clinically apparent

gastrointestinal bleeding.

Probably the best assessment in terms of the risk of lower gastrointestinal events on NSAIDs comes from population-based observational studies. While there is variance in that estimate, it looks like the lower gastrointestinal events probably contribute 10-20 percent of clinically relevant events when compared to all GI events that might happen on NSAIDs.

DR. GIBOFSKY: One last quick point, would your recognize that there might well be a population of patients whom you would stratify as low GI risk who, nevertheless because of either intolerance, as the last speaker asked, or lack of efficacy to traditional non-steroidals, would be candidates for another class of agents?

DR. CRYER: Sure. Their NSAID dyspepsia is a common phenomenon. I will say that when dyspepsia has been carefully evaluated in the prospective trials of COX-2 specific inhibitors in general there tends to be a reduction in the rates of dyspepsia associated with the COX-2 specific

inhibitors. However, when one evaluates the absolute reduction in rates of dyspepsia in the trials it generally tends to be a few percentage points. Finally, some of the other strategies that were mentioned to accomplish risk reduction, for reduction in GI events in patients on NSAIDs, also accomplished reductions in dyspepsia in patients who might experience NSAID-related dyspepsia.

DR. WOOD: Dr. Cush?

DR. CUSH: Byron, two time questions. One, is there a time point at which peptic ulcerations and bleeds plateau over time in NSAID users or COX-2 users? Second, what is the longest data set that we have as far as the use of a COX-2 agent in a clinical trial where observation is carried out? Do we have two-year data; five-year data?

DR. CRYER: Right. There does appear to be some plateau-ing of the effect. The data sets do suggest that after long-term exposure the rates of events with longer-term exposure are not as great as rates of events with initial exposure to

NSAIDs but, again, that may be attributable to the phenomenon of dropping out of susceptibles. The second portion of your question, Jack, was?

DR. CUSH: What is the longest data set we have on COX-2 agents?

DR. CRYER: Well, when one looks at the trials, the prospectively defined outcome trials--we have CLASS, TARGET, VIGOR--there are periods of observation out to 13 months. Having said that, we certainly have longer periods of observations of COX-2 specific inhibitors for trials in which the specific outcome of interest was defined for an endpoint that was other than upper GI bleeding, so specific polyp reduction, Alzheimer's disease, other trials that we certainly will hear about over the course of the next few days, many of which have gone out to periods as much as 3 years.

DR. WOOD: Is there anyone else who has a question that specifically addresses something on a slide that the speaker could show again? If not, we will come back to these questions and ask you,

Byron, if you would, to be available this afternoon.

DR. CRYER: Yes.

DR. WOOD: Are there any questions that somebody has specifically? Tom?

DR. FLEMING: Yes, could we go back to the slide that showed the CLASS trial with the time to complicated ulcer?

DR. CRYER: There were two. You can tell me which one you are referring to, this or the next?

DR. FLEMING: Both, this and the next. Basically, here what you are showing us is that in the presence of aspirin there doesn't seem to be a reduction in the complicated ulcers although in those that are not taking aspirin there is this reduction of about two-thirds. If you go to the next slide, that is at 6 months. Hence, we see at 6 months this reduction in the rate in the celecoxib group that is driven by those patients who are not on aspirin. But that effect, as you noted, has disappeared out at a year.

I know that is making a lot of a single data set but is this suggestive of the possibility that, in response to Steve Nissen's question, there

could be a group that is more susceptible and what you are doing, in the presence of aspirin, is achieving not effect; in the absence of aspirin you are achieving a delayed effect but, in essence, you are going to have the same overall incidence by a year even with the COX-2 specific inhibitor?

DR. CRYER: Sure, your point is that there are likely subgroups of susceptibility for GI risk on NSAIDs or on COX-2 specific inhibitors. But I would say also that underlying that argument, which I think is accurate, is the observation which confounds the whole discussion, which I have mentioned previously, which is that early on in any of these trials you are going to remove the most susceptible of the individuals and those who actually persist in the trial tend to be the least susceptible subpopulation.

DR. FLEMING: Indeed, but that is the essence of what I am saying, and this would be

consistent then with the theory that if there is a particular susceptible group, that group is going to have a higher risk and it is, in fact, going to have complicated ulcers. They just occur somewhat sooner with the non-specific NSAIDs. The COX-2s are not preventing that, they are just delaying the time to the occurrence.

DR. CRYER: I think we are in agreement there.

DR. WOOD: Richard?

DR. PLATT: To extend that, on slide 13 you list some risk factors for NSAID-associated GI toxicity. Can you tell us how well those discriminate low risk individuals from high risk individuals? And, if they do, what fraction of the population falls into low risk, medium risk, high risk? And, quantitatively what are those risks?

DR. CRYER: That is a complicated question but it is an important one. When people like myself have shown these risks we commonly lead to the assumption that these risk are numerically equivalent, which they are not. There are certain

risk factors which clearly place one individual at higher risk than others. The highest risk most consistently seen in trials would be that of having had a previous history of a gastrointestinal bleeding ulcer. But not far behind that would be the risk of taking an anticoagulant, such as Coumadin, in association with a non-selective NSAID. Age as a risk factor is a variable one. Although we suggest in our discussions of this that there may be a threshold of age below which one may be not at risk and above which at risk for having it. In fact, it is a continuum. In fact, the risk contributed by age is about a 2 percent increase in risk per decade of life, such that people who are in their 80s are at very high risk, much higher risk than people who are in their 40s.

With respect to your question of quantifying the risk in a population, that is a difficult issue because all of these risk factors do not individually present themselves in any one patient. The more risk factors one has--two risk factors present greater risk than one; three

greater than two. I would say, having said that and trying to give you a reasonable estimate, in my opinion the percentage of NSAID users who would likely be candidates for this is probably somewhere on the order of 20-25 percent, depending on how one assesses that. If one looks at an OA or RA population and concludes that age in and of itself is a risk factor, then you are close to 80 or 90 percent of the population that might be at risk based upon that risk factor of age. So, it really depends on which risk factor, and it really depends on the quantitative contribution of the risk factor being described. But, certainly, I would say the one that most clearly and consistently has presented itself as highest risk in the various trials has been the risk factor of having had a previous bleeding ulcer, and it is the one that I would like to underscore which does not appear to be sufficiently risk-reduced by either of the strategies which we have available.

DR. WOOD: Any other questions that are so burning that they have to be asked now and not in

the discussion? Ralph? Burning? And let's try and make the answers as brief as we can.

DR. D'AGOSTINO: What are the consequences of complicated ulcers in, say, the CLASS trial where you do see this differential and this catching up? Do they follow to see the consequences of these ulcers? Were they different over the time period?

DR. CRYER: I am sorry, I don't understand.

DR. D'AGOSTINO: What are the consequences? What happened to these subjects after? Were they reversible, the ulcer? Does it lead to mortality?

DR. CRYER: Right, what I assume is driving your question is whether there are differences in mortality--

DR. D'AGOSTINO: Well, morbidity, mortality, what happens.

DR. CRYER: Well, clearly, morbid effects are hospitalization and the complications of them having a massive gastrointestinal bleed, which can

be several. The ultimate complication or consequence of these morbid effects is mortality and in these outcome trials there were no differences in the level of mortality. With regard to the various other consequences, most of them are clearly going to be reversible after having suffered a significant hospitalization.

DR. WOOD: Any other smoking questions? Peter?

DR. GROSS: A question on the third to last slide, on recurrent ulcer bleeding in high risk patients, the so-called non-selective NSAIDs selected diclofenac to compare with celecoxib.

DR. CRYER: Yes.

DR. GROSS: Diclofenac is roughly comparable in COX-2 selectivity. Is that the right drug to test with PPI to show that the PPI plus a non-selective NSAID is comparable to a COX-2 inhibitor like celecoxib? Should they have picked a non-selective NSAID that was less selective for COX-2?

DR. CRYER: Sure. Your point is very well

taken and it is one which I tried to underscore throughout the talk, which is that there are clearly differences in the COX-1, i.e., ulcerogenic, effects of non-selective NSAIDs. Diclofenac clearly is an agent which is associated with a lower rate of gastrointestinal ulceration and complications than non-selective NSAIDs. So, in this evaluation of the comparison of diclofenac plus omeprazole compared to celecoxib there is a valid discussion that the results may have been biased in favor of the diclofenac plus omeprazole approach.

The reason I showed that is that that was a fully published paper. There are, however, other trials not yet fully peer reviewed, which have been presented in the gastrointestinal community, looking at other NSAIDs, such as naproxen plus a proton pump inhibitor compared to the COX-2 specific inhibitor approach, and the results of those observations again are comparable endpoints between the two strategies.

DR. WOOD: I am going to move us on now

and we will come back after the next talk. Dr. Cryer, we would like you to come back up if there are questions at that time as well. The next speaker is Dr. Garret FitzGerald. Garret?

Mechanism Based Adverse Cardiovascular Events and Specific Inhibitors of COX-2

DR. FITZGERALD: Thank you, Dr. Wood. You are, please, going to have to forgive me, I feel quite nauseated; I have a touch of the flu and I took a medicine to reduce my temperature, but I am not prepared to tell you what it is!

(Laughter)

I would like to thank Dr. Wood and the FDA and the committee for the opportunity to visit Gaithersburg at this time of the year.

(Laughter)

When I boarded the Metro last night at Union Station and began the apparently interminable trip to the sylvan embrace of Shady Grove I thought to myself it might be useful to try and summarize for you a message that will derive from my talk. The message is that, just as low dose aspirin

affords cardioprotection and a small but absolute risk of serious GI bleeds, as you heard from Byron just now, through inhibition of COX-1, so specific inhibitors of cyclooxygenase-2 afford gastroprotection and a small but absolute risk of cardiovascular events. So, I have titled my talk mechanism-based adverse cardiovascular events and specific inhibitors of COX-2.

Well, as every lawyer and broker and journalist knows, this is the cyclooxygenase catalyzed pathway of arachidonic acid metabolism. Arachidonic acid is mobilized for release from cell membranes by activation of phospholipases and it is subject to metabolism by two enzymes which we call prostaglandin JH synthases 1 and 2 but which are known more commonly as cyclooxygenases 1 and 2. They give rise to a series of lipid products called prostaglandins which activate receptors and have very diverse biological effects.

One of the reasons we are here is that this, although depicted in a very simplistic way, is actually a quite complex system. To illustrate

that, I will just mention two of these lipid products, prostaglandin E-2 and prostacyclin or prostaglandin I-2. When formed by cyclooxygenase-1, these two lipid products afford gastroprotection, and our thinking is that the common GI adverse events of typical non-steroidal anti-inflammatory drugs reflect the inhibition of COX-1-derived PGI-2 and PGE-2, thereby, exposing people to gastroduodenal liability.

But it turns out that when the very same lipids, prostacyclin and prostaglandin E-2, are formed by cyclooxygenase-2 as opposed to cyclooxygenase-1 they mediate pain and inflammation. Indeed, it is the suppression of the formation of these two prostaglandins by COX-2 inhibitors that retains the anti-inflammatory and analgesic efficacy of traditional non-steroidal anti-inflammatory drugs which inhibit the two enzymes together.

But it turns out that these two prostaglandins, prostaglandin I-2 and prostaglandin E-2, formed by cyclooxygenase-2 also afford

cardioprotection which can manifest itself in various ways, and suppression of that capability is the cogent mechanism which explains the cardiovascular hazard which has emerged.

Well, I am sure this audience well knows that cyclooxygenase-2 inhibitors do not inhibit platelet aggregation, a way that we look at platelet activation in people that have been administered drugs. This just illustrates the absence of an effect at several doses of celecoxib in healthy volunteers compared to the inhibition of this signal by a mixed inhibitor at the time of peak drug action. Of course, that reflects the absence of cyclooxygenase-2. There should be a big shade here on this Western Blot if it was present but, unlike cyclooxygenase-1, which is there in abundance, cyclooxygenase-2 is not present in mature human platelets.

The wrinkle in all of this is that if you look at two structurally distinct members of the class of COX-2 inhibitors, the depression of the formation of that protective lipid, prostacyclin,

as reflected by urinary excretion of its major metabolite which, believe it or not, is the gold standard of how you look at prostaglandin formation in people--this depression is comparable on specific inhibitors of COX-2 with the depression we see with structurally distinct mixed inhibitors like ibuprofen and indomethacin.

So, one might logically deduce from this that even under physiological conditions, never mind under conditions of pathology, a COX-2 might be induced by cytokines for example. It is a dominant source of prostacyclin. We hypothesized at the time that that reflected a mechanism which had been described in vitro by Topper and Jim Broney and which is illustrated here, which is when you subject endothelial cells to laminar shear force, which mimics the effect of the blood stream on the lining of blood vessels, you up-regulate the COX-2.

Well, that raised a question rather than answered a question even though it anteceded the approval of the first of these drugs. The first

proof of principle that prostacyclin did actually modulate cardiovascular function in vivo stems from this study where we used mice lacking the prostacyclin receptor, known as the IP, or the thromboxane receptor, known as the TP, or both together. Thromboxane is the lipid which is formed by COX-1 in platelets and has harmful effects on the heart and cardiovascular system, and suppression of thromboxane reflects the cardioprotection of low dose aspirin.

In these studies we looked at the response to vascular injury in mice and we found that there was a signal of increased proliferation in response to vascular injury in the mice lacking the prostacyclin receptor which accorded with its in vitro properties.

Furthermore, when you injure the lining of a blood vessels in a mouse, just as if you do it in humans by performing an angioplasty, you get an attendant increase in platelet activation which is reflected by a time-dependent increase in excretion of a major thromboxane metabolite. We were

interested to see that this signal was grossly augmented in the absence of the prostacyclin receptor, and that all of these reflections of the phenotype could be rescued by co-incidental deletion of the thromboxane receptor along with the prostacyclin receptor.

Now, these studies were criticized as to their relevance to the COX-2 inhibitor story mainly because people said, well, you have taken away the prostacyclin receptor but when we give the drugs, although we suppress prostacyclin, we do it to a substantial but incomplete degree, maybe 60-80 percent on average.

So, we performed these studies in another model of induced thrombogenesis in mice where we injured the vasculature in a free radical catalyzed fashion. In these studies we looked at the effect of a biochemically selective regimen of a COX-2 inhibitor, and we found that the response time to the thrombogenic stimulus was significantly accelerated. Furthermore, as opposed to looking at the absence of both copies of the prostacyclin

receptor, we looked at the effect of deletion of just one copy and we found a significant and intermediate phenotype.

More recently we have devised a technique which permits us to remove cyclooxygenase-2 from particular cells. What I am showing here is the removal of only one copy of cyclooxygenase-2 from endothelial cells. As you can see, that also accelerates the response to a thrombogenic stimulus. So, these new studies are proof of concept of precisely the mechanism that we originally proposed.

Well, I think this is a point that we will come back to. We have some scientific evidence that there is a very non-linear relationship between inhibition of the capacity of platelets to make COX-1 derived thromboxane and inhibition of thromboxane-dependent function, that is, aggregation.

To get into the red zone for inhibition of platelet function you certainly have to be in excess of 95 percent inhibition of capacity, more

like up in the 98 percent range. Where we have actually almost no experimental evidence is whether there is a discordance between that and the relationship between inhibition of prostacyclin and inhibition of its protective cardiovascular function. Perhaps the intermediate phenotype of the prostacyclin receptor deleted mice losing one copy of the gene may suggest that that is so.

So, we are back in the mouse model of induced thrombosis. The reason I am showing you this slide is that a theme that will recur and is relevant to the clinical consideration is whether inhibition of COX-1, along with inhibition of COX-2, modulates the implications of inhibiting COX-2.

So, in these studies we have looked at the rescue from thrombosis induced by intravenously administering arachidonic acid to mice at two different doses in mice that either lack completely COX-1 or in mice that lack 98 percent of the capacity to make COX-1 derived thromboxane by platelets. As you can see, these two genetically

modified mice behaved very similarly in terms of the rescue from arachidonic acid induced thrombosis or, indeed, the time to complete occlusion induced by the thrombogenic stimulus I showed you in the earlier slide. This accords with that non-linearity of the relationship for COX-1 that I showed you. You would expect that to be suppressed in the 98 percent inhibited mice.

Now, that is all very well because it is in mice. So, you would way, well, how would we address this in terms of seeking a proof of concept in people? Well, if you delete the prostacyclin receptor mice don't fall over dead with thrombosis. They are more responsive to thrombogenic stimuli. So, if you wish to seek proof of concept in people, you would move to a population that had hemostatic activation and you would postulate that in such a population you would detect a signal faster and in a smaller study than might otherwise be the case.

Indeed, given the widespread recognition that patients undergoing coronary-artery bypass grafting exhibit hemostatic activation, and some

suggestion also that they may be a model of aspirin resistance, it is perhaps unsurprising that we are able to detect a clear signal of cardiovascular hazard in two placebo-controlled trials in this condition.

Now, when I think of people at risk of thrombosis when one is considering where one goes with these drugs, I tend to think of middle-aged or elderly people who have suffered a myocardial infarction or stroke. But I think it is important to remember that risk of thrombosis can manifest itself in susceptibility to this cardiovascular hazard of these drugs in other populations.

This is a ventilation perfusion scan of a 23 year-old athlete who had been on the pill for 3 years, who went on a 6-hour car journey, having been put on valdecoxib for the antecedent 8 days and, at the end of the trip, developed left-sided chest pain; was misdiagnosed and continued on valdecoxib for another 10 days; had right-sided pleuritic chest pain that led to this VQ scan.

This is purely an anecdote but it brings

to mind that individuals who have environmental predisposition to thrombosis, with a relatively small absolute risk such as being on the pill or prolonged stasis or genetic predispositions like Factor V Leiden, might be susceptible to a geometric interaction of relatively low risk from this class of drugs.

So, as far as thrombosis is concerned, where does this take us? Well, first of all, we have evidence that at least in vitro COX-2 can be induced in endothelial cells and produce prostacyclin. We have evidence that it constrains platelet activation and thrombogenesis in vivo. Suppression of prostacyclin does not cause spontaneous thrombosis but augments the response to thrombogenic stimuli in vivo. So, the hazard from coxibs would be expected to be particularly evident in those otherwise predisposed to thrombosis, and we have evidence that this hazard is modulated by inhibition of COX-1 in the appropriate zone.

Well, there has been a lot of talk, as we all know, about mechanisms and one of the things I

have found really curious is the notion that hypertension is a distinct mechanism. People get hypertension on traditional non-steroidal anti-inflammatory drugs as well as COX-2 inhibitors for a reason. The reason is the same mechanism. Illustrated here from studies in mice by Matt Breyer and his colleagues is how inhibition of COX-2, shown in red, will augment the pressor response to an infused pressor like angiotensin-II. Again, as in the setting of thrombosis, COX-1 is not neutral. As you can see, if he uses a selective inhibitor of COX-1 he attenuates the response to angiotensin-II.

Now, these studies have been complemented by congruent data with gene-deleted mice. They raise the prospect that the incidence of hypertension would reflect not only the degree of inhibition of COX-2 but the selectivity with which it is attained. Indeed, in this week's Archives we have the first epidemiological evidence consistent with that concept.

Now, the products of COX-2 that buffer the

response to pressor agents include prostacyclin and PGE-2. Here we are looking at the effect on blood pressure, of deletion of the prostacyclin receptor and, as you can see, blood pressure is elevated and the response to salt loading is increased. One sees exactly the same phenotype deleting one of the receptors for PGE-2.

So, as far as blood pressure is concerned, suppression of COX-2 derived PGI-2 and PGE-2 increases blood pressure and augments the response to hypertensive stimuli in mice. Deletion or inhibition of COX-1 depresses the response to vasoconstrictors in vivo so again we see COX-1 modulating the hazard from COX-2 inhibition. Hypertension on NSAIDs would be expected to relate to the inhibition of COX-2 and the selectivity with which it is attained.

Let's think of a more chronically unfolding cardiovascular hazard. These data arbitration taken from Narumiya. They are looking at the development of atherosclerosis in a genetically prone mouse, and you can see that

deletion of the prostacyclin receptor accelerates atherogenesis in male ApoeE-deficient mice. In fact, the impact was most particularly marked at initiation and early development of atherosclerosis.

By contrast, deletion of the thromboxane receptor does the complete reverse, and other studies conducted by us and others have shown that inhibition of COX-1 selectively or antagonism of the thromboxane receptor will have the same effect as deleting the thromboxane receptor, as shown here.

So, as far as atherosclerosis is concerned, we see this buffering capacity between COX-1 and COX-2. Furthermore, we have shown recently that in a different genetically proned mouse model deletion of the prostacyclin receptor and inhibition of COX-2 dependent formation of prostacyclin is important in affording the atheroprotection conferred by estrogen in female mice.

So, here we see the atheroprotection in

terms of reduction of lesion development with estrogen treatment in vasectomized mice being dramatically reduced by deletion of the prostacyclin receptor, which raises a whole new set of questions about the use of these drugs in premenopausal women.

So, as far as this other manifestation of a cardiovascular hazard is concerned, initiation and acceleration of early atherogenesis occurs in response to deletion of the prostacyclin receptor. I haven't gotten into mechanism but it fosters platelet and neutrophil activation and vascular interactions of these cells, and removes the constraint on attendant oxidant stress.

Now, we know that hypertension, which is also a consequence of inhibition of this pathway, itself accelerates atherogenesis. So, one could imagine that the direct and indirect effect could converge to transform cardiovascular risk. Finally, again COX-1 is playing a modulatory role.

There is a lot of speculation, which will no doubt be addressed in this meeting, as to

whether in the APPROVe study we actually saw a delayed appearance of augmented cardiovascular risk. I think, for me, the answer is we are not so sure but, if we did, this mechanism would explain not only early events but also the delayed emergence of cardiovascular phenotype.

The other thing that is often trotted out is, well, but people on aspirin have had some of these events. Well, of course, people on aspirin also have myocardial infarctions. But I think it is worthwhile remembering as we consider that prostacyclin will buffer effects of thromboxane on blood pressure, atherogenesis, hemostasis and, indeed, cardiac damage, which I haven't gotten into today. It acts as a general constraint on any agonist that acts harmfully on these systems. So, one would expect aspirin, in a perfect world, to damp rather than abolish the signal.

So, I think, if you will pardon me just for a moment to muse, one could relate the ability to detect a signal, expressed here as maybe numbers needed to treat or trial duration, as a function of

the underlying cardiovascular risk of the patients involved. The higher the risk, the more you would be able to detect it easily. The lower the risk, it may require that you either perform a very large study or go on for a very long time because we are all mindful of the fact that clinical trials, even randomized clinical trials, are very crude detector systems for uncommon risk.

Additionally, other elements will impact on this, including elements related to drug exposure and the degree of selectivity that is actually attained in vivo. So, I think in some of the efforts to dismiss this idea of a class-based effect some have lost sight of the fact that one would expect not only the underlying substrate to be relevant, but elements of drug exposure like dose, duration of dosing, duration of drug action and, indeed, concomitant therapy to be relevant to the ability to detect a risk. So, one is looking for a needle in the haystack and, to some extent, when one finds the needle it doesn't really matter how long it has been in the haystack.

So, let's consider the extreme phenotypes of cardiovascular benefit and hazard in this pathway. First of all, let's consider aspirin.

Here we have a sustained mechanism of action that leads to complete and sustained inhibition of COX-1. Even low dose aspirin inhibits prostacyclin to a minor degree. But one would expect, and one sees, a cardiovascular benefit from aspirin, at least in the secondary prevention of stroke and myocardial infarction.

In the case of COX-2 inhibitors one sees a reversible inhibition of COX-2. One also sees variable degrees of inhibition of COX-1 but, because of that non-linearity that I mentioned to you in the relationship, effectively this makes these drugs selective for COX-2 because you have no inhibition of COX-1 dependent platelet function.

That brings me to the last topic that I would like to address, and that is what about the traditional NSAIDs? Well, here is one way of comparing aspirin to a prototypic NSAID, ibuprofen. You take healthy volunteers, you administer them

low dose aspirin to stead-state efficacy, or ibuprofen 3 times a day to a steady-state effect, and you look at the offset of effect on enzyme inhibition and inhibition of function.

With aspirin you see sustained inhibition over the 24 hours after stopping the drug. As you would expect, with stopping ibuprofen you see offset of this reversible inhibitor on the enzyme. From whatever I have told you about that non-linearity in the relationship, you are not surprised to see a steeper offset of inhibition of function.

Well, of course, we have no randomized, placebo-controlled trials of traditional NSAIDs. We have various overviews of the epidemiological experience, with all the limitations of that approach and we can see that ibuprofen looks like it is not really altering cardiovascular hazard. There seems to be a sort of 10 percent or so reduction with naproxen, particularly 500 mg twice a day which was the most commonly used dosage in these studies.

Now, this would be like a dilute aspirin effect and, obviously, has relevance to the interpretation of studies like VIGOR and some of

the experience with the etoricoxib that you will hear about as to whether naproxen is actually behaving like aspirin.

Well, I think actually the epidemiology is entirely consistent with the clinical pharmacology of naproxen. This elegant study was performed by Patrignani. Again we are looking at the offset action of aspirin and naproxen 500 mg per day administered to steady state. We are looking at inhibition of enzyme function, and we see with aspirin exactly what we would have expected, sustained inhibition. However, at the end of a typical dosing interval for naproxen we see heterogeneity of response. In fact, everybody is at 95 percent or lower, suggesting that within the dosing interval there is a variable degree of cardioprotection afforded through this mechanism, which would be consistent with the dilute aspirin effect from the epidemiology.

This is a plot of the IC-50 for inhibition of COX-2. This is inhibition of COX-1 in whole human blood. As we move in this direction we are getting more selective for COX-2. It brings us back to a point that arose in Byron's study, and that is that although there is a difference in

potency, celecoxib and diclofenac look remarkably similar.

I would also remind you that naproxen, bearing in mind the Aleve study fiasco, is on the other side of the line, just like ibuprofen is, and exhibits preference for inhibition of COX-1.

Well, you have had a nice job giving you a full data set, demonstrating that actually in whole human blood diclofenac and celecoxib are superimposable. So, I would contend that through various lines of evidence diclofenac is probably a selective COX-2 inhibitor like Celebrex.

Consistent with that is a pharmacodynamic interaction where we showed that prior occupancy of the COX-1 site by a typical mixed inhibitor like ibuprofen would block access of aspirin to its

target acetylation site. If we give aspirin and ibuprofen chronically we actually see a pattern that looks just like giving ibuprofen alone, an onset of action and a steep offset of function. However, if we substitute diclofenac for aspirin it looks like giving aspirin alone, which is consistent with the type of information you get with a selective COX-2 inhibitor like rofecoxib or celecoxib in this assay.

So, I think we can start thinking of diclofenac as Celebrex with hepatic side effects. It has the same selectivity in whole blood in vitro. It has no pharmacodynamic interaction with aspirin. It has no clinical interaction with aspirin in the one epidemiological study which has addressed this interaction with the two drugs. Also, it is consistent with the superimposition of the GI and cardiovascular events in the retrospective look at CLASS in non-aspirin users.

So, I would suggest the two trials that you will hear about, EDGE and the ongoing MEDAL, are actually the first trials that are a comparison

within the class.

Well, let's come back to this relationship. I would remind you that while we have very strong evidence for this being true, we have almost no evidence that this is true. The conjecture of this discordance underlies the argument for the fact that we have a problem with selective COX-2 inhibitors but, you know something, we have a problem with all of these drugs which clearly obscures the message. We have no evidence for that and you will hear people parsing in meta-analyses naproxen versus non-naproxen NSAIDs.

Well, I don't think that is a legitimate lumping of non-naproxen NSAIDs, which is really diclofenac plus ibuprofen in most instances. I think it is as legitimate to consider them all individually as it is to consider naproxen individually.

So, could there be a hazard from a non-naproxen NSAID like ibuprofen where there is coincident inhibition of COX-1 and COX-2 over typical multiple dosing interval? If there is a

discordance in the relationship between inhibition of enzyme function and inhibition of enzyme product, then there might be a narrow part of the dosing interval where there could be a potential exposure to risk. But the likelihood of detecting this notional risk would be much less than the likelihood of detecting the clear evidence-based risk of selective inhibitors of COX-2.

So, there is some suggestion that naproxen achieves sustained platelet inhibition in some individuals. I like to think of it as a dilute aspirin. There is evidence that diclofenac is Celebrex. There is evidence that ibuprofen may undermine the benefit from aspirin, although that is not yet answered one way or the other with a controlled trial. And, I would say quite forcefully there is no rationale for lumping diclofenac and ibuprofen as non-naproxen NSAIDs in meta-analyses and the like.

I am not sure when a canard becomes a dead duck--

(Laughter)

--so I decided to dismiss some of the things that I think are worth dismissing and call them dead dragons. First of all, naproxen clearly

is not the full explanation of VIGOR.

Here is another one that needs to be chopped down, hypertension is not a different mechanism.

There are a lot of off-target fantasies being touted around at the moment, strange chemical interactions that haven't actually been shown to occur in vivo yet but are postulated as the explanation for a drug-related rather than a class-based effect.

Oddly, we never heard any of this conjecture when we were considering how all the drugs in this class afforded relief from pain and inflammation.

Here is another nice notion that makes clinical pharmacologists squirm in their seat, it is just a matter of reducing the dose. Well, there is a lot of interindividual variability in response to COX-2 inhibitors and we all have our own

dose-response curves. It has been an approach in the past when a hazard emerges to suggest that in a population sense one just cuts the dose--perhaps in a population sense but it certainly does not obviate the possibility of individual hazard.

Finally, if there ever was one, I think we have certainly moved beyond the need for a trial of a COX-2 inhibitor in patients with acute coronary syndrome. Indeed, I feel that the evidence that supports a trial in patients at high cardiovascular risk to detect protection is scientific quite weak, and in the face of an emergent hazard is ethically questionable.

Indeed, in the case of mice if one combines a thromboxane antagonist as a surrogate for the suppression of thromboxane by low dose aspirin with a COX-2 inhibitor, one doesn't see any benefit in terms of atheroprotection, but what one does see is the loss of the fibrous cap in the combination and necrosis of the atherosclerotic core, consistent with destabilization of the plaque.

Finally, and you will be glad to know it is finally, I would just like to mention a couple of things relating to where we might go from here.

Well, I think clearly an easy thing to write down and perhaps a more tricky thing to do is to exclude patients at high intrinsic risk of thrombosis, and you have heard my views on that. Dose reduction alone is a simple message. It has a political and legal appeal but in pharmacological terms it is misleading.

I think we are likely to subject new drugs that might be approved from this class to significant hurdles before they are approved. It seems logical to me that existing drugs in this class should be subject to the same hurdles to retain approval, particularly for extended dosing. And, I think that frankly one should logically restrict the duration of dosing until the parameters of safety for extended dosing have been established.

I mentioned interindividual variability, and these are log scales but they illustrate

looking at inhibition of COX-2 either in the typical ex vivo assay or by excretion of prostacyclin metabolite or inhibition of COX-1, that with this sort of display of the data to highlight it, there is considerable interindividual variability of response. This is no surprise. It is true of all drugs.

But perhaps we can exploit the biochemical variability, the physiological response variability and, indeed, perhaps some genetic markers such as these polymorphisms associated with metabolism of drug or these polymorphisms in cyclooxygenase-1 to try and identify those patients at emerging cardiovascular risk before they culminate in events. So, you might say that the future of these drugs or the challenge to the future of these drugs is that if their value--and I believe they have value as a class--is to be harvested, then to manage the risk we have to actually move to an example of personalized medicine.

One would want to obviously restrict these drugs in some way to people who really needed them,

for GI reasons. We need to determine whether risk transformation actually occurs during chronic dosing and, if so, whether we can detect it. And, it is likely, because we have so few events in any one trial, we can only do this by a combined analysis across the class in relevant trials. Then, obviously, we would have to validate prospectively such an index of emergent risk in a prospective trial.

So, I really thank you for your patience and I would like to conclude. Selective inhibitors of COX-2 depress prostacyclin without a concomitant inhibition of
thromboxane-A2. This can result in an augmented response to thrombotic and hypertensive stimuli and acceleration of atherogenesis in mice. Indeed, the terrible beauty of this unfolding drama is how faithfully the emerging clinical information has fitted the predictable science, and that should reassure us in terms of the likelihood that the science can predict a way to conserve the value of these drugs while managing the risk.

An increase in MI and/or stroke has been seen at last count, as of yesterday, in 5 placebo-controlled trials with 3 structurally

distinct COX-2 inhibitors. Given the bulk of evidence, the mechanism-based evidence from mice and people, the pharmacopeidemiology and this, it seems to be that most rational people would accept a class-based mechanism as they did for efficacy.

Finally, hazard would be expected to relate at the individual level to the drug selectivity attained in vivo, dose and duration of exposure and to interindividual differences in drug response. Thank you.

DR. WOOD: Thank you. Just before you sit down, one thing you seemed to be saying is that we should exclude patients at high risk. The point estimate in the APPROVe trial for people with no symptomatic history of heart disease is 1.6 so that would be one way you would exclude people, I guess, but the point estimate remains 1.6. Does that bother you?

DR. FITZGERALD: No, as I alluded to, I

think the nature of the information we have in the APPROVe trial so far remains to be played out. Clearly, there was an attempt to exclude people at high cardiovascular risk but we all know that people who are at risk slip through any exclusion criteria. So, one question is, is all that we are seeing people who, for one reason or another, are predisposed to thrombosis and they are the people that are having events? Or, are we seeing people who through atherogenesis transform their risk? Or, are we seeing some combination of the two? I don't think we know the answer to that.

DR. WOOD: We are running behind time so we will call a break right now and give everybody a moment or two to get out. Before we do that, Dr. Galson wants to say some things and then, whenever he is finished, we will take a break and we will reconvene at 10:15. So, those of you who don't want to hear what Dr. Galson has to say can get out now and the rest--

DR. GALSON: No, no, just a very brief announcement, and that is we have a space problem

in this facility. There are more people than we have seats for. So, we have established a live video feed in our advisors and consultants conference room on the FDA campus at 5630 Fishers Lane, designed for FDA employees only. So, FDA employees who may be sitting in the public section, I strongly urge you to please move to that area to make more room for the public and, of course, you will need your FDA ID badge to get into that space. But it is ready now and if you could move at the break, it would be great. Thanks.

DR. WOOD: Okay, we start promptly at 10:15.

(Brief recess)

Committee Questions to Speakers

DR. WOOD: Let's get started and get the two previous speakers up for questions, Dr. Cryer and Dr. FitzGerald. Yes, Susan?

DR. MANZI: I have a question for Dr. FitzGerald. This is really in reference to your suggestion that we exclude people with high thrombotic potential. I think there is clearly

evidence that the natural aging process is associated with less effective fibrinolytic system, really increased thrombogenic potential with high levels of fibrinogen, PI-1 platelet aggregation, and considering that the elderly population is a huge target for non-steroidals, would you consider age as a risk?

DR. FITZGERALD: Well, I think, as you indicate, lots of things happen as we get older including the complexity of administering drugs and it ultimately culminates in death. But I think the issue of determining cardiovascular risk is actually a very challenging one because it includes continuous and discontinuous variables. It is easy to say if you have had a heart attack or a stroke you are statistically at greater risk of having another one. It is harder to say that at an individual level, somebody who hasn't had a heart attack or a stroke has a cluster of variables that, in the eyes of their physician, determines their cardiovascular risk.

With some of the discontinuous variables

like some of the genetic mutations we can have an attributable risk that we can measure but, again, that can play geometrically into other small but absolute risks. So, unfortunately, I think it is where the art and science of medicine intersect.

DR. WOOD: Richard Cannon?

DR. CANNON: You asked my question.

DR. WOOD: Joan Bathon?

DR. BATHON: We know that patients with rheumatoid arthritis and other inflammatory conditions are at higher risk for developing acute MIs and strokes, and these are the very patients who are taking NSAIDs chronically. This is a big, confounding problem in interpreting some of the data and I am wondering if you have any thoughts. The reigning theory is that there is more atherosclerosis and RA due to vascular inflammation but I am wondering if you have any thoughts about whether the NSAIDs might be the sole contributor to increased events in these folks.

DR. FITZGERALD: Right. As I indicated, through a COX-2 inhibitory mechanism one would

anticipate that the clinical substrate of underlying cardiovascular risk would be one of the modulators of either individual hazard or the ease of detecting hazard with this crude detector system we call clinical trials.

As you know, the relative risk of heart attack or stroke and RA is increased by about 50 percent on average compared to RA or no arthritis. As a population that would be one of the ingredients predisposing towards emergence of a hazard. Of course, within that population there is a very substantial interindividual variability conditioned by many other factors that impinge on cardiovascular risk. So, at the time when we were naval gazing, looking at the contrast between CLASS and VIGOR, amongst the many things that were discussed was whether the preponderance of RA patients in VIGOR versus the preponderance of OA patients in CLASS may have been a factor. I think it is reasonable to say it may have been a factor but I don't think we can really take it beyond conjecture in light of any current evidence that I

am aware of.

DR. WOOD: Garret, let's cut to the chase. Is what you are saying--that was such a long answer, I am not sure what it meant!

(Laughter)

Is what you are saying that you think that COX-2 inhibitors have an effect here that the most selective, so-called non-selective like diclofenac and naproxen may also have an effect, and the non-selective, non-steroidals do not have an effect, or at least have not been shown to have an effect? Is that your position? If it is not, correct that.

DR. FITZGERALD: No, I think that is pretty true.

DR. WOOD: So, that is what you wanted us to take away from all the mice and stuff, is it?

(Laughter)

DR. FITZGERALD: You have such a way with words!

DR. WOOD: Because I am a Scot.

(Laughter)

DR. FITZGERALD: You are very economical with them.

DR. WOOD: Exactly.

DR. FITZGERALD: Unfortunately, reality is conditioned by a lot of different factors. I think one of the things, both in terms of benefit and hazard, we have paid insufficient attention to is variability in drug response between individuals, and I think actually one of the things that has got us to today is not paying enough attention to that. But I think one of the ways out of the challenge that faces us today if we are to conserve the value is to exploit that variability in imaginative ways. So, I think that that is a tractable issue.

DR. WOOD: Okay. Dr. Abramson?

DR. ABRAMSON: Yes, Garret, even though you are under the weather I wanted to follow-up with Dr. Wood's question and put you on the spot a little bit. It is partly definitions because we use the word NSAIDs which we elect by inhibiting COX-2s. Based on your presentation, it is clearly a continuum and there are highly selective drugs.

There is a cluster of five or six drugs, like diclofenac, that are in vitro at least comparably COX-2 selected. Then you have these very complex stories of what one might call functional COX-2 selectivity, which is based on the fact that the COX-1 inhibition may be more transient effectively than a more prolonged COX-2, which would give you imbalance. So, I guess the "put on the spot" question is what do you define as the class? How do you propose we should think about this continuum and personalize medicine?

DR. FITZGERALD: I think you are right. I would remind all of us that COX-2 inhibitors are NSAIDs; they were never anything else. They are NSAIDs that are selective for COX-2 and, as you are rightly pointing out, this is a continuous variable and within each drug, as I tried to point out, there is the same continuous variable between individuals. So, my 800 mg of Celebrex may be your 200 mg of Celebrex for example.

So, I think all I am trying to raise is that there is clearly a mechanism which reflects

the selective inhibition of COX-2. That selective inhibition of COX-2, in terms of hazard, is modulated by COX-1 inhibition that occurs at the same time if it is sufficient to inhibit platelet activation for example. So, I can't simplify that because I believe there is that complexity, but within the class--and I am referring to the class as the mechanism by which selective inhibition of COX-2 is attained--I think there is clearly a mechanism that explains everything that we have seen.

At the individual level this issue of a continuum comes into play because not only is there a continuum in terms of drug action and the degree of selectivity attained in an individual, but also many other factors impinging on cardiovascular risk that condition the emergence of that hazard at the individual level.

DR. WOOD: Steve?

DR. NISSEN: Yes, I have two quick questions. You know, I want to talk with you a little bit more about this issue of dose

dependency. I want to make sure we didn't misunderstand you. What you are saying I believe is that there is sufficient overlap in the biological effects that a low dose in one patient may be equivalent to a high dose in another. But you didn't mean to suggest that we don't see evidence, as I think we do see from the trials, that the higher the dose of the drug on a population basis, the more we see--

DR. FITZGERALD: No, no, clearly there is evidence of a dose-related effect in populations. I am talking more at the individual level, that the assurance to a population based on population type evidence that all you need to do is reduce the dose and you, as an individual, will be protected from hazard is a false one.

DR. NISSEN: Yes, but it is quite relevant obviously to our discussions on Friday because one of the strategies to limit risk with this class of drugs is to limit dose--

DR. FITZGERALD: Sure.

DR. NISSEN: --and it may not make the

hazard go away but it may make it smaller, and we are going to have to explore that in some detail before we finish.

DR. FITZGERALD: Well, I think that distinction between reducing it as opposed to making it go away and the distinction between population hazard and individual hazard is an important one. It is the reason that I raised that particular point because I think that had not received sufficient attention.

DR. NISSEN: The second question I have is, you know, we have very few direct head-to-head trials amongst the so-called COX-2 inhibitors, but we do have for hypertension and there seemed to be really pretty striking differences in the hypertensive response between rofecoxib and celecoxib. Would your point of view be that those differences are strictly a matter of COX-2 selectivity of the two drugs, or do you think that it is possible that there is some dissociation in the hypertension response?

DR. FITZGERALD: I would make two points.

I would say, first of all, that in that particular comparison, again on average, we would anticipate that selectivity and duration of action would be confounded and it would be impossible to really segregate the two.

The second is that, in a sense you pressed my button, I believe we have not performed the studies in hypertension that let us address the key questions that are on the table, and that is standardizing for the degree of selectivity attained or the degree of COX-2 inhibition attained do drugs come apart? That question has been on the table since the mouse studies of Breyer and Kaufman, and perhaps the first signal of that is the epidemiological overview analysis from Australia. But, in fact, we have never performed a study to address the hypothesis and I think it is timely that we do.

DR. WOOD: I see Dr. Cryer. Did you want to say something?

DR. CRYER: Dr. Cryer has a question.

DR. WOOD: Go ahead.

DR. CRYER: Garret, you clearly made the point that diclofenac appears to have some COX-2 selectivity. In fact, I think you called it

celecoxib with hepatic side effects. You also made the point that we should subject drugs already approved to the same requirements. So, the specific question I have for you is are you suggesting that we should evaluate diclofenac as well for its potential cardiac effects?

DR. FITZGERALD: Yes, I think there are quite a few unanswered questions on the table. I think clearly the diclofenac question is one of them. I think there are other drugs that fall into potentially the same situation, like meloxicam and nimesulide which, again, based on the IC-50 comparisons look awfully similar to diclofenac and Celebrex but we just don't have the information even at a more fundamental level than outcome studies. So, I think those questions are on the table.

The reason I made the comparison between retention of approval and gaining approval is that,

to me, if we do actually have to address some questions to determine the parameters within which drugs in this class can be administered safely and that would be a hurdle that any new drug would be required to overcome, in logic to me, it would be sensible to apply the sam standard to the extended dosing of drugs that already are on the market as a condition of their retention of approval.

DR. WOOD: Dr. Shafer?

DR. SHAFER: Yes, this is the question we just talked about briefly at the break, but as you pointed out, low dose aspirin gives you 100 percent inhibition of COX-1. One might think then that low dose aspirin plus a COX-2 selective antagonist might give you the same risks as a non-selective NSAID. Yet, in all the studies where they had aspirin present and they showed a CV risk, when they stratified by aspirin, among aspirin users the hazard didn't go away. Now, what did happen is that some statistically significant hazards became non-statistically significant hazards but the actual magnitude of the hazard, at least as far as

I can tell in all the studies that I looked at, didn't change. I am having trouble understanding how that is consistent with the whole thing being the COX-2 imbalance.

DR. FITZGERALD: Right. So, one important missing dimension in your question is time. One of the key ingredients of aspirin's ability to afford cardioprotection is that while it inhibits COX-1 like a ibuprofen does, it does it molecularly in a quite distinct fashion. This results in sustained maximal inhibition throughout the dosing interval. By contrast, in the typical non-steroidal you are in the red zone for platelet inhibition transiently in the dosing interval. Therefore, one would not expect the combination of, say, ibuprofen with a COX-2 inhibitor to be similar to aspirin with a COX-2 inhibitor in terms of cardiac protection.

DR. SHAFER: Doesn't that head in the opposite direction?

DR. FITZGERALD: In terms of which?

DR. SHAFER: The fact that the aspirin's effect is sustained because, you know, it is

covalently bonded there--the fact that you are having a sustained aspirin effect means that you should absolutely--I mean, it would seem to me that that would really try to make the COX-2s look--

DR. FITZGERALD: Well, I will come back to what I said during my talk, and that is that I think a real mistake is to think of this as a yin and yang type of seesaw arrangement between thromboxane and prostacyclin. We know that prostacyclin acts as a general biological constraint on anything that will activate platelets, elevate blood pressure, accelerate atherogenesis, and so on. So, a priori we would expect that aspirin would damp rather than abolish the signal.

Now, I would contend that, first of all, we have never formally addressed this and, in terms of the trials that have events, although we have attempted to look at the relationship to aspirin the numbers are so vanishingly small that it is really conjecture. But one would expect a signal to be damped. Indeed, from some of the

epidemiology that is sort of what we are seeing, you know, a signal goes away at 25 mg of rofecoxib if they are on aspirin but not at 50, that sort of stuff. But I would be the first to agree that this is really a crude stab at the issue that you are trying to get at.

DR. WOOD: Yes, and these studies did not stratify by aspirin use. They were post hoc analyses in the majority of cases. Dr. D'Agostino?

DR. D'AGOSTINO: I would like to go back to the question that was asked right after the break about the age. If you tried to say, well, the perfect way of doing this is to make sure that people at high cardiovascular risk aren't going to take the drug, then males over 60, for example, are almost certain to be excluded. How realistic--

DR. FITZGERALD: Certainly I am not trying to be dictatorial--

DR. D'AGOSTINO: No, no, your suggestion is fine, it is just how do you implement it?

DR. FITZGERALD: Yes, so I think all one can really hope to do is set the bar at some low

level and then signal it in a way that is explicit and leave it to the patient-doctor relationship to divine the individual behavior. I would love to say there is a different way of doing it but, yes, as we get older our cardiovascular risk goes up and multiple other things. But that is where the balance against value comes into play. As we get older with get arthritis; as we get older we get more GI bleeds on non-steroidals.

DR. WOOD: Okay, we got it. Let's not go too far there. One more question from Dr. Gibofsky.

DR. GIBOFSKY: Dr. FitzGerald, in response to Dr. Nissen, I believe, you raised the notion and asked us to think about population variation as a factor in addition to individual variation. One of the things that I am struggling with is exactly that, and one of the concerns I have is to what extent then can one extrapolate observations in populations of patients who may have Alzheimer's disease or who may have taken a drug for polyp prevention to the population of patients who are

taking the drug for their arthritis?

DR. FITZGERALD: Well, I think in a way this whole cathartic experience is a cardinal point in the way that we look at drug development. You know, we have talked about individualized medicine for a long time and never really had to care, and here is a situation where we actually do have to care and it is at the forefront of how we may or may not be able to find a way out of this. You are absolutely right, there may be factors associated with an incident disease which is under study which modulates the importance or non-importance of the signal; modulates the way that drugs are metabolized; may be associated with genetic variance that influence outcome as well.

DR. WOOD: Any other questions for the last two speakers?

(No response)

In that case, let's move on to the sponsor's presentation. I understand Dr. Kim is going to present first.

Sponsor Presentation: Vioxx (Rofecoxib)

DR. KIM: Mr. Chairman, members of the advisory committee and FDA and ladies and gentlemen, my name is Peter Kim and I am President

of Merck Research Laboratories. My colleagues and I welcome the opportunity to present information at this advisory committee meeting, and I would like to begin with just a few introductory comments.

As you will hear, to determine both its risks and its benefits, Merck extensively studied Vioxx before seeking regulatory approval to market it, and we continued to conduct clinical trials after the FDA approved Vioxx.

As Merck continued to monitor the cardiovascular safety of Vioxx, we recognized the value and interest in obtaining additional cardiovascular safety data on this medicine. After deliberations with numerous outside advisors, Merck developed and discussed with FDA a plan to prospectively analyze cardiovascular event rates from 3 large placebo-controlled trials.

It was preliminary information from one of these long-term trials, the APPROVe trial, that led

to Merck's decision to voluntarily withdraw Vioxx. When Merck made the decision to voluntarily withdraw Vioxx from the market, we stated that we believed that it would have been possible to continue to market Vioxx with labeling that would incorporate the data from the APPROVe trial. We concluded, however, based on the science available at that time, that a voluntary withdrawal of the medicine was the responsible course to take given the availability of alternative therapies and the questions raised by the data.

Since that time new cardiovascular safety data for other COX-2 inhibitors have become available and were reported on just this week in the New England Journal of Medicine. We look forward to hearing and seeing presentations of these data and to hearing discussions and interpretation of them during this advisory committee meeting. Thank you, and now I would like to turn the podium over to Dr. Ned Braunstein.

DR. BRAUNSTEIN: Good morning, Dr. Chairman, members of the availability committee,

FDA, I am Dr. Ned Braunstein, Senior Director of Merck Research Labs.

Millions of patients suffer with painful arthritis and need effective therapies. The recent data that have come to light on NSAIDs and selective COX-2 inhibitors raise many questions. Patients and physicians need information and guidance on the use of these effective medicines that we know are not without risk. We recognize that the cardiovascular safety of the NSAID and coxib classes is an important public health issue and we welcome the opportunity to present this advisory committee information that we believe will help the FDA and the committee in their work in developing recommendations in the best interest of patients. To assist us today, we have brought along as consultants Dr. Marc Hochberg from the University of Maryland School of Medicine, Dr. Marvin Konstam from Tufts University School of Medicine, and Dr. Loren Laine from the University of Southern California School of Medicine. They are here to help answer your questions and

otherwise assist the committee.

Merck's objective today is to provide you with data on rofecoxib and review how those data affected our assessment of risk/benefit over time. The presentation will focus on GI and cardiovascular data or rofecoxib, starting with the data in the original NDA and proceeding through the voluntary withdrawal of Vioxx and the APPROVe data.

In talking about the data, I will try to highlight some of the methodology we used to obtain, adjudicate and analyze cardiovascular data, and I will spend some time discussing the considerations that went into designing a study of cardiovascular outcomes with rofecoxib as the information may be useful in considering similar studies.

The presentation of data will end with a presentation of new exploratory analyses that we have performed and I will follow with a risk/benefit assessment, the review the major outstanding questions of the day, and the next steps we are taking and/or propose.

I will start with an overview of the issues we face today. Starting with the GI tract, as you have already heard, NSAID gastropathy has

been the most common cause of drug-related morbidity and mortality in industrialized nations. The development of rofecoxib was based on the desire to limit and reduce this problem.

You have also heard already about the COX-2 hypothesis. I just want to emphasize two points. First, all NSAIDs inhibit COX-2 in a dose-dependent manner and selective COX-2 inhibitors do not inhibit COX-1 at clinical doses.

The rofecoxib develop program confirmed the COX-2 hypothesis and demonstrated a reduction in clinical upper GI events, that is, actual GI outcomes with rofecoxib versus non-selective NSAIDs. This was shown for rofecoxib in the VIGOR study and, based on that, rofecoxib was the only selective COX-2 inhibitor with a modified GI warning. Since that time we have accrued additional information that extend the GI benefit of rofecoxib and have shown that the reduction in

clinical upper GI events is consistently seen with rofecoxib versus diclofenac, ibuprofen and naproxen.

Although rofecoxib is associated with a reduced rate of upper GI events compared to these NSAIDs, rofecoxib is not placebo. In addition to the upper GI findings, we have also observed a reduced incidence of lower GI events compared to naproxen in VIGOR, So, although there remain some unanswered questions, for example for aspirin users, the GI benefit for rofecoxib is clear.

As we have also learned, there are important cardiovascular findings with these drugs and perhaps with the larger class of NSAIDs. In 1998 Merck had implemented an adjudication standard operating procedure to methodically study the cardiovascular effects of its COX-2 selective inhibitor drugs in clinical trials. Clinical data on thrombotic cardiovascular events with rofecoxib show an increased risk of events relative to placebo. This was seen in APPROVe with long-standing use.

In contrast to the difference seen from placebo, we have not observed a difference in cardiovascular event rates between rofecoxib and

NSAIDs other than naproxen. Long-term data, however, are limited. In contrast to what had been observed versus the placebo, the increased risk compared to naproxen appears after short-term use.

I think it is worth noting that similar observations have now been made with other selective COX-2 inhibitors. We believe that these new data on rofecoxib and COX-2 inhibitors raise several questions about these drugs important to the public health.

First, based on the data available, how do we currently assess the relative risks or benefits of selective COX-2 agents? I cannot speak to the data on all of these drugs but I can talk about rofecoxib. Clearly, there are risks versus placebo, and not just cardiovascular risks. however, placebo is not a choice for patients with chronic arthritis and pain who require chronic NSAID therapy. For these patients the question is

the risk and benefit of selective COX-2 agents versus non-selective NSAIDs. I will present data on this question related to the GI and cardiovascular safety of these drugs.

Second, can we identify factors associated with the observed increased risk for thrombotic cardiovascular events with these drugs? Although we do not have definitive answers, I will present the data that we have.

Finally, is the increased thrombotic cardiovascular risk that we have observed with rofecoxib indicative of a larger class effect of COX-2 inhibitor? If so, how big is the class? That is perhaps the central question of this meeting. At present we do not know the long-term cardiovascular effects of traditional NSAIDs. Other than aspirin, these agents have not been studied long term versus placebo. We believe that long-term studies are needed and, in particular, comparator studies between selective COX-2 agents and non-selective agents to better understand the relative risk/benefit profiles.

I will now turn to a presentation of the data, and will do so chronologically as it highlights the magnitude of data that were

ultimately needed to dine the long-term cardiovascular risks of selective inhibitors. This information may be useful regarding the development of future COX-2 inhibitors and in informing this committee on its decisions.

I would like to start by reviewing the initial GI and cardiovascular data that were in the new drug application. There were two main clinical components of the GI safety program in the original rofecoxib NDA, the GI endoscopy studies, which are described in your background package, and a pooled analysis of clinical upper GI events, shown here. Investigator reports of suspected upper GI perforations, ulcers or bleeds or PUBs were adjudicated by an external committee of blinded adjudicators, and the confirmed events formed the basis of this prespecified analysis.

The Kaplan-Meier plot of the data is shown on this slide. Throughout my presentation I will

be showing several of these so I would like to take some time to walk through this first one. Time is shown on the X axis, and below that the number of patients remaining in the studies at the different time points. Cumulative incidence is shown on the Y axis and also shown are summary statistics, relative risk confidence interval and a p value.

At the time of the original NDA a significant difference was demonstrated between rofecoxib and the combined NSAID comparators, mostly data on ibuprofen and diclofenac. The relative risk of 0.45 corresponded to a 55 percent risk reduction with rofecoxib and, thus, we believe that we had established a GI safety advantage over these older NSAIDs.

These are the cardiovascular safety data from the OA development program. Rates per 100 patient years of investigator reports or cardiac, cerebrovascular and peripheral arterial and venous serious thrombotic events were examined both in aggregate, as shown on this slide, and also in individually, as shown in your background package.

As you can see, then rates were similar for rofecoxib compared to the NSAIDs diclofenac, ibuprofen and nabumetone and for rofecoxib compared to placebo.

These cardiovascular and GI data, along with our other data, were submitted to FDA in 1998 as part of the new drug application for rofecoxib. They were discussed at the April, 1999 Arthritis Advisory Committee and the FDA concluded that there was a favorable risk/benefit profile for rofecoxib, and rofecoxib was approved in May of 1999.

Around that time we were completing our Phase III osteoarthritis studies. The results of studies that we were doing in collaboration with Dr. Garret FitzGerald became available, and he has already told you about those and the hypothesis that selective COX-2 inhibitors could be prothrombotic by inhibiting systemic prostacyclin production without inhibiting thromboxane production.

In addition to that hypothesis, there were other hypotheses being discussed in the clinical

literature and in the basic science literature at that time, including the possibility that NSAIDs, through their effects on COX-1, might decrease the risk of cardiovascular events. Another was that perhaps by inhibiting COX-2 there may be a beneficial effect by inhibiting the enzyme in atherosclerotic plaques.

Merck recognized that it would be important to continue to acquire cardiovascular data with its selective COX-2 inhibitors. To address these hypotheses, in 1998 Merck initiated a vascular event adjudication standard operating procedure to standardize the evaluation of cardiovascular events in all of its COX-2 inhibitor studies. Adjudication of events was based on predefined criteria. Under the standard operating procedure all source documentation on events was collected and the data were then reviewed by blinded, external adjudication committees. With this procedure, over 92 percent of cases had sufficient data for definitive determination and adjudication. Thus, we can be confident in the

quality of the data. By eliminating questionable events, we would amplify and improve the clarity of any signal if present. The standard operating procedure called for a pooled analysis of events across all studies to improve the precision of what would be obtained from individual studies.

In order to obtain more data on the effect of rofecoxib on GI outcomes Merck initiated the Vioxx GI Outcomes Research, or VIGOR, study in January, 1999. GI events would be adjudicated using the same approach as had been done for the osteoarthritis studies. The cardiovascular events in VIGOR fell under the new standard operating procedure.

VIGOR was designed to definitely assess the GI components of the COX-2 hypothesis. It was conducted exclusively in rheumatoid arthritis patients because Merck believed that a GI benefit had already been established in osteoarthritis patients. Rofecoxib of 50 mg, 2-4 times the recommended chronic dose, was chosen to provide a rigorous assessment of safety. We chose as a

comparator naproxen 500 mg twice a day to extend the GI findings to an additional NSAID and because that was the most commonly prescribed NSAID regimen in rheumatoid arthritis. Patients using aspirin were excluded to avoid COX-1 inhibition as this could confound the ability to rigorously assess the COX-2 hypothesis.

The primary endpoint was reduction confirmed clinical upper GI events. There were 56 events on rofecoxib and 121 on naproxen. The time to event curve separated early and they continued to separate, and the relative risk of 0.46 corresponds to a 54 percent risk reduction with rofecoxib. The p value, as you can see, was highly significant. A similar GI benefit was seen with confirmed complicated events, and in a post hoc analysis for lower GI events.

A second finding in VIGOR was the difference in the rates of thrombotic cardiovascular events between the two treatment groups. There was a relative risk of 2.4 for the confirmed events, as shown here. The p value,

again, was highly significant.

Examination of the individual types of events broken down by vascular bed, cardia, cerebrovascular and peripheral shows that the difference between treatment groups was largely driven by the difference in myocardial infarction, 20 on rofecoxib and 4 on naproxen. Of note, there were similar numbers of patients with strokes in the two groups.

Additional exploratory analyses were undertaken to better understand these cardiovascular findings. I will focus on the types of analyses that I will show later for APPROVe. In VIGOR the use of 50 mg, a dose 2-4 times the recommended approved chronic doses, was associated with a higher incidence of hypertension adverse experiences than with naproxen. In analyses described in the background package the relative risk of events was similar in patients with or without increases in blood pressure during the study. The relative risk of events was also similar in patients with or without baseline risk

factors for cardiovascular risk.

Finally, multiple analyses were performed to examine the patterns of risk and relative risk over time, both by Merck and the FDA. Merck's interpretation was that there was no significant increase in relative risk over time for rofecoxib versus naproxen. However, the FDA felt that a change in relative risk over time could not be excluded.

Because VIGOR did not have a placebo control, we turned to other data from other studies to better understand these results. Merck had initiated a program to assess the ability of rofecoxib to delay the onset of Alzheimer's disease in patients with minimal cognitive impairment or to slow the progression of Alzheimer's disease. In these studies, rofecoxib 25 mg was compared to placebo in an elderly population.

An initial review of the cardiovascular data, in March, 2000 when the VIGOR results were first learned, did not show an imbalance. In a subsequent review, undertaken in September, 2000,

in advance of the VIGOR advisory committee, which I will show you next, at that time there were over 2000 patients enrolled, with a median duration of therapy of approximately one year.

The analyses at that time were based on investigator-reported events since at that time few had been adjudicated. Subsequent analyses that I will show using the adjudicated data were consistent with these initial analyses. Clearly, there was no evidence to suggest an increased risk with rofecoxib based on the aggregate endpoint shown on this slide, or based on the analysis of individual type of events such as myocardial infarction or stroke shown in the background package.

Consistent with the approach envisioned in the adjudication SOP, we also performed a pooled analysis of all the available cardiovascular data to obtain more precise estimates of the relative risk for rofecoxib versus each of the various comparators. The pooled analyses include all randomized, controlled trials from Phase IIb

through our Phase V postmarketing trials of 4 weeks or longer duration that had been completed by September, 2000 and also included the Alzheimer's data that I just showed you.

Studies were included if there was a placebo or an NSAID comparator. For the pooled analysis we prespecified to use the anti-platelet trial as collaboration combined endpoint of myocardial infarction, stroke and vascular death. There were several reasons for this choice. First, the rofecoxib pooled analysis included data from studies that antedated the adjudication SOP. Investigator reports of the APTC endpoints had the highest confirmation rates in the studies that were adjudicated so restricting the analyses to these events ensured consistency among the data. Second, the APTC combined endpoint was a standard and would allow comparison to other published reports. The analysis pooled double-blind patient level data stratified by disease. In September, 2000 there were data from over 28,000 patients and over 14,000 patient-years of exposure.

In the analysis for the three data sets, placebo, non-naproxen NSAIDs and naproxen controlled data, a difference was only observed in

the naproxen data set. It was, therefore, considered not appropriate to combine the three data sets as this would tend to obscure the difference from naproxen.

In our plots the triangle points to the estimate of relative risk and the size of the triangle is proportionate to the overall exposure. The 95 percent confidence interval is shown as a horizontal line, and the same information is provided numerically along with the numbers of events in each data set.

In the placebo and non-naproxen NSAID data sets the data do not suggest an increased risk standard rofecoxib. The data in the naproxen set were largely driven by the VIGOR data and, consistent with VIGOR, there was an increased risk for rofecoxib compared to naproxen. The 95 percent confidence interval did not cross 1, consistent with the statistically significant difference.

Our conclusions: There was a clear evidence for GI safety benefit of rofecoxib compared to non-selective NSAIDs. Because the data did not suggest increased risk of cardiovascular events with rofecoxib compared to placebo or non-naproxen NSAIDs, we believe that the weight of

the evidence was most consistent with naproxen having provided a cardioprotective benefit in VIGOR. Data to support that naproxen 1000 mg can provide sustained anti-platelet effects, as well as animal data with naproxen and clinical data on agents with similar properties are all provided in the background package. Subsequent data with other selective COX-2 inhibitors would also show a cardiovascular difference from naproxen while having similar cardiovascular events with non-naproxen NSAIDs.

The Arthritis Advisory Committee agreed that the VIGOR study had shown a GI safety benefit for rofecoxib compared to naproxen. With regard to the cardiovascular data, they determined that the results were inconclusive. They recommended that

both the GI and cardiovascular data be described in the rofecoxib label. Those recommendations were, indeed, reflected in the approved labeling. There is now a modified GI warning acknowledging that the risk of GI toxicity with rofecoxib 50 mg once daily is significantly less than with naproxen 500 mg twice daily.

There was a new cardiovascular precaution which provided the cardiovascular results from VIGOR and from the Alzheimer's disease studies which concluded that the clinical significance of the cardiovascular findings were unknown. The specific precaution stated that caution should be exercised when Vioxx is used in patients with a medical history of ischemic heart disease.

Finally, because there were dose-related trends and NSAID type adverse experiences with rofecoxib 50 mg and no greater efficacy at 50 mg compared to 25 mg, the new label further emphasized that the chronic use of rofecoxib 50 mg was not recommended.

I would like to turn now to the period

starting after we learned the results of VIGOR up to the unblinding of APPROVe, and I will focus on the unique information that Merck can provide to this committee, information on our approach to the design of a study of cardiovascular outcomes that we implemented in 2002, and the final data from our programs in arthritis and Alzheimer's disease that were completed in this time frame. I will briefly touch on data that others will be presenting or have presented, such as epidemiology studies and the ongoing preclinical work, and will end this section of the presentation with our assessment of the data available before APPROVe.

In considering outcome study designs, we recognized two different approaches we could take. Each had different merits and would answer different questions. The first would be to perform an NSAID-controlled study. This could involve arthritis patients so we could study the patients in whom the drug was indicated, knowing, however, that a placebo control would not be appropriate in a several-year study of patients who require

chronic NSAIDs, and the use of chronic NSAIDs over several years was not appropriate in patients who did not have that need.

The alternative was to do a study versus placebo. Obviously, this would preclude the ability to study patients with chronic arthritis. So, the applicability of the finding to arthritis patients would need to be inferred. Despite this potential limitation, we decided for rofecoxib to answer the question for difference from placebo.

I think it would be useful to discuss with this committee how bit these studies need to be. As we all know, it is easier to prove a difference than to prove similarity. In order to exclude even a 30 percent increased risk with 95 percent confidence and with 90 percent power, you need data on over 600 confirmed events. Based on anticipated event rates and typical dropout rates on our studies, this would require enrolling approximately 25,000 patients for a study design to run over about 3 years. To exclude a 20 percent increased risk you would need approximately 1300 events and

over 60,000 patients. To exclude a 10 percent risk you would need approximately 4800 events and over 200,000 patients in the studies.

We considered several placebo-controlled designs. One study in acute coronary syndrome was rejected for a variety of reasons after extensive discussions with our consultants. First, these unstable patients are at particular risk for bad outcomes associated with GI or renovascular effects known to be present with rofecoxib, and considering the unknown benefit this raised concerns.

Second, these patients would all need to be taking aspirin and, as you recall, one of the hypotheses at the time, and it still continues to be a hypothesis, was that aspirin would abrogate any increased cardiovascular risk of selective COX-2 inhibition and, thus, a negative finding would not have answered the question raised by VIGOR.

However, the emerging data on possible chemopreventative benefits of COX-2 inhibitors and the extending database that we had of

chemoprevention studies with rofecoxib versus placebo provided an alternative means to address this question. In addition, these patients present a broad spectrum of cardiovascular risk similar to the arthritis patients in whom rofecoxib was being used. Thus, it was decided to develop a study of cardiovascular outcomes for rofecoxib based on a combined analysis of placebo-controlled chemoprevention studies.

The APPROVe study comparing rofecoxib 25 mg to placebo had already been initiated during 2000 and a second study, also comparing rofecoxib to placebo, was initiated in 2002, VICTOR, a study to assess reduction in colon cancer mortality. A third study examining the ability of rofecoxib to prevent prostate cancer in men at risk, the ViP study, was initiated in 2003. Together, these three studies would provide information on thrombotic cardiovascular events in over 25,000 patients and targeted to enroll 20-30 percent of patients on aspirin. The combined analysis had its own protocol analysis plan and an external safety

monitoring board to monitor the cardiovascular safety in the three combined studies.

The protocol for the combined outcome study was finalized in October of 2002 and was submitted to and discussed with the FDA and with the regulatory agency in the United Kingdom.

Also during the 2000-2004 time frame final data became available from our programs in arthritis and Alzheimer's disease. As the data became available, we performed updates to our cardiovascular pooled analysis and, in 2003, performed a final cardiovascular update. Also, in 2003 we updated our pooled analysis of upper GI clinical events so I will show you now the final GI and cardiovascular data from these programs.

Final GI data from the osteoarthritis and rheumatoid arthritis programs were analyzed in pooled analysis of clinical upper GI events using the same approach to the data as in the initial analysis I showed before, except now we had data that extend up to 30 months of treatment. The pooled analysis included all Phase IIb through

Phase V randomized clinical trials 4 weeks or longer and excluded VIGOR as those data would otherwise overwhelm the data in the pooled analysis, and that is shown separately on this slide.

As you can see, even excluding VIGOR, the relative risk of a confirmed clinical upper GI event for rofecoxib compared to the combined NSAIDs was 0.36, a 64 percent reduction, and a similar benefit could also be demonstrated for confirmed complicated events.

In this final pooled analysis there was sufficient data to assess whether the findings for the combined NSAID groups were consistently observed for each of the comparator NSAIDs, diclofenac, ibuprofen and naproxen and, as you can see, this was clearly the case.

I will turn now to the cardiovascular data. This is the Kaplan-Meier plot of the final data for the osteoarthritis Phase IIb/Phase III studies for rofecoxib compared to the non-naproxen NSAIDs. Over 30 months the curves are

indistinguishable from each other, although starting around 18 months, as you can see, the numbers of patients begin to drop off and the 95 percent confidence intervals begin to widen consistent with the data becoming sparse.

This is the time to event plot for the final cardiovascular data. For the Alzheimer's disease studies, these are the confirmed events from these studies. The average relative risk across the Alzheimer's program was very close to 1. However, in this data set there was a statistically significant non-constant relative risk, with an apparent decreased incidence for rofecoxib compared to placebo for the first approximately 24 months of the study and an apparent increased risk for rofecoxib thereafter. however, as the overall relative risk approximated 1 and as data in our pooled analysis did not suggest this pattern of changing relative risk in any of the data sets, the data from Alzheimer's were interpreted to represent variation about a mean and no difference between the treatment groups.

I want to point out that there were 90 patients with confirmed cardiovascular thrombotic events in the Alzheimer's disease data and there

have been over 70 in the osteoarthritis data set. Thus, each of these data sets was large enough to exclude the 2-fold increased cardiovascular risk with rofecoxib that we had seen in VIGOR.

This is the final update to the pooled analysis. The pooled analysis included data now from 28 studies in over 32,000 patients and over 19,000 patient-years of exposure. Again, relative risk for rofecoxib compared to placebo and rofecoxib compared to non-naproxen NSAIDs approximated 1. However, the relative risk compared to naproxen continued to show a difference with a 95 percent confidence interval excluding 1 and, thus, indicating statistical significance.

So, what was our assessment of the data in 2004 before we learned the results of APPROVe? The data available in 2004 came from three sources, observational epidemiology studies, preclinical studies and randomized controlled trials. There

were 10 observational epidemiology studies, either published or publicly presented, on the cardiovascular risk with these drugs and an increasing literature on preclinical models. These are described in detail in the background package and I will not go into these data as others will be speaking to them.

With regard to these other studies, I will just observe that the results were mixed and they did not provide clarity on the cardiovascular risk with rofecoxib or selective COX-2 inhibition. We believe that clarity would best come from the outcome study that we had initiated.

Also in this same time frame the TARGET study results with lumiracoxib were published. These were consistent with the pattern of overall cardiovascular findings that with had observed with rofecoxib, with cardiovascular event rates similar to a non-naproxen NSAID, in that case ibuprofen, but a cardiovascular event rate higher with lumiracoxib than with naproxen. With rofecoxib we had also observed similarity to placebo in the

Alzheimer studies. Thus, in assessing these different data we place the greatest emphasis on data from randomized clinical studies and, based on these, the assessment was that the risk/benefit profile remained favorable for rofecoxib. With regard to any remaining questions our ongoing study of cardiovascular outcomes would provide the answers.

APPROVe was the first component of the study on cardiovascular outcomes. It was anticipated to complete in November of 2004. However, on September 23 we received a call from the administrative committee that they had accepted a recommendation from the external safety monitoring board to terminate treatment in the study.

APPROVe studied rofecoxib 25 mg versus placebo in approximately 2600 patients. Stratification was by baseline aspirin use because aspirin had been shown in previous studies to reduce the incidence of colon polyps. There was a 3-year on drug treatment period and 1-year off-drug

period. Colonoscopies were performed at screening, year 1, year 3 and there was a year 4 follow-up after withdrawal of therapy to assess the possibility of rebound. The primary endpoint was the cumulative incidence of patients with adenomatous polyps at year 3. The first patient was screened in December of '99 and the first patient was randomized in February, 2000.

Patients had to be 40 years or older and have a histologically confirmed large bowel adenoma at screening. Patients with a prior history of thrombotic cardiac events could be enrolled if they were more than a year post event; 2 years for a cerebrovascular event. Patients were excluded if they were medically unstable, for example, if they had uncontrolled hypertension or angina or CHF at rest.

The data that led the ESMB to terminate the study early are the data on this slide. These are the preliminary data from the ESMB September meeting. In the final data, which are now published on-line, there were two additional

events, one myocardial infarction in each treatment group so the current curves look very similar. Overall, there was an approximately two-fold increase in risk with rofecoxib compared to placebo. However, there was a statistically significant change in relative risk over time. Event rates were similar to placebo over the first approximately 18 months, consistent with our previous data. Starting after 18 months of treatment the curves began to separate with the difference becoming significant.

Looking at the types of events, you can see that there were imbalances in myocardial infarction, 20 versus 8 here or, in the final numbers 21 versus 9, and imbalances in stroke, 11 versus 6. In addition to these findings, we also observed differences from placebo in NSAID-like renovascular effects, for example, edema, congestive heart failure and hypertension.

After APPROVe our assessment of the risk of cardiovascular thrombotic events with rofecoxib had changed. APPROVe was the first study to show a

statistically significant increased risk of cardiovascular thrombotic events with rofecoxib 25 mg versus placebo. Although the risk had been similar to placebo for the first approximately 18 months, the risk in APPROVe began to diverge from placebo starting after approximately 18 months.

The mechanism for this finding at that time was uncertain. At the time, available clinical data on other agents did not support a class effect so we were left with a potentially molecule-specific effect. As I previously indicated, the administrative committee indicted its recommendation to terminate study treatment to us on September 23 and, on the basis of the data Merck voluntarily withdrew Vioxx from the market on September 30th.

APPROVe was the first clinical trial with rofecoxib that showed an increased cardiovascular risk versus placebo. At the time alternative therapies were available without evidence of a similar cardiovascular risk and, thus, Merck believed that voluntary withdrawal best served the

interests of patients.

Since withdrawal of Vioxx we assiduously worked to obtain the final data from APPROVe and preliminary data from the other placebo-controlled chemoprevention studies, VICTOR, the colon cancer study, and ViP, the prostate cancer study. I will start with the final analyses of the APPROVe data and additional exploratory analyses that we performed to identify possible relationships between various risk factors with increased relative risk.

I want to start by pointing out, however, that we performed numerous post hot exploratory analyses of the data to identify factors that might predict patients with increased relative risk. We looked at well over 10 different baseline risk factors. We looked in multiple different analyses and we also examined patients who were not taking aspirin. We also examined over 40 analyses of blood pressure. We analyzed these by one subgroup factor at a time with tests for treatment-by-subgroup interaction.

Given the large number of subgroups tested and the post hoc nature, the data that I am about to show you need to be regarded as hypothesis

generating and not definitive. So, let me start with the analyses of risk factors other than blood pressure.

This slide shows the relative risk for rofecoxib versus placebo for different cardiovascular risk factors. To conserve time, I am only showing the few in which possible trends were seen. Patients with what we called increased risk are patients with two or more baseline cardiovascular risk factors, or a history of symptomatic atherosclerotic cardiovascular disease; aspirin users in the study which we defined as patients who used aspirin at least 50 percent of the time on study and before an event; patients with diabetes; and patients with a history of atherosclerotic cardiovascular disease. However, these four subgroups were not independent. The events in the patients with a history of atherosclerotic cardiovascular disease were also

included in the aspirin user and in the increased risk subgroups and, in fact, were driving the differences in these subgroups. So, what we have are potentially two independent risk factors, patients with a history of atherosclerotic cardiovascular disease and patients with a history of diabetes. For these two subgroups, the test for treatment-by-subgroup interaction was borderline, with a p value between 0.05 and 0.1. At this time these observations can only be regarded, as I said, as hypothesis generating.

We also looked at blood pressure in APPROVe. Blood pressure was measured in this study once per visit which occurred at 4-month intervals. The blood pressure measurements, however, were not standardized across sites for example with respect to time of day or measurement technique. And, blood pressure changes in APPROVe were typical of what had been published for NSAIDs, between group differences and the change from baseline and systolic blood pressure of about 4 mm Hg systolic and for diastolic about mm Hg. Baseline mean

systolic and diastolic blood pressure data from population studies or from studies on the cardiovascular effects of lowering blood pressure, the change in mean systolic and diastolic blood pressure we observed in APPROVe would not appear to account for the magnitude of the cardiovascular findings that we have observed. Nonetheless, we performed numerous analyses to assess whether associations could be identified between the blood pressure and cardiovascular data.

Multiple blood pressure analyses are described in your background package. Neither the preliminary nor the final analyses identified consistent patterns or consistent patient subgroups or covariates associated with increased relative risk. Variables assessed included baseline blood pressure, change from blood pressure, on treatment blood pressure and hypertension reported as an adverse experience. The one subgroup of the many we tested in which a trend was identified was in patients with systolic blood pressure greater than or equal to 160. However, other data sets, in

particular VIGOR and our placebo-controlled data from the pooled analysis, did not show a similar trend when assessed in this manner.

With the final data we also learned the results of the efficacy endpoint. The primary efficacy endpoint was the cumulative incidence of patients with recurrent colon polyps over the 3-year treatment period. The primary approach to the data was intention-to-treat, and the primary population was patients at increased risk for colorectal cancer based on baseline risk factors such as histology and number of polyps. Rofecoxib use was associated with a 24 percent reduction in the risk of colon polyp recurrence, and the p value was highly significant.

As I indicated earlier, the study of cardiovascular outcomes was the pooled data from APPROVe, ViP and Victor. We have preliminary data from ViP and VICTOR and wanted to share those preliminary data with you as well.

This slide shows a pooled analysis for the primary endpoint that we had prespecified for the

cardiovascular outcome study confirmed thrombotic cardiovascular events. Again, I want to emphasize that VICTOR and ViP data are still preliminary. There are still five cases that are pending adjudication to which we remain blinded. For VICTOR we have very limited information on overall exposure and on patient demographics.

The study was conducted by Oxford and they are working hard at getting the information to us. Given the preliminary nature of the ViP and VICTOR data, we are unable to draw at this time definitive conclusions from these data.

Also with the data available, we can provide a comprehensive perspective on mortality in the rofecoxib clinical program. Shown is all-cause mortality. This is a bit busy so let me orient you. Rofecoxib is shown in yellow; NSAID comparators are shown in blue; and placebo is shown in white. The figure provides mortality rates per 100 patient-years and 95 percent confidence intervals.

Compared to the NSAIDs, overall mortality

rates were similar for rofecoxib. In one instance, the osteoarthritis Phase IIb/III studies, there were significantly fewer deaths on rofecoxib than the comparator but this was not reproduced in other data sets. With respect to placebo, mortality rates were similar between rofecoxib and placebo in all the data sets except the Alzheimer's disease where there was a significantly higher rate on rofecoxib and the difference was statistically significant.

We looked at this carefully. Although some of the imbalance was due to a difference in mortality due to thrombotic cardiovascular events, the larger part of the difference was due to trauma, poisoning and infections, causes that one would not expect to be associated with an NSAID type drug effect. So, we don't have an explanation for this observation in the Alzheimer studies.

What do we believe the implications of these data to be? As I alluded to earlier, we believe that there are several public health questions raised by the new data. The first is the

risk/benefit for selective COX-2 inhibitors relative to standard of care in their established indications. Rofecoxib has a GI safety profile superior to ibuprofen, diclofenac and naproxen.

The cardiovascular profile is more complex. Although there have been no differences observed between rofecoxib, ibuprofen or diclofenac, based on what we learned from APPROVe, the type of long-term data needed to establish similarity to these agents does not exist and at the time we withdrew data for a class effect of COX-2 inhibition was limited.

Amongst the non-selective agents, naproxen 100 mg appears to have the lowest risk of thrombotic cardiovascular events, but also the highest risk of upper GI clinical events. Can we identify risk factors associated with increased risk for thrombotic cardiovascular events with these drugs? I have shown you our data to support the effect of duration in our exploratory analyses on patient demographics. More work needs to be done to investigate the hypotheses raised by our

data. With regard to dose, our data cannot definitively address this.

Finally, is the increased cardiovascular risk that we observed with rofecoxib a class effect of COX-2 inhibition? We believe that the data that have been reported on celecoxib from the APTC study and on valdecoxib and from the CABG study, together with the APPROVe findings, strongly suggest an effect of COX-2 inhibition on increasing cardiovascular risk.

If the committee agrees that this is a class effect, the next critical question will be determining the size of the class. Traditional NSAIDs such as ibuprofen and diclofenac have not shown a different cardiovascular risk profile from the selective COX-2 agents. However, those data are limited beyond one year. We would argue that long-term comparative studies of these agents are needed to better assess the relative cardiovascular risk.

Well, what do we think are next steps? At Merck, we are continuing to analyze our clinical

data and we will be analyzing, for example, frozen samples from patients to try to identify markers that correlate with an increased relative risk of cardiovascular events with COX-2 inhibition. In addition, patients in APPROVe are being followed off-drug as had been prespecified in the protocol, and we are in the process of meeting with consultants to further explore scientific hypotheses for the findings.

We are also aware of efforts that are under way to analyze data across the different drugs, and we support those efforts.

Finally, comparative outcome studies, we believe, are needed to determine the relative risk amongst these agents in relevant populations. Dr. Curtis will talk to you tomorrow about one such study that we are conducting at Merck, the MEDAL study. This is the largest study in arthritis patients ever conducted and compares the long-term safety of etoricoxib with that of diclofenac, the most widely used traditional NSAID worldwide. We believe MEDAL will provide the kind of information

needed to weigh the risk/benefits of these drugs and improve the ability of physicians to make recommendations for arthritis pain and treatment that is in the best interest of their patients. Thank you, Dr. Chairman, members of the committee, FDA. I am available for your and the committee's questions.

DR. WOOD: Great! Thanks very much. As I am sure you would agree, the primary job of this committee is to assess all the risks and benefits that these drugs can produce, and we have certainly been encouraged to do that by everybody who has spoken so far.

That being the case, I was very surprised not to see the Kaplan-Meier curve for pulmonary edema. can you show us that from the APPROVe study?

DR. BRAUNSTEIN: Certainly. That would be slide 213.

DR. NISSEN: Yes, heart failure and pulmonary edema would be helpful.

DR. BRAUNSTEIN: We certainly examined

that. You know, the question that has been on the table--we believe the hypothesis we were exploring was the incidence of thrombotic cardiovascular events. Pulmonary edema is a mechanism-based effect of selective COX-2 inhibition that has been well appreciated and, in fact, is already described in product labeling.

So, we did see an effect. This is in our publication. As shown here, we saw an effect. This is a combined endpoint of congestive heart failure, pulmonary edema of cardia failure, so all congestive heart failure type of events that we observed in the study.

DR. WOOD: And this had a hazard ratio of 4.6 and a p value of less than 0.004. Right?

DR. BRAUNSTEIN: Yes.

DR. WOOD: So, I mean, it is important for the committee--and this goes to all the speakers I think, that if there are other hazards with a hazard ratio of 4.6, that we see these as they are presented so that we can make some cumulative estimates of what the hazards are for these drugs.

Just because they are in the label does not mean we shouldn't hear about them here, it seems to me.

The second question I have, which has always worried me, is when you go back to the original label change that you made, you know, when you changed the label to say caution should be exercised when Vioxx is used in patients with a medical history of ischemic heart disease, as a physician what am I supposed to do with that? Am I supposed to say to patients take the drug slowly, or swallow it with milk, or only take it with the lights on? Tell me what I am supposed to do with that information. I am not being facetious here because as we go through this process we are going to have to decide how we make whatever labeling changes we make, if that is the decision we make, and that doesn't seem to me to have been helpful. But maybe you knew something that I didn't. So, what did you intend me to do with that information?

DR. BRAUNSTEIN: At the time when we conducted negotiations with discussions with FDA on that labeling, there were no specific data that

showed a statistically significant increased risk in one patient group or another. However, given the uncertainty in the data, it was felt to be prudent to recommend that caution be exercised in that patient group if you are considering using the drug.

What we meant by that was that you need to carefully weigh the risks and benefits of the different treatment options. We think that when evaluating the options on patients it needs to be done on an individual patient case-by-case basis. Patients differ with respect to their cardiovascular risks, with respect to their GI risks, with respect to their history of allergies and with respect to how they responded to these different medications in the past, and all of that information needs to be taken into consideration when assessing and determining what type of therapy should be used versus another. And, we felt that one of the things that should be considered was cardiovascular history, and that is what we meant by that.

DR. WOOD: Okay. Other questions? Stephanie?

DR. CRAWFORD: Thank you. I appreciate

the presentation. I heard both the speakers say that the sponsor, Merck in this case, made the decision to voluntarily withdraw rofecoxib in the interest of public health although the drug could have been continued on the market. When we look at adverse events we desire to predict uncontrollable events and control controllable events. The bottom line question which is really important to me as we consider these issues when we look in this case at the issue of hazard of cardiovascular events is how much is too much? In other words, how did the sponsor come to the conclusion that the evidence was so compelling as to take the step of voluntarily removing the drug product from the market?

DR. BRAUNSTEIN: Well, at the time when we saw the increased risk compared to placebo there were not data to allow us to conclude that this could be a class effect, and we felt that there

were other options available to patients, including therapies that adverse event not known to have this increased cardiovascular risk. So, given those options and alternatives, we felt that the responsible action at the time was to withdraw Vioxx.

DR. CRAWFORD: Excuse me, but I am asking specifically what was that signal that was at the level where, in the interest of caution or whatever the mechanism was, you said this level is unacceptable at this time based on the given evidence?

DR. BRAUNSTEIN: Well, we saw overall a two-fold increased risk and that was seen versus placebo so it was something that we knew was statistically significant. The magnitude of the risk was on the order I think of one or two percentage points, but still at the time the other agents--it was a determination that amongst the choices that patients had available to them there were other agents that were not known to have this risk and, given the ability for patients to have

alternatives that they could discuss with their physicians, we felt that we should withdraw Vioxx at that time.

DR. WOOD: Dr. Shafer?

DR. SHAFER: Two questions. I will make them fast. Do any studies show improved analgesia on Vioxx?

DR. BRAUNSTEIN: No. I mean, all of our efficacy studies show very similar results at comparable doses to NSAIDs.

DR. SHAFER: Okay. The other thing is can you go to slide number 36?

DR. BRAUNSTEIN: Yes?

DR. SHAFER: I just can't help but notice, but the upper bounds of the confidence intervals for the first two groups encompass the mean of the naproxen comparison. Does that give you pause in justifying excluding naproxen as a separate comparison group? If you take a look at the upper bounds, they include the mean of naproxen which might suggest that statistically those groups really shouldn't be segregated as you have done.

DR. BRAUNSTEIN: Well, when you look at this, if you were to combine all the data one would not see a statistically significant difference. It

would tend to obscure the naproxen finding, and we felt, given what we observed in VIGOR and what we had observed all along the program, that that wasn't the right way to go, especially given the difference pharmacologically. I mean, in terms of looking at the data we also were taking into context what we understood about the pharmacology of these agents and the ability for naproxen to provide that kind of inhibition of COX-1 that Dr. FitzGerald talked about. So, we thought that not only were there differences in the clinical data but there were differences in the pharmacology data that supported keeping naproxen separate.

DR. WOOD: Dr. Gibofsky?

DR. GIBOFSKY: One of the stratifications we are asked to do during the next three days is, of course, the risk/benefit relationship. I am wondering if you have calculated the risk/benefit of cardiovascular thrombosis outcome versus the

benefit of cancer prevention in the population. I can understand where the relative risk of 1.92 is. I understand what it means when the relative risk goes up above a certain number above 1.0 but, you know, you can't go much below 1.0. So, have you calculated to what extent your risk of cardiovascular events is related to your protection against cancer?

DR. BRAUNSTEIN: Well, we didn't actually study cancer as an outcome. We were looking at polyps which are precancerous lesions.

DR. GIBOFSKY: The same question basically.

DR. BRAUNSTEIN: Well, even there, you know, polyps are easily--there is a different mechanism. There is an alternative therapy available for the treatment of polyps. So, in order to evaluate risks and benefits one has to compare the risks and benefits of one treatment option versus the risks and benefits of another treatment option. In doing so, I think that this wouldn't--

DR. GIBOFSKY: Well, let me ask it another way then, if you did not see a cardiovascular signal in APPROVe would you have concluded that the

reduction in risk in polyp formation was efficacious?

DR. BRAUNSTEIN: We concluded that the reduction in risk in polyp formation was efficacious regardless of the cardiovascular finding. Are you asking whether the overall risk/benefit would have been favorable???

DR. GIBOFSKY: Yes.

DR. BRAUNSTEIN: That would be speculative for me. We haven't looked at the data with that specific question in mind. I think we would need to take a look at all the patients that we looked at in all the different subgroups to see if that remained the case. You know, you saw some congestive heart failure. We say NSAID type typical effects that one would see in one of these studies, not just cardiovascular risk but there was a small increase in ulcers, not as much as one would anticipate to see with a non-selective NSAID

but still present. There was a small increase in other NSAID type effects like edema and hypersensitivity. So, we haven't made a formal risk/benefit assessment.

DR. GIBOFSKY: Just one last point, you stressed the concept of their being other modes of therapy available and so that factored into your decision to take this agent off the market. But there are other ways of treating polyps as well, which leads me to question in that context the rationale for the APPROVe study.

DR. BRAUNSTEIN: We thought this was an interesting and important scientific question that had been raised in the literature.

DR. WOOD: That sounds like a retrospective question so I will let you off the hook. Let's move on. Ralph?

DR. D'AGOSTINO: Two quick questions. In slide 48 you, I think quite sensibly and again post hoc, split out the cardiovascular risk and redid the analysis. Now, if this were preplanned and I got a result like that I would say that this is

great; this shows me that placebo is better no matter what I do. I mean, the cardiovascular does increase a bit but the placebo is still maintaining itself even in individuals without cardiovascular risk.

DR. BRAUNSTEIN: This slide shows the relative risks in each of these groups. It is not placebo and then rofecoxib.

DR. D'AGOSTINO: Well, it is all against placebo.

DR. BRAUNSTEIN: It is all compared to placebo, yes.

DR. D'AGOSTINO: Right, and placebo wins everywhere. So, no matter if you have cardiovascular risks or not, still placebo was better. Am I misinterpreting this?

DR. BRAUNSTEIN: You know, in this we only see trends for some subgroups and in others we don't identify particular subgroup factors where there is an important difference.

DR. D'AGOSTINO: Well, that is a subgroup and it sort of indicates consistency to me. In

slide 42 there was consistency regardless of CV risk. In slide 42, if I look at those numbers on the bottom, I presume those are individuals available. You are dropping about 100 individuals after 12 months or so. Do we know anything about the loss to follow-up on these individuals?

DR. BRAUNSTEIN: We did not see differences, for example, in changes in cardiovascular risk associated with patients who discontinued--

DR. WOOD: Wait a minute, these are not all patients who dropped out, are they?

DR. BRAUNSTEIN: These are all the patients who remained in the study.

DR. WOOD: So, some of these patients may not have advanced to the end of the study.

DR. D'AGOSTINO: Well, if you start at the beginning--that is my question, I mean it is randomized, right? So, there must have been about a 50-50 break so you would think at each point you would have approximately the same numbers in the two groups.

DR. BRAUNSTEIN: Well, there is a differential dropout due to adverse experiences for example that one would normally see in an NSAID

trial against placebo.

DR. D'AGOSTINO: Well, why couldn't they be followed for CV events? Why wasn't it like an intent-to-treat analysis or something?

DR. BRAUNSTEIN: Yes, the way we had prespecified the analysis was that all events were determined up to 14 days after discontinuing therapy. The only intention-to-treat analysis was one done for mortality overall.

DR. WOOD: Dr. Nissen?

DR. NISSEN: Yes, I think Ralph's point is very, very important. We need to see an intent-to-treat analysis. You are telling me that 14 days after they dropped out of the study these folks were not followed beyond that?

DR. BRAUNSTEIN: We are following patients who are off-drug, who terminated treatment in the study, and we don't have data yet on that.

DR. NISSEN: Because there are a lot more

people dropping out of the rofecoxib arm and the question is why are they dropping out and what happened to them. The signal here could be a lot stronger than we see using this somewhat selective analysis. I am used to an intent-to-treat analysis, Ralph, for a trial like this and I am confused as to why it was done in this way. You know, a cardiovascular hazard, if this is a pro-atherogenic therapy, is going to persist quite a while after you stop the drug. So, I think we really do need to see--I mean, to clear the air here we have to see that intent-to-treat analysis. I would track those people down and find out what happened to them.

As a cardiologist, I obviously use a lot of low dose aspirin so I am very familiar with the low dose aspirin literature, and we see in low dose aspirin perhaps up to a 20 percent reduction in cardiovascular risk in individuals who are at risk. So, what I am really confused about is that you attributed what you found in VIGOR to the beneficial effects of naproxen, but you are talking

about a 4- or 5-fold difference in myocardial infarction rates and I just want to know how you came to the conclusion that that amount of difference could be explained by naproxen. Naproxen would have to be a lot more effective than aspirin. We know aspirin inhibits platelets as well as anything else out there. So, how did you guys arrive at that conclusion that it was naproxen related?

DR. BRAUNSTEIN: Well, other than in addition to the data that support that naproxen can have this effect, and specifically with regard to the magnitude that you are pointing out in myocardial infarction, there were only 24 events in VIGOR. The cardiovascular outcome studies that you are referring to oftentimes have hundreds, if not thousands, of events that they are assessing and that allows one to very carefully and with precision identify what the relative risk reduction is. In VIGOR we had fairly wide confidence intervals and, in addition, VIGOR studied exclusively patients with rheumatoid arthritis.

These are patients with chronic inflammatory disease, elevated C-reactive protein and in those patients we know that the effect of aspirin is also magnified. So, given those factors, we felt that it was certainly compatible with an aspirin-like effect.

DR. NISSEN: Again, I am not sure I buy that. You know, post-MI patients have a very elevated risk and the most we ever expect from aspirin is perhaps a 20 percent reduction in recurrent events. Even with dual platelet antagonism with aspirin and clopidagrel we don't get a whole lot more than that. So, this story about naproxen, as I think Garret FitzGerald apply discussed--it doesn't stand the test of any kind of scientific rigor.

I guess the other question I wanted to challenge you on is this comment that you made that the blood pressure effects in APPROVe were consistent with what is seen in other NSAIDs. I hope many of you have had a chance to look at the Archives manuscript that compares a meta-analysis

of blood pressure effects. It sure looks like rofecoxib is an outlier here, showing a weighted mean difference of about 5.5 mm Hg or almost 6 mm Hg compared to NSAIDs which are substantially smaller. Is it your position that rofecoxib does not produce greater degrees of hypertension than comparable NSAIDs?

DR. BRAUNSTEIN: Most of the studies that are referenced in that analysis, unfortunately, are confounded by dose. We think it is very important when one looks at a pharmacologically mediated effect, especially one that is known to have a dose-dependent association, that the drugs be assayed at doses that provide pharmacologically equivalent degrees of inhibition of COX-2. For example, for rofecoxib and celecoxib that would be 25 mg of rofecoxib and 200 mg twice a day of celecoxib.

DR. NISSEN: Okay. I want to clear the air on one more thing and, obviously, this drug has been the subject of a great deal of public attention and I think it would be a great

opportunity for you to explain, from your perspective, why did it take 14 months, from February of 2001 to April of 2002, for the label to change? Were you fighting the FDA? Was there a big battle over what the wording ought to be of the label? I mean, it seems like 14 months is an awfully long time after an advisory committee meeting that recommended a warning to take for agreement to be reached about what that warning ought to say.

DR. BRAUNSTEIN: The advisory committee--

DR. WOOD: I think that is something probably we should let him pass on--unless you want to; go ahead.

DR. BRAUNSTEIN: No, no, no.

DR. WOOD: Go ahead.

DR. BRAUNSTEIN: After the advisory committee there were a lot of discussions with FDA. There were data requests from them which we provided to them. We submitted at that same time the NDA supplement for rheumatoid arthritis because we felt it was important. As you know, VIGOR had

been conducted in rheumatoid arthritis patients at 50 mg and it was important to communicate to physicians that the appropriate dose in those patients was 25 mg. So, there was a lot of information for the FDA to review. They also asked for updated analyses of all our safety data. So, they had a lot of work cut out ahead of them, and we worked diligently with them to provide the information, conduct the analyses that they requested, and collaborated in that way to make sure they had that information, and then we worked assiduously to conclude a label. So, I don't think, considering the wealth of information, that the time frame is unusual.

DR. WOOD: And after 14 months, it was "take the tablets slowly."

DR. BRAUNSTEIN: Well, after 14 months the advice was that cardiovascular risk factors, cardiovascular history should be taken into account--

DR. WOOD: Well, that is not what it said. It is most important to remember it didn't say you

shouldn't give it to people with cardiovascular risk factors. It didn't say it shouldn't be given to people who had had an MI or any other expletive statement like that. It said caution should be exercised in patients with history of heart disease. That is quite different.

DR. BRAUNSTEIN: What I tried to say or at least what I was trying to communicate was that the risk/benefit assessment we felt needs to be done on a patient by patient basis and, in addition to taking GI risk into account, one should also take cardiovascular risk into account given the uncertainty of the data that was available at that time and, as the label said, the clinical significance of these cardiovascular findings were unknown and that, therefore, the cardiovascular information should be taken into account when considering the use of rofecoxib.

DR. WOOD: Dr. Hennekens?

DR. HENNEKENS: I would be interested in knowing the total number of deaths in the randomized trials of rofecoxib against all other

comparators and then against placebo, non-naproxen NSAIDs and naproxen.

DR. BRAUNSTEIN: You have that on your slide. The numbers of deaths are underneath the rows. I don't have the numbers at the top of my head. We would have to do a quick tally. Also, the only problem with looking at the numbers is that the numbers themselves don't take into account imbalances in exposure, which is why we showed them as rates per 100 patient-years because it certainly takes into account the differences in exposures. Compared to the NSAIDs we did not see differences in the rates, and compared to placebo we did not see differences except, as I pointed out, in the Alzheimer's disease study where there was a statistically significant higher rate with rofecoxib.

DR. WOOD: Dr. Cannon?

DR. CANNON: You mentioned in the VIGOR and APPROVe clinical trials that the major driver for the increased cardiovascular events on rofecoxib was acute myocardial infarction. My

question is were these myocardial infarctions apparently random events or was there any setting in which they seemed to occur more frequently? For example, in relationship to a procedure, including a coronary interventional procedure, or surgery, or were the myocardial infarctions random events? I am thinking in terms of Dr. FitzGerald's presentation and the recent valdecoxib experience with bypass surgery.

DR. BRAUNSTEIN: We haven't identified any kind of associations such as you are asking. But I am not sure that we have specifically looked at the question the way you are asking. So, I am not 100 percent sure.

DR. WOOD: Dr. Abramson?

DR. ABRAMSON: Yes, I guess one of the surprises or unexpected findings in APPROVe was that it took 18 months for these curves to separate with rofecoxib. I was unaware of the heart failure and pulmonary edema data until this morning. Often fluid retention occurs early in the course of putting people on NSAIDs. So, I am wondering could

you tell us more about when those heart failures occurred over the course of time. Were they early events, or was this also something that took some time to appear in the population?

DR. BRAUNSTEIN: As one would expect from an NSAID, fluid retention, heart failure were early events. If you look at discontinuations for example due to edema-related adverse experiences, including heart failure, patients tended to discontinue--if they were going to discontinue, they discontinued early and then the two groups continued in parallel. But, yes, it was an early finding as you would expect.

DR. WOOD: Tom?

DR. FLEMING: Could you show us the curves back from the VIGOR trial that looks at complicated confirmed upper GI?

DR. BRAUNSTEIN: Complicated confirmed upper GI?

DR. FLEMING: Correct.

DR. BRAUNSTEIN: We don't have those.

DR. FLEMING: You just quickly referred in

your presentation to the results being positive.

DR. BRAUNSTEIN: The results were that the two curves showed the same V-like difference and they continued to separate over time. I am just looking here and apparently we don't have that slide.

DR. FLEMING: You showed us the confirmed upper GI and those cumulated to rates of 4.5 against 2.1. The data we have been provided separately for the complicated confirmed upper GI are 1.4 against 0.6. So, it is the same relative risk but a much less frequent event.

DR. BRAUNSTEIN: Sure, yes, and those were mostly GI bleeds.

DR. FLEMING: I was just curious to see a pattern as to whether that is, in fact, cumulatively increasing or more apparent early in time.

Let me go on to the next point. That reflects approximately numerically almost exactly the same number of prevented cases of complicated confirmed upper GI as there were excess numbers of

thrombotic cardiovascular SAEs. In essence, what you have said is that the analgesia was comparable. So, essentially what we are really looking at is relative safety profiles and the goal here is to reduce the upper GI. And, we are essentially preventing an equal number of upper GI complicated events for equivalent numbers of excess events in the thrombolytic cardiovascular arena. Yet, essentially I think you were saying the latter didn't seem as established yet numerically it was the same.

There were also in the trial excess numbers of deaths of 22/15 and when you presented the Alzheimer's data you gave us I think slide 35 that indicated that when you looked at the Kaplan-Meier curves for confirmed thrombolytic cardiovascular events that didn't seem to reinforce the excess rates that you were seeing with VIGOR and, yet, it did reinforce the excess mortality as you have now circled back and reported at the end. In 2003 the excess mortality is quite significant but it was also significant in 2001. The latter

date is in Tab G, page 2 but the former data is in Tab F, page 39 where excess mortality was significant at 33/20 and the cardiovascular were 8 to 4. So, you were seeing from these two sources excess mortality and you were seeing excess numbers of thrombolytic events that were equivalent in number to the number of prevented complicated confirmed upper GI events. Am I correct on this summary?

DR. BRAUNSTEIN: Well, no. There are a couple of points I would disagree with. First, in VIGOR the difference in mortality was not statistically significant and also in terms of looking at the causes of death, cardiovascular mortality which is the difference we would see was not different between the two groups. There were 7 on rofecoxib and 6 versus naproxen. So, I am not sure--

DR. FLEMING: Well, I don't think we disagreed. I am not talking about statistical significance here. I am talking about what the data are actually suggesting in what is available--

DR. BRAUNSTEIN: Well, I must say there is a lot of data that you pointed out to me and--

DR. FLEMING: Well, just to summarize the

essence, while you have emphasized appropriately the upper GI events being decreased, when you look at the actual number prevented in complicated confirmed upper GI it is numerically almost identical to the number of excess thrombolytic cardiovascular SAEs that were seen in VIGOR. You also saw a numerical increase of a relative risk of 1.5 on mortality, which was also seen in the Alzheimer's study which you were saying at the time was contradicting the sense of concern related to the overall thrombolytic excesses. And, what you were seeing at the time, even back in 2001, was a statistically significant excess in death rates with a doubling in cardiovascular-related deaths.

DR. BRAUNSTEIN: Let me ask Dr. Reicin because she perhaps has a better handle on it and I am sort of getting lost in the mass of data that is coming up.

DR. REICIN: I think there are two issues

that I think you brought up.

DR. WOOD: Sorry, just for the record, can you identify yourself?

DR. REICIN: I am Dr. Alise Reicin, Vice President of Merck Research Labs. In terms of looking at VIGOR, I think you are correct. There was excess in cardiovascular events on Vioxx and there was a decrease in the complicated GI events on naproxen.

DR. FLEMING: Which numerically were almost identical.

DR. REICIN: And I think that that is also fair to say. If you compare our data versus diclofenac and ibuprofen at the time, there was no difference in cardiovascular events. In fact, numerically it was in favor of Vioxx and, yet, there was a significant reduction in GI events. So, that takes care of that. So, versus naproxen, I think you are right, there was excess in CV, lower in GI versus ibuprofen and diclofenac, however, no evidence of an increase in CV and a reduction in GI.

In terms of the mortality data that we had at the time, we had a significant reduction in mortality on Vioxx versus non-naproxen and the

NSAIDs that we had in our Phase III OA studies, and at the time we actually did not make a lot of those. We thought it was potentially by chance. That was actually driven by CV mortality in the non-naproxen group.

In VIGOR there was a numeric imbalance, 22 to 15 in deaths, but cardiovascular mortality was similar. In terms of Alzheimer's I don't think there was statistical significance back at the time of VIGOR. There was a numeric imbalance. In terms of cardiovascular I think the numbers were 8 versus 4. They were put in the label. So, pretty small numbers. The rest of the difference that we saw was due to things like poisoning, electrocution and other things that we thought were no drug related.

DR. FLEMING: You are correct, it was 8 versus 4 in cardiovascular related deaths, but it was statistically significant in total mortality at that time as well. It was 33 against 20, with p

values reported, depending on the method, of 0.007 to 0.26.

Now, the final data are significant but even the early data were significant and reflected the level of excess mortality that VIGOR was establishing but not in a significant fashion.

DR. REICIN: Again, we didn't see it though in any of our other data sets. In fact, in the early data sets statistically it went the other way, non-naproxens had higher one. I think you can see that in RA also there was no evidence of an excess. In ADVANTAGE there was no evidence of an excess. You see now in ViP and--

DR. FLEMING: But there was in ADVANTAGE. There was an excess.

DR. REICIN: Not in overall mortality.

DR. FLEMING: Yes, in overall mortality--oh, I am sorry, in Alzheimer's.

DR. WOOD: Tom, have you finished?

DR. FLEMING: Yes.

DR. WOOD: Dr. Shapiro?

DR. SHAPIRO: I guess I want to follow up

on a comment that you, Dr. Chair, made. I am still concerned about the label change and how helpful or not helpful it was, not only because it may not have been as helpful as it might have been to clinicians but also to patients in the informed consent conversation. What else was made available or should have been made available or could have been made available to clinicians to make some sense out of this, caution should be exercised when Vioxx is used in patients with a medical history of ischemic heart disease?

DR. BRAUNSTEIN: Were you addressing me or the Chairman? Me? What we made available were the data. I mean, I think that is the answer to the question in terms of the labeling and in terms of what we had published.

DR. SHAFER: So, the VIGOR and Alzheimer's results were made available. You just weren't going to analyze them to make any more definitive statements at that time about what clinicians should take away?

DR. BRAUNSTEIN: Well, by 2002 we were

also starting to implement our outcome study. We thought the important message to clinicians was that there is a GI benefit and there is also a cardiovascular finding that we don't understand given the differences between the two data sets. It says the clinical significance was unknown and that this information needs to be taken into consideration when assessing the risks and benefits of these drugs in individual patients. Individual patients differ in terms of their risk profiles and that decision on which drug to be used is best made on a patient by patient basis.

DR. WOOD: Dr. Ilowite?

DR. ILOWITE: Rofecoxib was pulled from the market approximately three weeks after its approval in children with juvenile rheumatoid arthritis. I have two quick questions. Were there any cardiovascular events in any of the trials in children?

DR. BRAUNSTEIN: No.

DR. ILOWITE: Second, did you give any consideration to the fact that there were no other

COX-2 inhibitors, other than one NSAID that was available as a liquid, before you made the decision to pull it from the market?

DR. BRAUNSTEIN: The focus I think was on the list we had seen versus placebo in the adult patients. This kind of disease, cardiovascular disease, is not very common in children and we hadn't seen anything like that in our population.

DR. WOOD: Dr. Boulware?

DR. BOULWARE: I want to go back to the previous question. What I heard was a discussion about an offset between complicated GI events and it sounds like non-fatal MIs. If I understood the discussion back and forth here, they are roughly comparable. Now, in patients requiring an NSAID, and I am not talking about the APPROVe data here but in patients requiring NSAID treatment if there is roughly comparability of complicated gastrointestinal events with non-fatal MIs, it sounds like Merck's thinking was that the risk of a non-fatal MI far outweighs, in a patient requiring NSAID treatment, the risk of complicated GI events

and that that was what drove the decision.

The reason I am interested in this is that obviously this meeting is entirely about how you make a risk/benefit calculation. So, your thoughts in September about this issue are I think helpful to us in thinking about these risk/benefit issues.

DR. BRAUNSTEIN: I wouldn't put it exactly the way you stated it, and that is because the individual patients at risk for these problems differ and there were alternative approaches for patients with GI risk that were available at the time. Now, we recognize that rofecoxib had met the highest standard. Well, yes, it had met the highest standard but there were alternatives available and we did not have data on what one could do for more studies. The data was unclear as to the mechanism so we felt that given those options, the withdrawal made the most sense.

DR. BOULWARE: Can I just make a little follow-up comment? It sounds like you are trying to have your cake and eat it too. On the one hand, you would have liked to have said pre-September

that rofecoxib was the only COX-2 selective drug that had demonstrated effect in reducing GI toxicity. Now you are saying, after you pulled it from the market, there are lots of other alternatives that are almost just as good. I don't really understand.

DR. BRAUNSTEIN: I couldn't say "almost just." There haven't been head-to-head studies to answer that latter part of your question. There were alternatives. We did not know that there is a class effect for cardiovascular.

DR. WOOD: Dr. Manzi?

DR. MANZI: This question actually may better be answered by Dr. FitzGerald, I am not sure--is he here?

DR. WOOD: Here he comes, just in time.

DR. MANZI: He eloquently pointed out that there is clearly variability in individual dose response with regard to COX-2 inhibition. Since we are grappling with this issue of class effect versus a specific drug effect, is it feasible or helpful to look at the degree of COX-2 inhibition

in association with these events?

DR. WOOD: You are up, Garret. Just take that microphone.

DR. FITZGERALD: I would say yes amongst all those things.

DR. WOOD: Amongst all those things? I don't understand.

DR. FITZGERALD: I mean one of the issues that you would hypothesize is relevant to outcome is the degree of selectivity attained in an individual.

DR. WOOD: You mean amongst other things related to the drug?

DR. FITZGERALD: Amongst other things related to the drug and underlying--

DR. WOOD: Sure. Dr. Platt?

DR. PLATT: Compared to other NSAIDs, do I understand properly that 98 out of 100 patients who take the drug would have about the same outcome? That is, the significant difference between the regimens is approximately--2-fold means about a 2 percent absolute difference.

DR. BRAUNSTEIN: Which outcome are you referring to?

DR. PLATT: To the GI outcomes.

DR. BRAUNSTEIN: There is a range. There is a small range because it does seem that we have a larger difference--you know, if you line them up it is a little larger with naproxen and a little smaller with diclofenac but I would say on average it is about two-fold.

DR. PLATT: Right, but that 2-fold translates into about two patients out of 100 having a different outcome than they would have if they had taken the comparator. I am trying to get at the question of whether we can identify those two patients with greater certainty than just treating everyone. And, I would ask the same question about the cardiovascular complications. That is, in this complicated business of risks and benefits, can we do better than we have at guiding both clinicians and their patients in having at least semi-quantitative estimates of what the risks will be and what the benefits will be so they can

make an informed judgment?

DR. BRAUNSTEIN: We know that from the VIGOR results because we looked at patients with different baseline risk for GI disease, and this is something that is well understood, what the different risk factors are for GI disease, including things like prior history of a GI event, and we saw the same 50 percent reduction across all the different risk factors. In terms of cardiovascular, we are still introduction he process of trying to see if we can identify particular risk factors that would correlate. So, that is still an open question based on our data.

DR. PLATT: But saying 50 percent really obscures the fact. Some people may have a baseline risk of a serious GI event of 20 percent or 30 percent, in which case 2-fold is a very big improvement for them--

DR. BRAUNSTEIN: Yes, of course.

DR. PLATT: If we knew enough we would know that most people have effectively a zero risk. So, there is very little benefit for them. Have

you put the data together in a way that helps us identify the people who stand most to benefit and the people who stand most at risk, and is it possible that those are different groups?

DR. BRAUNSTEIN: Dr. Reicin can I think provide more information on the VIGOR results because she was involved extensively in the VIGOR study.

DR. REICIN: Dr. Laine may come up to help me if I don't remember something. We actually published a paper on looking at specific subgroups in the VIGOR study. What we found is very similar to what Byron talked about during his discussion. Patients with typical risk factors, age more than 65--do you want to add something?

DR. LAINE: I agree absolutely. The reason I actually took these data and published this paper with the VIGOR results is that I have had the same idea. Relative risk isn't important in practice; it is the absolute change, the number needed to treat. So, we looked at that with absolute incidence of number needed to treat and

for clinical events, for instance, if you had a prior event you only have to treat ten people for one additional event. But if you don't have a prior event you have to treat, let's say, 60 or 70. The same with age, if you are over 75 you only need to treat ten people for one additional event. But if you are under 65 you need to treat 50 or 60. So, I agree absolutely that at least with the VIGOR data, we stratified by these different clinical risk factors that Byron showed earlier.

DR. WOOD: We have three more questions, Dr. Shafer, Dr. Cush and then Dr. Temple.

DR. SHAFER: Two questions. Can you go to slide 48?

DR. BRAUNSTEIN: That is the subgroups, yes?

DR. SHAFER: Yes, is the one on various subgroup analyses. Can we show the slides? Just to highlight what the question is, in slide 48, this is following on the comment by Dr. Nissen regarding the aspirin use, what you show in the APPROVe trial is that the risk factor for those

with aspirin on board, in fact, is 3.25 with a confidence interval which is wide, as Dr. FitzGerald has suggested it might be because of small numbers, but it goes from 0.98 to 13.81.

Now, the hypothesis behind VIGOR and interpreting VIGOR as an aspirin-like effect, was that aspirin was going to confer safety. Doesn't the data on slide 48 essentially disprove the naproxen hypothesis in VIGOR?

DR. BRAUNSTEIN: No, there is no naproxen in the study--

DR. SHAFER: Right, but the hypothesis was that naproxen was acting like aspirin.

DR. BRAUNSTEIN: Yes.

DR. SHAFER: Yet, here in the presence of aspirin to provide the safety, you are not seeing benefit.

DR. BRAUNSTEIN: I would argue that the mechanism for what we saw in VIGOR, which was a very early difference between the two treatment groups, is qualitatively very different than what we see in APPROVe. So the mechanism for the

cardiovascular difference in the two studies is not necessarily the same and, therefore, whatever difference we are seeing here or not seeing with aspirin doesn't really relate to what we saw in VIGOR. I would also point out, as you have already pointed out, there are wide subgroups. I think Dr. Villalba has pointed out that when we looked at the APTC endpoint, which was just myocardial infarction, stroke and vascular death, the difference actually seems to go away but, again, there are very small numbers and we don't want to over-interpret at this point what the data say.

DR. WOOD: But the major point here, just to help you here, is that these people were not randomized to aspirin. So, people who were on aspirin were a different subset than the people who were not on aspirin in terms of cardiovascular risk and so on. So, it is not like naproxen.

DR. BRAUNSTEIN: Yes. Yes, of course. Sure.

DR. WOOD: The one thing I would say while you have that slide on there is that I think is

going to be important for us is that our job is not to identify groups that are at particular risk, Richard. Our job I think is to see if we can identify patients who are at low risk--

DR. PLATT: Yes.

DR. WOOD: I am not arguing with you. I am just making a generic point and it is not clear to me that there is such a group identified there.

DR. PLATT: Well, it seems to me that there will always be risk--

DR. WOOD: Right.

DR. PLATT: --the question is can we help inform decisions that patients have to make?

DR. WOOD: Dr. Cush?

DR. CUSH: Dr. Braunstein, a few times you mentioned that you made this decision based on the signal that you found in the alternatives existing, and not knowing if it is a class effect. If you knew that this was a class effect would you have made the same decision? And, knowing what your COX-2 potency is, does that factor into that?

DR. BRAUNSTEIN: I couldn't go back and

speculate what decision we would have made based on a different set of data.

DR. WOOD: I think that is a fair answer. Let's move on to Dr. Cryer.

DR. CRYER: I would like to come back to a consideration of the potential gastrointestinal benefits of COX inhibitors and specifically Vioxx, and I am going to use your slide 33 to help me with my questions and comments.

You repeatedly made the point that Vioxx, rofecoxib, was unique in its labeling with respect to its gastrointestinal benefit and that was a label revision that was largely derived from a discussion of the data in the VIGOR trial in which naproxen was the comparator.

I want to underscore that the conclusions reached may be as much of a reflection of the comparator as they could be a reflection of properties intrinsic to the COX-2 specific inhibitor. As I look at the pooled analyses from the rofecoxib experience and specifically look at diclofenac, it does not appear that the difference

in reduction compared to diclofenac is statistically significantly different.

So, the question that I have for you is do you think that the revisions in the label would have been the same with respect to the GI observations in VIGOR had diclofenac been the comparator rather than naproxen?

DR. BRAUNSTEIN: In an adequately powered study. I think the failure here in these confirmed events, in order to have the confidence interval narrow enough we would need enough power to do that. In fact, when we looked at investigator reports of these events, in all, including the unconfirmed, we did have statistical significance. So, I think that, yes, in an adequately powered study we would show a difference from diclofenac.

DR. WOOD: Bob?

DR. TEMPLE: Actually, I wanted to pursue something Dr. Shafer raised. The aspirin subgroup is a baseline subset. People are probably reasonably well randomized to whether they get--

DR. WOOD: They didn't get aspirin.

DR. TEMPLE: No, I know. They were different populations from people who were on aspirin but they are randomized to the two

treatments, and there is about a thousand of them. From everything that I would have understood from Dr. FitzGerald's talk, when you are on both aspirin and rofecoxib you are not on a selective drug anymore, or probably not because you have plenty of COX-1 inhibition. But the hazard ratio there is higher than the other people. I wonder whether that is easily explained, or it could be explained by blood pressure effects which, of course, aspirin will not reverse. Because I think it needs some kind of explanation.

DR. WOOD: So, is that addressed to Garret?

DR. TEMPLE: Either.

DR. BRAUNSTEIN: With regard to aspirin data, they are not robust enough. We are talking about a total of 11 events, as I recall, in that analysis for the APTC. There are not a lot of events in that analysis.

DR. TEMPLE: There were 16.

DR. BRAUNSTEIN: Right, 16 events. There are very wide confidence intervals, as you know. So, I think it is difficult to draw specific conclusions about aspirin. With regard to blood pressure, as I indicated, when we looked at that

the blood pressure changes that we observed would not appear to explain the magnitude of the cardiovascular findings that we observed in APPROVe.

DR. TEMPLE: One of the reasons to worry is that people with underlying heart disease or diabetes are probably more sensitive to blood pressure effects. There is some evidence of that. Anyway, just a thought.

DR. WOOD: Garret?

DR. FITZGERALD: I would just say one can over-parse extraordinarily small amounts of data in retrospect, and that there is enough flexibility in what one would expect to see to account for that. For example, we don't actually know if inhibition of COX-1 has no impact on the blood pressure

response to a COX-2 inhibitor. In fact, from what I showed you in mice, one would anticipate if one actually designed a study to address that question that the answer would be yes. So, I think that, coupled with the fact that aspirin, even if one had loads of data, would be expected to modulate rather than abolish the hazard through this mechanism really means that it is not an answered question rather than an answered one.

DR. WOOD: Great! Well, let's stop at this point and break for lunch. We will restart at exactly one o'clock.

(Lunch recess.)

A F T E R N O O N P R O C E E D I N G S

DR. WOOD: Merck has a couple of slides they wanted to show to address the blood pressure issue that came up in the previous discussions. So, let's go ahead and do that first quickly.

DR. REICIN: The first was in relation to the issue about congestive heart failure, which is a known side effect of all NSAIDs and COX-2 inhibitors and is reflected in their labeling. Since the only data we showed was from APPROVe, we had an expected difference from placebo but if you look at this slide you see that in our OA database the incidence of congestive heart failure was low, and it was generally similar to ibuprofen. You can see that it ranged from 0.1 to 0.4 percent on rofecoxib; 0.4 percent on ibuprofen; and 0.8 percent on diclofenac--so, generally similar to the NSAID comparators. I will acknowledge that there was one epidemiologic study that suggested that the rate was higher on rofecoxib.

DR. WOOD: But the data in the APPROVe study are up to 1.5 in the rofecoxib group, and

this is for serious heart failure--congestive heart failure, pulmonary edema. Right?

DR. REICIN: It was versus placebo. The rate was higher in that study than we have seen in other studies.

DR. WOOD: Right. But it is not a question of whether it is against placebo or not. The underlying rate is much higher.

DR. REICIN: The rate was higher in that study. We didn't see it as high in our other studies.

The other slide, 232--it was a question about whether rofecoxib had effects on blood pressure that were very different than the other NSAIDs. This was a study done in elderly patients. It was not an ambulatory blood pressure study but blood pressure was measured in these patients 4 times a day. If you look, rofecoxib 25 mg was compared to celecoxib 200 mg BID. That is the highest recommended chronic dose for both of these medications. The medications at that dose had similar inhibition of COX-2. We compared it also

with naproxen 500 BID and placebo, and I think you can see that the changes in systolic blood pressure and diastolic blood pressure are similar among the active treatments and greater than placebo.

DR. WOOD: Okay. Thanks very much. These are helpful comments. Are there any questions specifically and only on these two things? Steve?

DR. NISSEN: Could you show us the use of antihypertensive agents in the two arms of APPROVe? I would be interested in seeing if there was a difference in use of antihypertensive drugs. I am also interested--you know, these mean changes are useful but it is also useful to know the fraction of patients that had sustained increases of, say, 15 mm or more because that is the kind of level of increase that would constitute a substantial risk. So, I am interested in use of antihypertensive drugs and I am interested in the number of people who had greater than a 15 mm sustained increase in each arm.

DR. NORGAN: Kevin Norgan, Merck. The use of antihypertensive drugs in the APPROVe study, at

baseline it was approximately 30 percent. It was 30 percent in one treatment group and 29 percent in the other treatment group. Then, during the course of the study the numbers increased to approximately 40 percent in the rofecoxib group and approximately 35 percent in the placebo group. The actual numbers are in the publication that is on the Internet.

DR. NISSEN: And was that difference statistically significant?

DR. NORGAN: I don't recall. I think it was but we would have to check.

DR. WOOD: Then 25 patients dropped out because of hypertension versus 7 in the placebo group. Right? So, that should be added to the number that actually ended up on antihypertensives in the APPROVe study.

DR. NISSEN: What about the issue of the 15 mm or greater? Do you have any data on that? Bob Temple, isn't that something you guys like to look at in the FDA, the sort of 15 mm outlier group?

DR. TEMPLE: I don't know. I think we look at mean just as often.

DR. NISSEN: All right, but I would like

to know because I didn't see that.

DR. REICIN: We will get back to you later with that data, Dr. Nissen.

DR. WOOD: That being the case, let's move on to the next presentation which is from the FDA.

FDA Presentation: Vioxx (Rofecoxib)

DR. VILLALBA: Good afternoon. My name is Lourdes Villalba and I am a medical officer in the Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products. I have been the primary reviewer for Vioxx since 1998 when the NDA was originally submitted for approval.

DR. WOOD: You need to move closer to the mike.

DR. VILLALBA: So the important thing, I have been the primary reviewer for this since 1998, since its original submission for approval for the treatment of acute pain, dysmenorrhea and osteoarthritis.

I am going to show you an overview of my presentation. First of all, my goal is to show you that we were not sleeping behind the wheel, that we have been actively engaged in reviewing the enormous amount of data that came to our division throughout the years, and this has been a very

challenging application, a very complicated process to review a lot of information that was not always that clear to interpret.

The other issue is that I want to point to some observations that may help you to think about the best study designs. Everybody is talking about future studies to clarify the question but the issue is exactly what kind of studies we need; what should be the comparator; how long, etc.

So, first of all, I am going to show you a brief background with a chronology of events to point out just some specific areas that I want you to remember. Then I am going to give you an overview of the Vioxx data sources we reviewed and that will be presented also in a chronological order. Then I am going to spend a few minutes

talking a little bit again about the different classification of cardiovascular events. Then I will go into the different Vioxx databases showing cardiovascular safety in the way we saw it at the time they were presented to us. Then a summary, pointing out again to the challenges in interpreting this data.

This is a busy slide and I apologize for it but I want to point out a few areas here. The NDA was originally submitted in 1994 and it was approved in '99 after the data was presented at an advisory committee meeting. Around the time of approval there were all sorts of submissions of IND investigational new drug applications for other indications. One of them was submitted to the Division of Neuropharm. Products for the evaluation of the role of Vioxx in the prevention and treatment of Alzheimer's disease. Another one was submitted to the Division of Oncologic Drug Products and that was approved, the adenomatous polyps prevention trial that now led to the withdrawal to the product. It was initially

submitted to the oncology division and then was switched to GI. That is just a detail. This was back in '99.

Then we had the results of VIGOR in the year 2000. The advisory committee meeting of February, 2001, and after that we reviewed a lot of information and finally got the labeling changes in April, 2002. Later on, in October of that year, there was a submission of another study in the Division of Reproductive Products to evaluation the role of Vioxx in the prevention of prostate cancer. About the same time Merck came to us with a proposal for conducting a pooled analysis of some of these studies, particularly APPROVe, the prostate cancer prevention and another study that was being conducted in Europe.

The Alzheimer's data was very important data that I will go into detail later, but I want to mention that preliminary data from these studies that were placebo-controlled studies were initially submitted in July, 2001. The final data from this database was provided to us in March, 2004.

This is an overview of all the databases we reviewed and this does not include APPROVe. As you can see here in the first column, although it

says "indication" the indication refers to the line. But here we have the treatments. We have Vioxx at 3 doses, the 2 approved for chronic use and also for acute pain, the 50 mg, as well as some comparators, ibuprofen, diclofenac, nabumetone and placebo. The original NDA did not have naproxen.

Then with have VIGOR which had Vioxx 50 and naproxen. We had other studies. Unfortunately this slide is not the last one. There are missing 2 important marks, the 25 mg dose in study 102, also known as ADVANTAGE study, and that was 25 mg versus naproxen; then the rheumatoid arthritis efficacy database that compared Vioxx 12.5, 25 and 50 to naproxen and placebo.

Then we had several studies, safety outcome reports for various indications with different comparators and also with placebo. I want to point out here with placebo that in the NDA database we had up to 18 weeks. Most of the

studies were 6-week studies but there were 18-week placebo-controlled studies that were endoscopic studies.

We have placebo here in the rheumatoid arthritis efficacy data base, but the most important data we had was here, in the Alzheimer's studies that were long-term placebo-controlled in an elderly population. We had data for at least 3 years. So, we put a lot of weight on this information. We also had access to the adverse event report system but, unfortunately, it is known that it is not very helpful to look in this way when we are talking about relatively prevalent events such as cardiac events. Then we also have literature, epidemiologic studies, re-analyses and meta-analyses of data that had been published.

Before I show every database I want to spend a few minutes on the cardiovascular endpoints because there are many different ways of looking at cardiovascular endpoints. At the FDA we routinely look at all adverse events reported under that category--cardiovascular deaths, discontinuation

due to cardiovascular adverse events, serious cardiovascular adverse events--this is routine and this is what we did in the NDA application. We did the same as well with all the other organ systems. So it is a very in-depth review.

At the time of VIGOR and all studies subsequently, the sponsor used a standard operating procedure that used a subset of cardiovascular serious adverse events, a category of cardiovascular and thrombotic adverse events, and these were referred for adjudication to a blinded adjudication committee. The committee of three cardiologists would determine if the events were confirmed or not confirmed. Another definition that was used was if they were part of the APTC definition or not.

So, these two ways of looking confirmed cardiovascular/thrombotic and APTC are not a subset of one analysis; they are complementary. The APTC endpoint, the composite endpoint that looks at cardiovascular and unknown cause of death is non-fatal myocardial infarction and non-fatal

stroke. It includes ischemic and hemorrhagic events, but does not include unstable angina, transient ischemic attack and peripheral events. These kind of events are included in this definition up here. But this does not include hemorrhagic events.

So, we looked at the data in all these different ways. Again, at the NDA stage we looked in this general way and we became more sophisticated and looked in all ways, the original one and the others.

This is very important. Let me show you just an example from VIGOR so you can have a clear idea of what I mean. You have different ways of looking at it. If you look at all investigative cardiovascular and thrombotic events you are going to have more events. If you look at confirmed or adjudicated events you still see the difference but the number of events is small. The same with the APTC. Therefore, this way of looking is more specific because it looks at the hard endpoints. Although it may be less sensitive, the other way of

looking--let's say we have here all cardiovascular events submitted under that category, we would have for VIGOR 600 events and 400 events.

So, in my presentation I am going to use the APTC way of looking at it because it also makes very clear if there were cardiovascular deaths or not. This is a different way of presenting the data that was already presented by the sponsor.

Here we have the NDA database. The NDA, submitted in 1998, was very large and involved 5400 patients with substantial exposure in multiple dose trials of 6 weeks, 6 months and up to a year studies. Some of the 6-week studies had extensions to 21 months.

I want to point out that this number is a substantial number for an NDA. This is greater than most NDAs. Although most of the COX-2 selective agents have had this kind of size of NDA, but before that we used to approve products based on much smaller data. These numbers are above minimum requirements by the International Conference on Harmonization Guidances.

In this database, looking the way I told you, looking at all adverse events that were cardiovascular adverse events and were potentially

thrombotic, serious and non-serious, this is what we found. This was kind of a definition that I made myself to look at these events. This has not been validated but, in any case, this is what we saw.

In the 6-week studies with Vioxx with all doses we have 0.7-1.1 rate, and these are crude rates here. There was 0.4 with ibuprofen; 0.2 with placebo. Therefore, we said, okay, there may be something here but if you look at the number of patients exposed, they were different. There were more patients exposed to the Vioxx doses. And we didn't really know what to do with these percentages. What dose it mean with an endpoint that is not really well defined?

Then, in the 24-week studies that had placebo, up to 18 weeks, the crude rates on Vioxx at all doses were right between ibuprofen and diclofenac. Ibuprofen was 0.5 percent; diclofenac,

2.0; and placebo was 0.8 which was also in between. So, based on these data, based on the fact that they looked similar to the other NSAIDs and that it was a pretty large database, of course, not designed specifically to address cardiovascular issues, what we said was that there doesn't seem to be a big problem here, however, we cannot rule out that there could be something but this is not the right database to address it. On the other hand, this was 1998. There were theoretical concerns regarding that inhibition of prostacyclin could induce prothrombotic events. But based on these data, there was not much to say about it. Also, Celebrex had recently been approved, in December, '98, and Celebrex had not shown anything either.

So, again, based on adequate evidence of efficacy, safety for the intended uses and the similarity to the comparators, this drug was approved in May, 1999. If you look at the safety profile, it was pretty similar to other NSAIDs. Cardiovascular safety was between ibuprofen and diclofenac. Hypertension, there was a very clear

dose response with the 50 mg being greater than the 12.5 and 25. Endoscopic data suggested that Vioxx was better than ibuprofen and the liver suggested that Vioxx was better than diclofenac. So, it was an NSAID.

The sponsor wanted to pursue the claim that this was a COX-2 selective agent; this needs to be different. We really don't want to see the GI warning template in our label. And, that was even before the NDA was submitted. It was discussed a long time before. If you really want to have a substantial change in the GI label, then you have to do large outcome studies or at least one large outcome study. That is why we had VIGOR. VIGOR was not a requirement. It was something that the sponsor decided to do because they wanted to distinguish themselves from the other NSAIDs.

We know the result of VIGOR. I am showing here the APTC results. From now on I will use the same format for all my slides. So, please bear with me for this first slide. We have the APTC total events in the first row; then cardiovascular

deaths; non-fatal myocardial infarction; non-fatal stroke; and non-fatal hemorrhagic stroke. We have the comparators here. N is the number of patients randomized. Here, in the footnote, I have the number of patients in patient-years of exposure. N gives you the number of events. Rate is the rate based on 100 patient-years of exposure, and the relative rate is the overall rate for Vioxx as compared to the comparator.

I think I don't need to spend too much time describing VIGOR. It was a large study, 400 patients per arm; patients with rheumatoid arthritis, 60 percent using corticosteroids, 40 percent using methotrexate and most were women, and patients on low dose aspirin were not included in this study.

This is what we found. There was a difference in rate of cardiovascular/thrombotic events or APTC events, and the different risk was driven by the non-fatal myocardial infarction. This number was statistically significant.

But if you look at cardiovascular deaths

there was no difference. Non-ischemic stroke, there were no differences. So, this was the first time when we saw the signal of Vioxx being different from naproxen. This is the time to vent plot that shows the cumulative incidence of events over time. This is for the cardiovascular/thrombotic events but it looks very similar for the APTC events.

I did show this slide back in 2001 at the advisory committee meeting that we had to discuss VIGOR. You see that the curves start to separate here, at 6 weeks, but this separation is more marked after 8 months. So, if you look at the overall hazard ratio it is 2.4, but after 8 months that hazard ratio increases and is 4.0. There was a lot of discussion with the sponsor about the interpretation of this part of the curve and our position was that there was increased risk after 8 months. Finally we got that into the 2002 label in the form of a table that shows an analysis of cumulative rate of events over time that shows that the hazard ratio increases after 8 months.

In any case, that difference between naproxen and Vioxx was driven by the non-fatal myocardial infarctions. There wee 9 myocardial

infarctions during the last 3 or 4 months of the study on Vioxx and there were none on naproxen. The position of Merck was that this was the cardioprotective effect of naproxen. However, we did state clearly at the advisory committee back in 2001 that we were very skeptical about that interpretation and that actually there was biological plausibility for a prothrombotic effect of Vioxx as well.

This is another study that was submitted to us in June, 2000 along with VIGOR. That was also presented to the advisory committee meeting in 2001, showing study 090 and 085. These were two identically designed studies, placebo-controlled, 6 weeks in duration comparing 12.5 mg of Vioxx with nabumetone and placebo. Of note, they have a 2:1 randomization. That means that the number of patients in the active treatment groups was twice the number of patients on placebo.

In this study, study 090, showed 3 non-fatal myocardial infarctions and 1 non-fatal stroke on Vioxx, 1 on nabumetone and none on placebo, and no cardiovascular deaths. Study 085 showed only 1 non-fatal myocardial infarction in the Vioxx 12.5 mg and nothing else in any of the

other arms. Therefore, with this information, the small number of events, the fact that study 085 did not reproduce the findings in 090 which, to start with, were very mild, we didn't know what to do with this. This was discussed at the advisory committee and there were not any meaningful conclusions from these studies. Again, I want to mention that there were twice the number of patients in the Vioxx group as compared to placebo.

The conclusions of the advisory committee were that Vioxx showed a superior GI safety profile as compared to naproxen; that the cardiovascular signal was of concern, however, given the study design it was unclear how it would apply to other populations, other doses, NSAIDs other than naproxen in populations that were at high

cardiovascular risk because this trial had excluded patients using low dose aspirin. And, that labeling changes should reflect both benefits and potential harms and that additional data were needed to clarify these issues. There was no recommendation for a specific trial to be conducted, or specific design. That is why I think it is important that today you actually give some kind of firm recommendations and give us direction as to which kind of studies you want to see.

We asked for more data and we got more data. That came continuously right after the advisory committee and at the end of February we had the application for the rheumatoid arthritis efficacy indication. It was relatively large. There were 1500 patients on Vioxx and the active comparator was naproxen. There were not other comparators. There was also placebo here.

There were 5 studies. The endoscopic studies were 12-week studies but the other studies had a 12-week base study with re-randomization of patients who were on the lower doses of Vioxx to

Vioxx 25 and 50. And placebo here, to 25, 50 or naproxen. So, it was a pretty complex NDA to review.

In any case, here we have the summary. This follows a different format but this is the summary of the results. In the first column you have the treatment and the number of APTC events; patient years at risk; and risk per 100 patient-years. As you can see here, it is clear that Vioxx 25, 50 and 12.5 showed a greater risk than naproxen and than placebo. However, if you look at the number of patient-years at risk you really cannot reach the conclusion that there is a clear signal against placebo. What is clear is that there is a signal against naproxen because exposures to naproxen and Vioxx were closer. I think that the risk with the 12.5 dose is 6.9 as compared to 0.3. So, there is something wrong; you have too small numbers to compare. If you were to believe this, I mean, here naproxen had half the risk of placebo.

So, the conclusion was that Vioxx 25 and

50, both doses, in a rheumatoid arthritis population had a higher risk of cardiovascular/thrombotic events as compared to naproxen.

Then we had the ADVANTAGE study. I am presenting you this data on one slide but this took months to review, and we were not looking only at cardiovascular safety; we also looked at GI, renal, liver, everything, fractures, so anything that was of a theoretical concern we were looking at. So, this took months. Also, when you get the information you get questions, get the responses within one or two months so it is a long process for each one of these studies.

That was for the RA. This was ADVANTAGE. ADVANTAGE, or study 102, was submitted in March and another piece in April, 2001. This was a 3-month study in patients with osteoarthritis comparing Vioxx 25 mg with naproxen. Approximately 2700 patients were randomized to each arm. Here you have the patient-years of exposure, although I don't like to use this number because this is a

3-month trial but, still, you have it there in case you are interested. But if you look at the numbers, the number of APTC events was about the same. There was a signal for cardiovascular death and non-fatal MIs. There were 9 events here and 1 here. However, there were 6 non-ischemic strokes on naproxen and 1 on Vioxx.

So, again, the conclusion here is that there is a signal. There is a signal for Vioxx as compared to naproxen but we still didn't know what the role of naproxen was here because it may have some role but it wasn't clear what the extent of that was. Based on epidemiologic data, the data were conflicting. I think I would like to know if someone knows exactly what is the role of naproxen from all these findings.

Then we had several safety update reports that came in July, 2001 that included studies in the original NDA and that were follow-up from patients who had been included in the original NDA. There were also new studies, short-term studies and long-term studies. The most important was the

study 083, the bone density study with Vioxx 25 versus ibuprofen. The most relevant data for us was the Alzheimer's data that compared Vioxx 25 with placebo. That included 3 long-term studies.

There was also an updated meta-analysis of cardiovascular events. The sponsor had presented a meta-analysis in February, 2001 at the time of the advisory committee initially and here there was an update. Basically there was no difference in confirmed or thrombotic APTC events. Actually, I am talking about these other studies because the meta-analysis was done with APTC events only.

Here is a description of the Alzheimer's studies. There were 3 studies, 2 of them on established Alzheimer's disease that had identical design, 15 months in duration, placebo-controlled, 350 patients per arm, with age of at least 65 years or older.

One of these studies has been completed and showed no efficacy, and the median exposure in this trial was 13 months. The second one being conducted was stopped because the first one had not

shown efficacy. The median exposure was 6 months. Then there was another study that was ongoing at the time of the safety update. That was study 078 that was designed as a 2-year study and was eventually extended to a 4-year study and had 730 patients per treatment arm. At the time of the safety update report that we received in July, 2001 the exposure in this study was 18 months. Regarding the population here, 60 percent of them were male with a mean age of 75 years, and aspirin was not allowed in this study initially but it was then amended to allow low dose aspirin for those patients who needed it. Approximately 7 percent of patients were on low dose aspirin.

Here we have the results of that study. Again, here you have the APTC events. I am sorry, this is wrong. This should be 0.73 but still it is below 1.0. If you look at total events you have 17 and 27. This doesn't look bad for Vioxx. If you look at cardiovascular deaths, yes, there were 8 and 5, of which 3 were thrombotic and 1 was hemorrhagic and the other was a ruptured aortic

aneurysm. There was twice the number of non-fatal myocardial infarctions and 12 non-fatal ischemic strokes.

So, based on these data, it was puzzling that cardiovascular deaths tended to be against Vioxx but, still, the number is relatively small. You have 8 versus 5. Looking at the myocardial infarction and stroke, there were more events on placebo than on Vioxx. So, that is why I am saying the interpretation of this data was very challenging. How do we put together this information for 14 months, because there was a median of 14 months. Putting the 2 large studies together, 091 and 078, had a median duration of 14 months and here we do not see the signal that we saw with VIGOR.

Here is the table with the summary of the meta-analysis that was conducted by the sponsor, the updated meta-analysis comparing Vioxx all doses with placebo events. I think this is the most valuable part of this slide because the other one is comparing non-naproxen NSAIDs and I would agree

that not all non-naproxen NSAIDs are the same. But the total number, in any case, doesn't look bad for Vioxx. The relative risks are below 1.0.

Here is what we had so far. In the NDA database in '98 where we didn't look specifically at APTC but, let me tell you because I forgot to mention it before, there were 3 cardiovascular deaths with the 12.5 mg dose of Vioxx. There were no cardiovascular deaths with the 25 and 50 mg doses, and there were 3 cardiovascular deaths with diclofenac, and diclofenac had much lower exposure, number of patients and time of exposure, as compared to Vioxx. So, there were not signals in the original NDA.

Then we had VIGOR that showed a signal in APTC and non-fatal MIs. Then we had the rheumatoid arthritis ADVANTAGE study that, as compared to naproxen, showed trends. Again, this should be all yellow and this, here, should be "no" because there were no cardiovascular deaths in the rheumatoid arthritis database.

Then we have the safety update reports

with the Alzheimer's studies that had 14-month, placebo-controlled studies without difference in MIs and strokes, but with that cardiovascular trend.

After 2001, after the presentation at the advisory committee meeting of 2001, there were several epidemiologic studies and re-analysis of the data that had been presented or published, and meta-analysis but they showed conflicting results. Basically we had to do our labeling changes. By this time we were around October, November probably of 2001. After negotiations with the sponsor, we ended up in April of 2002 including a label that for many of you may be very confusing or not helpful, but that was the situation in which we were at that time. We had conflicting data. So, what we did, we put the result of VIGOR there. We included two tables showing the cardiovascular events over time, the list of cardiovascular events by category. There was also some language in the precautions section and the indications because the rheumatoid arthritis indication was approved now,

after we reviewed all the data, not 6 months before when we should have approved--not 6 months, we have a 10-month clock to review efficacy supplements.

Anyway, they were not approved until we had reviewed a substantial amount of data. There was something also in the adverse reaction section that pointed out to the risk of hypertension in patients with rheumatoid arthritis with the lower dose. Before we had something that referred to the 50 mg dose being worse than the 25 and 12.5 but in rheumatoid arthritis patients the 25 mg dose also showed to be worse than naproxen. There was also some language in the dose and administration.

I am not going to go through all this, don't worry, but I just want to point out that we put a lot of information there and we said that we didn't know how to interpret this data; that prospectively designed studies have not been conducted.

Following these label changes--again, I am not going to insist on this but we also had language regarding the 50 mg dose not being

recommended for chronic use.

In October, 2002 we had the proposal by the sponsor to conduct a prospective analysis of cardiovascular thrombotic events that I mentioned earlier in the 3 long-term placebo-controlled studies. One of them was ongoing already since early 2000. Another one was being conducted or was going to start soon in Oxford. They submitted the prostate cancer prevention study at that time so it had not even started. But all the 3 studies together were going to provide approximately a 25,000 patient database that was placebo controlled. the prostate cancer prevention studies were planned to be up to 6 years in duration. So, we had potentially a lot of information there.

We agreed with the concept of pooling these studies and we specifically said it is possible that these studies may address the question we have, however, we cannot assure you that if you don't show anything in this study you are out of the woods So, that was a review issue. Also, there were a lot of discussions regarding the

data analysis plan for these pooled analyses.

Here we have the result of the updated data from the Alzheimer's studies. This was submitted to us in March, '04. As you can see here, the rate of APTC events still is not worse than placebo. It is about the same. There are more events on placebo but there was also longer exposure if you look at patient-years of exposure. There was no difference in cardiovascular deaths as adjudicated by the committee. There were 14 and 14 non-fatal myocardial infarctions; 17 and 6 non-fatal strokes. The strokes were all in the placebo group--sorry, not all. The point is that here we don't see a signal on stroke; we don't see a signal on MI. Death kind of is there, maybe or maybe not, because if you look at the subset of cause of death then you may argue that, okay, there were more sudden deaths in Vioxx as compared to placebo maybe but all together they looked about the same.

So, this is what we had up till March. Actually, when the APPROVe study was presented to

us this application was still under review. It is still under review because we had requested additional information so it takes time until it comes to us and we can review that data again. So, there are still many questions we have regarding this database.

Let me show you the Kaplan-Meier curve first. This is again the percent of patients with events versus time. As you can see here, placebo was about here up to almost 24 months and then they completely overlap. But the confidence intervals all along were very wide.

If you look at this table that I took from the sponsor looking at relative risk over time, again you see that after 18 months the risk was higher on placebo as compared to Vioxx and after 18 months the risk switches and is higher on Vioxx compared to placebo.

Again, if you look at adverse events with an overall risk you have a number, but it is very important to look at risk over time because down here, after 36 months, it seems that Vioxx is

picking up. But, still, I mean the confidence intervals are so wide we can't make any conclusion out of this.

This is the total-cause mortality in the Alzheimer's studies. As I think has been pointed out before, there was a difference in total-cause mortality in Vioxx versus placebo, but if you look at the cause of death they were kind of not clustered under one specific organ system. They were all over. Also, this is the first time that we had a placebo-controlled database of 3 years of an NSAID or a COX-2 selective NSAID. So, it is very hard to make any conclusion based on a comparison of Vioxx with placebo when we do not have any information on diclofenac or ibuprofen, the same kind of data up to 3 years. Still, it is of concern because, as I said, we are still reviewing this application.

Then I want to mention the epidemiologic studies because there were many epidemiologic studies and re-analyses and meta-analyses. Although I will mention that those meta-analyses

did not include substantial information that we had access to. Unfortunately, we could not share that with the world if they were not published in the literature. But epidemiologic studies in general, the ones looking at Vioxx and the ones looking at naproxen--some of them were conflicting. What was consistent was that there was increased cardiovascular/thrombotic risk for Vioxx 50 and that was in the label already. Actually, we have said that for everyone with ischemic disease people should be cautious. There was no clear evidence with the 12.5 and 25 mg dose. Again, we had seen the signal but as compared to naproxen, not to placebo. And, there was conflicting evidence regarding the cardioprotective effect of naproxen. Out of 9 studies, 5 would say it is cardioprotective and another 5 would say it is not, or 4 would say it is not and 1 would say it actually causes myocardial infarction.

So, I think that up to today I am not clear as to what is the role of naproxen. I think that it is possible, it is plausible that there is

a prothrombotic effect of Vioxx but that big effect that we saw in VIGOR and in the other databases as compared to naproxen--I think that naproxen does have a role there too but that does not explain everything, for sure.

In the meantime, during this time we were awaiting the results of the long-term placebo-controlled studies and then we had APPROVe. This is data submitted to us in January, 2005. So, I am not sure if they are exactly the same numbers that the sponsor has shown because there was another submission from October that is slightly different. Anyway, the point is that here it is very clear if you look at APTC events--for fatal MI there was only 1. So, if you look at non-fatal MI, there were 10 and 8. For ischemic stroke there is also a signal, but not for hemorrhagic stroke. But looking at cardiovascular deaths, there were 6 and 5.

This is the time to event plot that you already saw several times. I want to show you this later. What I want to show you now is that up to

here what we had was a signal for Vioxx as compared to naproxen. That is clear. But compared to placebo, in the Alzheimer's data the only thing is there was a trend for cardiovascular death. In APPROVe it is completely opposite. You have a negative effect on cardiovascular/thrombotic events, non-fatal MIs, stroke, but not in cardiovascular death. If you look throughout, this is the first time where stroke appears as being a problem with Vioxx.

This refers more to the second goal that I had. Well, first of all, it was to show you that you need to look at risk over time. The other issue is what is the role of aspirin in these studies in how it may affect different endpoints. This is how it affects APTC endpoints. Don't even look to the left side. There are too many numbers here. The point is that the difference in cardiovascular and thrombotic events or in APTC events is driven by the non-aspirin users. In the aspirin users the relative risk decreases, particularly because there is an increase in the

patients in the comparator. I think that this has to do with the kind of population that you want to see in the studies. You would want to see patients at high risk but not all patients at high risk because I think that use of aspirin may make it actually difficult to find a difference between treatments. Anyway, we should have both high risk an not high risk. These were not very high risk; they were just patients that needed aspirin.

I am going to show you this slide just quickly. I know that Dr. Temple is going to spend more time talking about blood pressure. The sponsor conducted several analyses of blood pressure and I chose this one, which is a very simplistic one but, still, I think it makes the point that when you look at on-treatment hypertension those who develop no hypertension still had increased risk for Vioxx 25 compared to placebo. The risk is very obvious here, that it increases in patients with hypertension. This is using the definition of patients who develop a diastolic blood pressure of 100 or systolic blood

pressure of 160.

The point of this slide is that if we are going to look at those patients with very high blood pressure we are missing the boat here because we need to look at those patients who have not as bad hypertension. We need to look at those patients who are within the range of 140/90 or maybe even high normal blood pressure.

This is again a busy slide and I am not going to walk through it, but just to make the point that if you go through different databases you have different numbers, all over, and the rate of events in the Alzheimer's studies was higher, particularly in placebo. Here in the Alzheimer's study it was 2.07--I am sorry, I am going too fast. Let me start again. You have VIGOR, Alzheimer's database and APPROVe with Vioxx/naproxen; Vioxx/placebo; Vioxx/placebo. Here with have APTC events, myocardial infarction and total-cause mortality. N is the number of events and this is the patient-year rate in 100 patient-years of exposure.

The point was that placebo here--the patient-year rate is 2.07 while here it is 0.54 in the APPROVe study. Naproxen here is in between in

the VIGOR study. The point is different populations, different background rates in the active treatment and also in the comparator treatments. So, again, we need to define what kind of population we want to have in these studies.

The other point is that if you look at total-cause mortality, the one that looked bad was Alzheimer's. There was no difference in total-cause mortality in APPROVe. There was a mild imbalance here in VIGOR and in the other databases there was no difference in total-cause mortality.

So, I hope you understand how challenging it was for us as we were reviewing this data. There was a clear signal compared to naproxen that was not consistent when compared to placebo. And, we have no comparative data, particularly cardiovascular safety data, for Vioxx and non-naproxen NSAIDs or not a lot of data on long-term placebo controlled with traditional

NSAIDs.

We still need to clarify the role of blood pressure and what is the role of aspirin in protecting for cardiovascular events. I think that is it. I kind of said this while I was talking. So, this is the end of my presentation.

Committee Questions to the Speakers

DR. WOOD: Thank you very much. Could you go back three slides, and then I am sure Dr. Fleming will want to ask you a question?

DR. VILLALBA: Which one?

DR. WOOD: The third last slide in the handout. That one.

DR. VILLALBA: This one?

DR. WOOD: Yes. Am I right?

DR. FLEMING: You read my mind. I wanted to follow-up on this because it is also a follow-up to a question I asked this morning. Just to get a sense of what the totality of the data is telling us about whether there is an all-cause mortality risk increase, and the two studies on the left definitely strongly suggest that there is. In the

discussion this morning it was pointed out that there are other sources of data that might complicate the interpretation, the ADVANTAGE trial being one of those. But if you look on sponsor slide 54, which we won't go back to now, the other studies are all very small relative to the numbers of events. More than a half of the total deaths in the meta-analysis of all the studies are from the VIGOR study and the Alzheimer's studies and that is where we are seeing the signal. The ADVANTAGE study that we were told about that didn't show significance still had one more death, and you said in your presentation it was 4 versus 0 in the wrong direction. There are 2 in the cardiovascular.

I guess my concern here is that when I look at this it is on-drug, and I think it is getting back to a question Ralph was asking earlier today. All of these analyses, are we correct, are only giving us that deaths that occurred within--what?--30 days of being on drug?

DR. VILLALBA: Two weeks actually.

DR. D'AGOSTINO: Yes, I raised that

morning. I mean, why weren't these individuals followed till the end of the study to find out about mortality?

DR. VILLALBA: Well, actually that is a good question to the sponsor because we know that they were followed as much as they could do it, but it was not mandatory. They tried to collect all the data they could but it was actually--I would prefer them to answer.

DR. WOOD: Well, let's not involve motivation right now. Let's just keep going with the facts. So, Tom, keep going.

DR. FLEMING: Well, that is the essence that I wanted to get at. It was just to understand that this is just on-drug and there is nothing else you can provide us in terms of a true ITT? Is that correct?

DR. VILLALBA: There were more deaths also after but there was not a balanced exposure.

DR. WOOD: No, what he is asking is do you have an intention-to-treat analysis?

DR. FLEMING: Correct.

DR. VILLALBA: No, I don't have it with me. That is why I said this is still under review. There is pending information.

DR. WOOD: But before we leave this slide though, it is important to remember why we are here. I mean, this is a drug whose indication is a safety indication, and the reason to give the drug was to reduce an adverse event which is always thrown up as causing this terrible outcome, although the outcome has improved substantially over the last 10, 15 years.

It is certainly worrisome when a drug that is supposed to produce a safety benefit, in fact, is producing an increase in mortality, it seems to me, and that is worthy of some discussion. Certainly, an ITT analysis would have been important.

DR. VILLALBA: Again, I completely agree. We are concerned, but we don't know how other NSAIDs would look here.

DR. WOOD: I understand.

DR. VILLALBA: We need to put it into

context.

DR. WOOD: That is what my teenaged kids say as well. Curt?

DR. FURBERG: I was wondering whether you, within the agency, considered the risk of heart failure. I mean, when I look at the tables and in your presentation you are using the term heart arrest signal in a narrow sense. There is nothing in your tables on heart failure. It is an issue. As the Chairman found out a little bit earlier, in the APPROVe study, a 4-fold increase in a long-term trial. Do you have information from the Alzheimer trials on heart failure? If you look at the adverse effects of the drug, we shouldn't just narrow it to heart attacks and stroke. Let's broaden it to heart failure and make that part of our evaluation.

DR. VILLALBA: Yes, I don't have slides with me regarding congestive heart failure but, again, we don't have the data for other NSAIDs. That is the only thing that I can keep saying. But there was more heart failure, for example, in VIGOR

clearly as compared to naproxen.

DR. WOOD: I sense that there is a response coming from the sponsor. Do you want a couple of minutes to think about that before you get up? You can take a couple of minutes and we will take another question, if you want. Take your time; we won't forget you. Dr. Bathon?

DR. BATHON: I am a little confused about the aspirin issue. On your slide 35 you showed a decreased hazard ratio or relative risk for the aspirin users compared to non-aspirin users. But in Dr. Braunstein's presentation it was the opposite. I realize that the outcomes were measured a little bit differently.

DR. VILLALBA: That is a very good point. These are APTC endpoints and the way that Dr. Braunstein showed it was all cardiovascular/thrombotic events that included also peripheral events, unstable angina and TIA. So, the point of this slide is precisely that when we design a study that is going to address these issues in the best possible way we need to choose

the right endpoint. And I don't know what that endpoint is because if you look at all cardiovascular events you may see more than if you look only at APTC.

DR. WOOD: Dr. Shafer?

DR. SHAFER: I know it is always easier in retrospect to try to make sense of things than prospectively when you are looking at many possible adverse outcomes and trying to figure out where to focus one's attention. But if you could go back to slide 23, what we see here, in slide 23, is a lot of suggestions of danger signals. Dr. Braunstein made an interesting point earlier when he said that it would take about 30,000 patients to demonstrate an increased risk, and yet we see danger signals in very small studies of short duration. So, that has obviously to be a cause for concern.

Then along comes the VIGOR trial. As I understand, basically VIGOR had a 2-5X increase in serious adverse cardiovascular events depending on the endpoint you chose to look at. Now, there are two possible interpretations of that. One

interpretation was that rofecoxib increased risk. At the time you had this background worrisome signal rate which was consistent with the mechanisms that Dr. FitzGerald spoke about, and if that were the true state of things, then potentially millions of patients were being placed at risk.

The converse choice is that Naprosyn decreased risk. There were very weak data to support that. As we heard from Dr. Nissen, the effect was too large to be really explained by any known effect of aspirin. And, the safety data that were used to support the safety of rofecoxib was far less than the 30,000 patients that would be required to significantly show the difference. By Dr. Braunstein's own statements, you know, it would take far more patients to really statistically significantly show that up.

What I first thought was the company and the FDA chose to give pretty good credence to the naproxen hypothesis. It sounds from the comments today that that is still the position of Merck.

What would it have taken, what kind of data would it have taken, given the results of the VIGOR trial and the two alternative hypotheses, for the FDA at that point in time to either put a black box warning or perhaps even remove Vioxx from the market? What kind of data would you have had to have in addition to what you have?

DR. VILLALBA: I cannot answer that question. What I can tell you is that this was as compared to naproxen. We never bought the naproxen theory, but we also did not have evidence that Vioxx was worse than placebo or other NSAIDs.

DR. SHAFER: You have great evidence in VIGOR though.

DR. VILLALBA: I completely agree but it was naproxen, and I think the presentation tomorrow with the epidemiologic data on naproxen will be very informative about how confused we are until today.

Regarding the signals, yes, those were observed but that was after VIGOR, not before. Again, we have that long-term, placebo-controlled

data in Alzheimer's patient elderly population that had shown no difference in myocardial infarctions or strokes. There was that signal of cardiovascular death that, by the way, was put in the label. But there were 8 versus 3 events and we didn't know what to make of that.

DR. KONSTAM: Hi, there. I am Marv Konstam. I am from Tufts University and I am here with Merck as a consultant. In 2001 I was first author on the overall pooled analysis for the entire rofecoxib database so I just think I want to speak to it, and the interpretation of VIGOR and where the company I think was, and the world was, at that point.

I think it is really difficult to look at individual studies with very, very small numbers and find signals, and one can draw all kinds of conclusions from them; and there may be signals in the other direction in some of the other small studies.

So, what was done at that time was, you know, there was a signal from the VIGOR study.

This finding was unexpected. It showed an adverse effect on cardiovascular endpoints. Now, one thing I want to stress about that is that of all of the information that could be brought to bear, I think the point estimate for the hazard ratio from that is probably the least important to me. You know, you are looking at very small numbers of events, unexpected finding, wide confidence intervals. So, I just want to point that out.

What was done at that point was that the entire rofecoxib database to that point was reviewed in a systematic way, and all of the data were pooled. They were divided, as you heard, between Naprosyn comparator, other NSAID comparator but, most importantly, the placebo comparator. Because VIGOR was an active controlled study and none of us to this day know exactly to what extent the result was contributed to by an adverse effect of rofecoxib, a favorable effect of Naprosyn or a combination. So, the most valuable data are the placebo-controlled data. And, reviewing all of the placebo-controlled data to that point, pooling all

of those data, there was 3000 patient-years of follow-up, there was not a hint of an adverse signal--not a hint of an adverse signal.

Now, granted, there were confidence intervals around that signal so that is real. We still didn't know, and I think we know a lot more today thanks to the APPROVe study, but at that point in time if you look at all of the placebo-controlled data that existed there was not a hint of a problem, which I think led me at that time and I think led others at that time to say this may be contributed to by a significant beneficial effect of Naprosyn.

DR. WOOD: Just let me make sure I understand. Are you saying that that is still your position?

DR. KONSTAM: No, no. That was the position at that time. One might then ask, okay, what is different between the APPROVe data, and I might say that I was on the data safety monitoring board for APPROVe, and why is APPROVe different than the pooled placebo-controlled at that time? I

think that is a really cogent question to ask and I have asked myself that question.

I believe the difference now, in retrospect, is exposure time. From APPROVe we see no evidence of a hazard in the thrombotic events through 18 months and then there is a separation. The median follow-up in that pooled analysis that I just referred to is relatively short. I don't know what it was exactly but it was months. It certainly wasn't the 9 months that was there in the VIGOR study or the 2.4 years in the APPROVe study. So, that is a substantial difference. There are other differences, but to me that may be the explanation for why the pooled analysis, back in 2001 and as it went forward, showed no problem but APPROVe then came and did show a problem. I think it probably was the exposure time.

DR. WOOD: But just to be absolutely clear, you are not saying that you still believe the VIGOR study was due to a totally protective effect of naproxen, are you?

DR. KONSTAM: No, no, I am not.

DR. WOOD: Good. I just wanted to be clear on that.

DR. SHAFER: While you are there, Dr.

Konstam, in terms of the relative risks of the two possible choices--either rofecoxib increases risk or Naprosyn decreases risk--was that part of your thinking as well? What are the possible outcomes of the two competing hypotheses? The truth is probably somewhere in between.

DR. KONSTAM: Well, first of all, let me just add one other point that I should have mentioned. The other point about the VIGOR study was the dose. So, there was a very high dose used in VIGOR and there were lower doses in the pooled analysis. APPROVe was 25 mg; an intermediate dose.

What was your question again? I am sorry.

DR. SHAFER: There are somewhat different potential concerns with the conclusion that rofecoxib increases risk as opposed to the conclusion that Naprosyn decreases risk. Was that part of your decision analysis at the time?

DR. KONSTAM: Yes, thinking back at that

time, there was no adverse signal from the placebo-controlled data. I don't think, you know, most people were completely satisfied with that. If you look back at what the company did at that point, first of all, there was a warning put on the label and we can argue whether that was good enough or not. But then we embarked on a large placebo-controlled program with a prespecified adjudication process for cardiovascular events, and that is the process that led to the definitive finding of APPROVe, even with a much smaller N than they were planning to do so they had a much larger program planned and we decided to stop APPROVe because we saw it in APPROVe.

DR. WOOD: Let's go on. Dr. Nissen?

DR. DOMANSKI: We have heard a lot of discussion about who know what, when, and we have seen a tremendous amount of data presented, and in the end this committee is going to have to make some recommendation about what to do going forward. I am very interested, if we could, in hearing from each of the pharmaceutical manufacturers, as well

as everybody else of course, before they sort of go away into the distance. I am very interested, given the totality of data that are currently available--not what you knew when or who should have known what, how or when or who should have done something else--I am very interested in what you think ought to be done now going forward, knowing what we know. What recommendation would you make? What would you like to see come out of this? Or, maybe what do you think we should see come out of this?

DR. WOOD: Dr. Nissen?

DR. NISSEN: Yes, a quick comment and a question. The comment is--and I think for people in the audience who may not fully understand why we are drilling down on this intent-to-treat aspect of the analysis--that it may be that the individuals who are dropping out of these trials because of adverse events, that received the COX-2 inhibitor, they may be pharmacogenomically more susceptible to the adverse effects of COX-2 inhibitors. So, you are taking out of the trial the people that are at

greatest risk. If you don't follow those people you may not find that out.

This idea of censoring events after two weeks--you know, I think we have to all learn something from what happened here, and this is the first time I really realized that that was the way these studies were conducted. That was a mistake. Once a patient is exposed to drug you ought to follow him as long as you can because there may be a persistence of risk and we learn something from that. So, a lesson is learned. I think it is a useful lesson to learn.

I guess the second question--and, you know, you may or may not want to answer this but if you had to do it all over again would you do it differently?

DR. WOOD: Let's keep the tense in the future tense. Let's not keep regurgitating that. Bob, do you want to say something in the future tense?

DR. TEMPLE: Yes. I just want to remind people that intent-to-treat analyses are generally

loved by people because they are conservative analyses. They ten to make effects go away. That is why we like them. If you are worried about informative censoring and other stuff like that--

DR. WOOD: But it tends to make efficacy effects go away.

DR. TEMPLE: That is correct. They also make time effects go away.

DR. WOOD: Not if you are dead.

(Laughter)

DR. TEMPLE: No, no, you have to count the deaths. It is not that you shouldn't follow people up but the analysis that includes all people long after they are off the drug has a very high likelihood, I believe, or not showing the effect of the drug. You have to remember it is a conservative analysis for looking for effects. Before we get too enthusiastic about it, if I make the effect look less when it really doesn't deserve to look less--

DR. FLEMING: Could I just quickly add to that? Historically we look at safety and often we

do truncate follow-up after two weeks or a month. That is based on the premise that safety risks are acute. If they are, in fact, acute, then you are going to get a clear sense of what is going on with the type of approach you are talking about. Mortality effects, I would think, are much more difficult to justify as being purely acute. There is a basis to what you are saying. If you follow everybody for a long time after they are off therapy there could be some diluting. Nevertheless, if you want an unbiased assessment of the truth you need to do what Steve is talking about, an ITT analysis, and then make your judgment as you look at the hazard ratio over time.

DR. D'AGOSTINO: We are sitting here and we don't know the answer. It may have washed it away and it may not have.

DR. TEMPLE: I am not saying don't get the analysis but, for example, our ordinary position in an outcome study is that we want to see the intent-to-treat analysis.

DR. WOOD: Let's hold this for the

discussion. Let's just keep focused on the questions right now. Any further questions for the speaker? I am not forgetting about you. Hang on just a moment. Dr. Holmboe?

DR. HOLMBOE: I just had a question to the speaker. Again, we are trying to give you some advice and some guidance as to this. Given, as Alastair said earlier, that this drug was really evolved for a safety indication, therefore, being compared to another class of drugs, in retrospect learning that those comparisons were based on drugs approved prior to new knowledge that has been accumulated, such as presented by Dr. FitzGerald, it would be helpful for me to hear what has the FDA learned about the process or form? What can you tell us that might help in the future when you are faced with these sorts of things? For example, the diclofenac is a perfect example, well, it turns out that maybe it is not, you know, your run-of-the-mill NSAID. A lot of what you presented in the original data was, like, well, it was between ibuprofen and diclofenac, therefore, we

determined it was probably okay. So, I would be anxious to hear what you have learned since you have been with this project now for seven years.

DR. VILLALBA: Well, actually we wanted to have the recommendation from you to know how to proceed now because we have close to 20 approved NSAIDs so what do we do with them?

DR. WOOD: Ever the optimist, right! Dr. Domanski?

DR. DOMANSKI: I guess before Merck gets away I would still like to hear their view of where we should go from here. I am really quite curious about that. I understand about intention-to-treat. We do clinical trials. But I would just like to hear what their thoughts are.

DR. WOOD: Their thoughts on what?

DR. DOMANSKI: What their thoughts are on where we should go from here.

DR. WOOD: I thought we were talking about where we have been. I am happy to hear them on where they should go. Do you have thoughts on that, Bob?

DR. DOMANSKI: No, I am asking that of Merck.

DR. WOOD: Oh, I am sorry.

DR. BRAUNSTEIN: I think we showed that on our last slide. Can I see our last slide, 57? I mean, for the short term what we are trying to do is trying to better understand our data; trying to better understand which patients were at increased risk for the events that we observed in APPROVe based on both the clinical data and also the specimens that we have from these patients. We also are working with various people to try and explore different hypotheses for the data, and we are collaborating with others who are looking at the data across all the drugs in order to get a better feel to see if we can understand when we pool all the data because I don't think any one data set that we have is powerful enough to address these questions. So, hopefully, by pooling the data we will be able to get a better feel for this. The last is that we think we need to do comparative outcome studies to better understand the relative

risks of the selective COX-2 agents with the traditional NSAIDs. There are not long-term data on the traditional NSAIDs to really establish what their cardiovascular risk profile is, and we think that the study that we are doing, for example the MEDAL study is one such study in the right direction.

DR. WOOD: Merck wanted to present some other data. Right?

DR. REICIN: I think there was a question about congestive heart failure in the Alzheimer studies.

DR. WOOD: Right.

DR. REICIN: So, just put up slide for us 12-22 and then we will go to 12-28. I showed you this slide just at the beginning and you noted that in our 6-month population--so this is a shorter population than either APPROVe or what I am going to show you in Alzheimer's--the rates were quite low and they were similar to the NSAIDs.

If you go now to 12-28, in the Alzheimer's studies, in protocol 078 which was a 4-year study,

interestingly, the rate of congestive heart failure was similar between the two groups, 2.2 percent on rofecoxib 25 mg, 2.6 percent on placebo. In 091, however, which was a one-year study the rate was a little bit higher on rofecoxib, 3.2 percent versus 1.4 percent. I think these rates are more what you would expect in an elderly population. The mean age of this patient population was 75 years old.

DR. WOOD: Thanks.

DR. REICIN: One other thing, there was a question about ITT mortality. In APPROVe we are following patients in an ITT way for mortality. That is still ongoing. To date, there were 3 thrombotic events in each treatment group following that 14-day period.

DR. WOOD: Dr. Paganini?

DR. PAGANINI: I have a question on the comparative data with other NSAIDs. Is there not a post-approval period of time for drug review, and from that post-approval Phase IV type studies can you not draw anything from that to compare to?

DR. VILLALBA: Phase IV commitments are

made at the time of approval. If there were not specific agreements between the FDA and the company to conduct those studies we have no legal power to mandate any kind of studies. So, some studies are done basically pursuing different--I mean with promotional, advertisement or whatever there are many studies. But those are really not usually large outcome studies. They are short studies with small numbers of patients. I don't know if I answered your question.

DR. PAGANINI: You did in a way. One of the issues that I think we are going to have to face is how do you compare these things, both things that have already been approved and new, to the same standards when they were approved back then to current standards? Perhaps one of the ways around that might be an approval comparison with longer Phase IV commitments by companies to follow-up on what is happening to that drug over time. That way, you would have the ability to compare a new to a similar in a similar population of patients.

DR. VILLALBA: Absolutely. That is something that we learned, yes.

DR. WOOD: Ralph?

DR. D'AGOSTINO: I am all for torturing data and during Lent I always read Dante's "Inferno."

(Laughter)

But shouldn't we be impressed with the APPROVe study? You leave us with a table that compares a lot of studies and you throw out some obviously important questions, but shouldn't we sort of look very seriously at the APPROVe study? It was well designed--

DR. VILLALBA: Of course.

DR. D'AGOSTINO: --and shouldn't we sort of diminish in our view some of the previous studies?

DR. VILLALBA: The Alzheimer's studies, do you mean? Now, yes. What I was saying is that these are different populations and I do not have a good explanation for why we didn't see the same in an elderly population.

DR. D'AGOSTINO: Well, could it be that the APPROVe study was going after a particular set of outcomes and the others weren't, and it was more retrospective?

DR. VILLALBA: No, because in the Alzheimer's studies they also used the same

standard operating procedures to adjudicate the event.

DR. D'AGOSTINO: But do they have the same ascertainment? You know, in designing a placebo-controlled study where you go after something retrospectively, looking at that and trying to say the ascertainment might have been the same.

DR. VILLALBA: You are completely right. That is possible but that is a question to the sponsor, if the ascertainment could have been different in the Alzheimer's studies.

DR. WOOD: Dr. Hennekens? Actually, I would like to ask Marvin a question. Marvin, the APPROVe study was scheduled to terminate at about 6 weeks after the early termination on the basis of

the board's recommendation that you were on. As I recall, the numbers of events were 45 and 25 at that time. So, was the board unanimous in its decision to terminate, and was the basis clearly related to that particular endpoint?

DR. KONSTAM: Yes. Yes, that is exactly right. I would say that the reason, if I might say why we recommended termination--the reason we recommended termination is that we felt at that point in time that we had a definitive piece of information that wasn't going to change. The reason we recommended termination was that we felt the patients in the APPROVe study were not aware of this and had not been consented to this adverse effect. So, in our judgment, you know, from an ethical viewpoint if you were going to continue you would have to go back and re-consent them and that certainly wasn't practical at that point in time. So, that is the specific reason we recommended termination.

DR. WOOD: But you told them that caution should be exercised in patients with heart failure.

Right?

DR. VILLALBA: May I say something?

DR. WOOD: Sure.

DR. VILLALBA: I don't want to leave you with the impression that we think or I think that APPROVe is not important. I just want to show you how puzzled we were with all the data. So, until APPROVe we didn't have a firm reason to really take a regulatory action that was different from what we had done up to that time.

DR. WOOD: Ralph again?

DR. D'AGOSTINO: In terms of the Alzheimer's study, do you have information on the all-cause mortality? I forget what you said. Do you have anything about CVD, cardiovascular mortality when off drugs?

DR. WOOD: Let's take that under advisement unless you have it right there. Do you? No? All right, we will get back to that. Any other questions? Yes?

DR. TEMPLE: Actually, I wanted to respond to Ralph. The thing about APPROVe is that it was

longer than the rest of the studies and most of the effects were seen sort of late. So, it provided the kind of information that really didn't exist before.

DR. D'AGOSTINO: When we come to the discussion of designing the trial, there is so much emphasis on how many events we should have and I am always bothered by that because I would like to make sure people have taken the drug for a long enough time. I think this is a case where you are seeing where length is where something is happening.

DR. WOOD: Unless there are any other questions, let's stop our discussion of Vioxx at this point, rofecoxib, and take a ten-minute break. We will reconvene and start on celecoxib when we get back.

(Brief recess)

DR. WOOD: If you will get to your seats we can get started, otherwise we will be here half the night. Just go ahead.

Sponsor Presentation: Celebrex (Celecoxib)

DR. FECZKO: Dr. Wood, thank you. I will keep these introductory remarks brief, briefer than I was planning. I will just introduce our

presentation today. I am Dr. Joseph Feczko. I am President of Worldwide Development at Pfizer. I would like to thank the Food and Drug Administration and the advisory committee for this opportunity for Pfizer to share their data that demonstrates the cardiovascular safety profiles of our COX-2 inhibitors, Celebres and Bextra, especially in comparison to the non-selective NSAIDs.

For Celebrex questions arose recently from the preliminary data from a longer-term study, the APC trial sponsored by the National Cancer Institute. A cancer prevention trial would suggest an increase in cardiovascular risk compared to placebo for patients taking Celebrex at daily doses of 400 mg and 800 mg per day. The important findings must, and will, be put in context and evaluated with the large body of prior data on Celebrex.

Celebrex has been extensively studied both by Pfizer and by independent investigators in randomized, controlled clinical trials and epidemiologic studies. With all this research, we continue to investigate GI toleration in arthritis patients and the ability to treat rare form of

precancerous polyps, familial adenomatous polyps, for which we have an indication.

We also are continuing to study Celebrex in cancer prevention, and we have a large number of trials in cancer treatment where Celebrex is added to conventional chemotherapy for a variety of cancers.

In a moment Dr. Kenneth Verburg will outline for you several bodies of data. One, he will review the cumulative safety tolerability data for Celebrex. Two, he will review the results of a new meta-analysis of Pfizer's database, one of the largest analyses of its kind conducted to date. This includes extensive information looking at Celebrex in comparison to other widely prescribed non-selective NSAIDs. Third, Dr. Verburg will also

present results of multiple published epidemiological studies which show a consistent lack of the cardiovascular signal for Celebrex when used in the real-world setting in arthritis patients.

Throughout the presentation we will also look at this issue of whether or not there are differences or similarities in a class of COX-2 compounds or across the non-selective NSAIDs. I think we all know that within a class of compounds there are still opportunities for individual variation of individual drugs. We see that frequently, especially when we look at severity, incidence or frequency of uncommon or common side effects. So, we hope to bring this out within our presentation.

With no further ado, I will turn this over to Dr. Kenneth Verburg and we will be happy to delve into any other questions that you have at the end of his presentation.

Cardiovascular Safety and

the Risk/Benefit Assessment of Celecoxib

DR. VERBURG: Thank you, Dr. Feczko. Good afternoon, everyone. Again, my name is Ken Verburg. I lead the clinical research and

development programs in arthritis and related conditions for Pfizer. In this respect, I have been studying celecoxib, valdecoxib and parecoxib for nearly eight years now.

My presentation over the next 40 minutes or so is focused to the cardiovascular safety of celecoxib and a risk/benefit assessment of this compound. I am joined here today by several of my Pfizer colleagues, as well as external experts in the field of cardiology, gastroenterology, rheumatology, epidemiology and other disciplines as listed on this slide. I will not spend the time to read each of the individually but they are here to contribute to the discussion afterwards.

So, what is Pfizer's position with respect to the cardiovascular safety of celecoxib and the risk/benefit of this compound? Our position is perhaps best summed on this slide in terms of conclusions. First, there are few therapeutic

alternatives for patients with chronic arthritis pain. Patients who discontinue celecoxib then will likely turn to NSAIDs for treatment.

In our view, celecoxib is an effective and safe therapy for arthritis patients, and we base that on the following conclusions: First, celecoxib provides improved GI safety compared to NSAIDs. Secondly, all lines of evidence show that the cardiovascular safety of celecoxib is similar to NSAIDs for up to one year.

The caveat on this is that beyond one year little is known for any of these agents, and evidence for coxib versus NSAID class effect on cardiovascular safety is not established. Thirdly, rofecoxib appears to be distinct celecoxib and NSAIDs with respect to cardiovascular safety. Finally, only further study of NSAIDs and coxibs would define the longer-term cardiovascular risks against the known risks of GI ulcer complications.

I want to begin my discussion by going back and framing it in terms of the patients who require these therapies. In 2002, it was estimated

that 1/3 adults suffer from arthritis or other related joint conditions, and that is an estimated 70 million individuals. Of these, about 7 million have significant impact on their daily activities.

Here are shown some data from the Centers for Disease Control, indicating that arthritis and other related conditions, joint conditions, results in significant functional impairment as compared to other diseases. About 39 million physician visits per year occur with arthritis patients and there are more than 500,000 hospitalizations due to arthritis each year.

NSAIDs are an important treatment option for arthritis patients. The American College of Rheumatology and other professional societies have indicated that first-line therapy is acetaminophen. That is perhaps an appropriate choice. But acetaminophen in many patients with moderate to severe forms of the disease does not provide adequate control of pain and other symptoms.

The data on this slide are from a double-blind, randomized, cross-over study in which

one group of patients was randomized to receive first acetaminophen therapy for 6 weeks, followed by a washout period, and then to receive diclofenac in combination with a gastroprotective agent, misoprostol. In comparison, the second group was randomized first to receive a diclofenac-misoprostol combination, then following a washout period, was to receive acetaminophen for the subsequent 6 weeks.

Very quickly, the point that I want to make on this slide is that diclofenac offers significant improvements in terms of the Womack Target Joint Score, which is a composite score of pain, joint stiffness and physical function, as compared to acetaminophen at a total daily dose of 4000 mg, so a full dose of acetaminophen.

We have known for over two decades now that the efficacy of NSAIDs comes at a cost, and that cost is the risk of upper GI ulcer complications, that is, ulcers causing GI bleeding, perforation or leading to gastric outlet obstruction.

Largely, this risk was identified and characterized by pharmacoepidemiology studies. One such study is shown on this slide. Here we are

showing the absolute incidence in terms of events per 1000 patient-years, the incidence of hospitalizations for GI bleeding or for perforations. Current users of NSAIDs are shown in the yellow line, subdivided by men and women, and they are compared to non-users of NSAIDs, shown in the white line.

What is readily apparent is that the absolute risk of hospitalization for GI bleeding or perforations increases substantially as a function of age. However, for each 5-year interval of age we see that NSAIDs increase the risk over non-users by approximately 4- to 6-fold. Of course, arthritis patients lie over to the far right-hand portion of this curve. This is the same population that is often characterized by cardiovascular risk factors or underlying cardiovascular disease.

Well, the discovery of the consistent enzyme and the characterization of the resulting

biology around this enzyme led to the hypothesis, in 1992, that inhibition of COX-2 selectively would offer efficacy in the disease targets of arthritis and pain while obviating the side effects associated with the inhibition of COX-1.

Indeed, the discovery of celecoxib and the subsequent clinical development program supported that hypothesis. Here we show data from a trial of over 1000 rheumatoid arthritis patients in which efficacy was evidenced at 100 mg, 200 mg and 400 mg twice daily of celecoxib. What we see relative to placebo is that all of these doses provided significant efficacy in terms of the ACR-20 Responder Index. This efficacy was comparable to that observed with naproxen at a full therapeutic dose of 500 mg twice daily. The treatment period was 12 weeks in duration.

So, if we focus now on the right-hand panel of the slide, we are looking at the incidence over 12 weeks of endoscopic ulcers. What we see is that celecoxib at full therapeutic doses and a super-therapeutic dose was associated with similar

incidences of endoscopic ulcers as compared to placebo treatment. This is in contrast to the naproxen treatment group which had an incidence rate of 25 percent and was significantly different than all other treatment groups. Thus, 1/4 patients treated in this trial over 12 weeks with naproxen was found to have an endoscopic ulcer.

This is data from a meta-analysis that will be published this month. This meta-analysis was based on 31 arthritis randomized controlled trials of Celebrex and included over 39,000 patients with osteoarthritis and rheumatoid arthritis, with a mean exposure of 7 months. The GI safety benefit is split into 3 different looks. The first is symptomatic ulcers and GI bleeding. The second is clinically significant blood loss, defined as reductions in hemoglobin of 2 gm/dL or more. Then also we focused on withdrawal due to GI intolerance.

As compared to NSAIDs, which are comprised basically here of naproxen, ibuprofen and diclofenac, we see that the relative risk for any

of these events favors celecoxib, significantly so. This occurs at both the therapeutic doses of 200-400 mg or at any dose of celecoxib.

The data from the randomized, controlled trials has been further substantiated by observational epidemiology studies, and I will show data from two of these studies.

the first study that was published in 2002 evaluated the risk of hospitalization for upper GI bleeding with celecoxib, rofecoxib, the combination of diclofenac and misoprostol and NSAIDs. The point estimate of relative risk for the NSAID treatment group as compared to the non-users was 4. That relative risk agrees very well with a large body of literature evaluating NSAIDs in the epidemiology or observational setting. Celecoxib was similar to non-users in terms of the relative risk of hospitalization for upper GI bleeding.

The data from the first study was basically confirmed in the second study. In this case, the risk of hospitalization for GI bleeding was evaluated in patients with prior

gastrointestinal disease who would be at high risk for subsequent GI ulceration.

Again focusing your attention over here, to the right, NSAIDs were associated with a relative risk of hospitalization for upper GI bleeding of a little over 3, significantly different from non-users. Celecoxib users had a similar risk of hospitalization as compared to non-users.

To sum then our conclusions regarding the safety benefit of celecoxib are stated as follows: The medical need for improved GI safety is fulfilled standard celecoxib. This is based on evidence from randomized, controlled trials in which celecoxib has a favorable GI safety profile versus NSAIDs, and also from emerging data from epidemiology studies which indicates that celecoxib is associated with a lower risk of hospitalization due to GI bleeding than non-selective NSAIDs.

So, the results that I just reviewed basically supported the fundamental hypothesis put forward in 1992 regarding selective COX-2

inhibitors. What emerged at the same time, however, was a concern over cardiovascular safety, and the first clinical evidence for an increased cardiovascular risk with a selective COX-2 inhibitor was observed with rofecoxib 50 mg once daily versus naproxen in the VIGOR trial.

At the same time, however, data emerged from the CLASS trial with celecoxib at 400 mg twice daily, 2-4 times the full therapeutic dose, demonstrating that the cardiovascular safety profile of celecoxib was no different than the NSAIDs diclofenac and ibuprofen combined introduction he CLASS trial.

For the remainder of my presentation this afternoon, what I would like to do is focus on cardiovascular safety using the following organization, and then conclude with some comments on risk/benefit.

So, let's begin with the longer-term studies evaluating celecoxib and its cardiovascular safety profile versus placebo treatment. Although we have been through this several times already, it

stands to reason that we should spend a moment to define some of the fundamentals of the cardiovascular event definitions as we go through them.

So first, as we have heard already today, the APTC endpoint is a well-recognized endpoint with respect to the evaluation of cardiovascular therapeutics. It is comprised of non-fatal myocardial infarctions, non-fatal strokes or vascular deaths, as outlined on the slide.

The meta-analysis results that I will provide or review shortly have a similar construct to the APTC but they are based on investigator reports of serious adverse events to the company. In other words, there was not a process of adjudication and, of course, unlike cardiovascular endpoint trials, there were no definitions a priori about what a cardiovascular event would or would not be in order categorized appropriately.

Finally, we need to recognize that epidemiology studies rely on hospitalization for acute MI alone as their endpoint or in combination

with coronary death predominantly.

So in collaboration with the National Cancer Institute, Pfizer and the NCI initiated two three-year placebo-controlled trials, beginning in 1999 or so, evaluating the effect of celecoxib on the prevention of sporadic adenomas. These trials are known as the APC and the PreSAP trials. The hypothesis being tested in these trials was that celecoxib would reduce polyp recurrence by greater than 35 percent in a high risk cohort, that is, patients who had a history of a prior adenoma.

Importantly, the setting allowed for the first longer-term comparison of celecoxib versus placebo. Trials of similar duration would be very difficult, if not impossible, to do in an arthritis population. Also, celecoxib was an obvious agent of choice here based on the emerging data demonstrating that it had superior GI safety to non-selective NSAIDs.

Dr. Ernie Hawk and Dr. Bernard Levin will review the results of these studies separately and go through them in some detail later this

afternoon. To sum the results though, there was a significant cardiovascular risk associated with celecoxib in the APC trial and no such risk was observed with celecoxib in the PreSAP trial.

As we go through the studies and the data sets, it is useful and perhaps instructive to keep a score card of some of the study descriptions, as well as the patient populations because, as we have heard, none of these trials a priori were conducted to evaluate cardiovascular safety. That was not their primary objective. Thus, the types of patients, the durations entered into these trials can vary substantially.

So, beginning with the APC and PreSAP trial, you can see that over 1500 patients were enrolled in each of these trials. At the time study drug administration was discontinued there was about 2.5 years of exposure. And, the number of cardiovascular events, and these are APTC events, was 41 in the APC trial and 31 in the PreSAP trial. The mean age was about 60 and these patients were characterized by a fairly significant

degree of underlying cardiovascular risk factors or cardiovascular disease. What is interesting is that there seems to be a little bit of a difference in the use of concomitant aspirin between the two trials, nearly twice as great in the APC trial as in the PreSAP trial.

Next, turning to a brief description of the Alzheimer's disease anti-inflammatory prevention trial, known as the ADAPT trial, this was a randomized, controlled trial. First of all, this trial was conducted and sponsored by the NIH. Pfizer's role in this study was to provide blinded study medication in the form of placebo and celecoxib only.

This was a randomized, controlled trial evaluating celecoxib at 200 mg twice daily or naproxen at the over-the-counter dose of 220 mg twice daily versus placebo treatment. Elderly patients were enrolled in the trial, all greater than 70 years of age, who were at risk for Alzheimer's disease, that is, they had a first-degree relative with the disease.

Except for uncontrolled hypertension, there were not other restrictions for cardiovascular disease in order for patients to be

eligible for the trial. The hypothesis being tested was that celecoxib would reduce the incidence of Alzheimer's disease by over 30 percent in a high risk cohort.

So, this represents the first longer-term placebo-controlled experience with a non-selective NSAID. Most of the results have not yet been disclosed into the public domain. What we do know though from the investigators is that naproxen was associated with a significant increase in all cardiovascular events, as well as all cerebrovascular events, versus placebo and no such effect was seen with celecoxib.

We also know from this trial, again in terms of preliminary information, that naproxen was associated with a significantly elevated increase of upper GI bleeding as compared to placebo treatment and, again, no significant difference was seen in celecoxib users.

Returning to our score card, in the ADAPT trial near 2500 patients were enrolled. The mean exposure at the time the trial was stopped was about 1.6 years per patient. The number of events reported and in the public domain appear to be about 70. Those are probably APTC endpoints-plus

some. And, we know nothing about the underlying patient population at this point.

So, the conclusions that we can draw from the information so far, and as the week unfolds we will see if these conclusions hold, are as follows: In the APC trial celecoxib was associated with a cardiovascular risk as compared to placebo after approximately one year of continuous administration.

In the companion PreSAP trial no differences were observed with continuous treatment of celecoxib for up to 3 years of exposure.

In the ADAPT trial naproxen showed a cardiovascular risk compared to placebo over an exposure period of about 1.5 years, and this was in contrast to the findings with celecoxib.

When you distill this information down even at this point it is obvious that celecoxib requires further study to estimate the longer-term cardiovascular risk. An NSAID comparator in such a trial would be critical in our view.

Next let's turn to a comparison of celecoxib predominantly versus NSAIDs, and we will use a meta-analysis of the randomized controlled trials to do so. So, 41 completed randomized

controlled trials and a total of over 44,000 treated patients were included in this meta-analysis. They were predominantly patients with osteoarthritis or rheumatoid arthritis. There was a small minority of patients with chronic low back pain, ankylosing spondylitis or Alzheimer's disease.

Of these patients, nearly 25,000 received celecoxib; 4000 receiving placebo; and over 15,000 patients were treated with an active comparator. We evaluated all doses of celecoxib, ranging from 50 mg to 800 mg daily. The primary NSAIDs in this comparison were naproxen, ibuprofen and diclofenac.

The study durations ranged from 2 weeks to 1 year.

In terms of the comparisons to NSAIDs, the celecoxib exposure is shown down here, in the yellow box. Of the patients in the meta-analysis treated with celecoxib, 55 percent were treated for 3 months or longer; 12 percent were treated for 9 months or longer; and 4 percent, a total of 803 patients, were treated for 1 year or longer.

I too will review the results using the APTC-like construct, first reporting a composite endpoint of any cardiovascular death, non-fatal MI or non-fatal stroke, and then I will report the results of each of these components individually.

Back to our score card one more time, here now we are comparing and juxtaposing the study descriptions and the patient populations for the meta-analysis in comparison to the longer-term trials. So, we see that the number of patients is increased substantially in the comparisons of celecoxib to placebo or NSAIDs. We also take note of the fact that the mean exposure is much less, being on the order of only 6 weeks in the

comparison of celecoxib to placebo, and on the order of about 3.5 months for celecoxib compared to the NSAIDs.

The number of events is fairly similar from placebo across to the other settings, about 2-3 time the number of events in the comparison of NSAID to celecoxib, meaning that each was approximately the same as the polyp prevention trials. And, there was a significant degree of underlying cardiovascular risk in this population but perhaps less so than in the polyp prevention trials.

So, first the results of the meta-analysis comparing celecoxib versus NSAIDs are shown on this slide. Here we are reporting the absolute number of events that occurred in each treatment group, and then the event rate in parentheses as events per 100 patient-years. What we have done here is we have taken all doses of celecoxib, 200 mg or greater, and combined them. So, we are looking at full therapeutic doses of celecoxib and super-therapeutic doses of celecoxib. In essence,

this is 200 mg, 400 mg and 800 mg daily.

What we see here is that in terms of the composite event rate of cardiovascular death, non-fatal MI or non-fatal stroke there are no apparent differences between the two treatment groups, and that is generally true for cardiovascular death. There is an apparent increase in the event rate in terms of non-fatal MI in the celecoxib treatment group and a reduction in non-fatal stroke in the celecoxib treatment group when compared to the NSAID group.

If we evaluate the data in terms of the relative risk and 95 percent confidence intervals, the following results are evident: First, the relative risk for the composite endpoint is slightly below 1 favoring celecoxib, as was cardiovascular death and as was stroke. Non-fatal MI was slightly above 1 favoring NSAIDs. However, in all cases the 95 percent confidence interval for this comparison did not exclude 1 with the exception of non-fatal stroke in which the relative risk was nearly 3 times lower than in NSAID users.

If we now break this down a little bit further and evaluate the risk of celecoxib versus the NSAIDs that comprise the predominant exposure

in the aggregate NSAID treatment group, i.e., naproxen, diclofenac and ibuprofen, we see no real pattern of difference in the comparison of celecoxib to these three drugs individually.

As a point of reference, I am also putting on this slide the comparison of celecoxib to placebo and you can see that the relative risk was 1.26 favoring placebo but not significantly different.

Next, if we subdivide the celecoxib 200 mg or greater treatment group into its component doses, again using the composite endpoint of cardiovascular death, non-fatal MI or stroke as the endpoint of interest here, we see no obvious dose-response relationship in the relative risk of celecoxib as compared to the NSAIDs.

Two of the trials in the meta-analysis included patients with substantial exposure to celecoxib. Those trials were the CAESAR trial and

the CLASS trial. The CAESAR trial was a trial of a little over 800 patients with osteoarthritis who were treated with either celecoxib or diclofenac for a period of one year. The CLASS trial was a trial of nearly 8000 patients, with a median duration of exposure with respect to celecoxib of 9 months and 15 percent of patients treated with celecoxib were treated for one year or more.

Here we are showing the time to event analysis comparing celecoxib in these two trials and at doses ranging from 200 mg to 400 mg per day versus the NSAIDs used in the two trials, which were diclofenac and ibuprofen. We see no difference in the APTC composite endpoint between the two treatment groups through the exposure period.

So, our conclusions from the randomized, controlled trials are as follows: There is no association for increased cardiovascular risk detected with the use of celecoxib up to one year compared to the NSAIDs combined and also compared to naproxen, diclofenac or ibuprofen individually.

And, a dose-related increase in cardiovascular risk with celecoxib was not apparent.

Next let's turn to a consideration of risk factors. We will stay within the construct of the meta-analysis. About 33,000 patients or so were available for this analysis with respect to cardiovascular risk factors and, again here we are going to be comparing celecoxib to the NSAIDs. The risk factors were based on either a history of hypertension, diabetes or hyperlipidemia or coronary heart disease as evidenced by a previous MI, a history of angina or other significant ischemia or revascularization procedure.

So, the patients with none of these risk factors are shown in the white bar; with one risk factor only are shown in the yellow bar; and with two or more risk factors are shown in the orange bar. Again, what we are showing is the absolute event rate in terms of events per 100 patient-years for celecoxib users over on the left, NSAID users over on the right, and here we show a breakdown by the composite endpoint and each of the components

of the endpoint. What catches your eye is that as the patients are characterized with greater risk factors, the absolute event rates increase in both treatment groups.

Did they increase proportionally? This is the relative risk now comparing celecoxib versus NSAIDs by cardiovascular risk factors. So, no risk factors here; one risk factor; greater than two risk factors over to the far right. First a quick inspection across all three risk strata suggest that there were no significant differences in the relative risk between celecoxib and the NSAIDs, with the exception of non-fatal stroke in patients with no cardiovascular risk factors.

The second point I would like to make on this slide is that if you scan across to evaluate whether there were any patterns that were occurring that were altering the relative risk between the two treatment groups as a function of risk factors, that is not readily apparent when evaluating either the composite, cardiovascular death or MI. There is a trend for favorable comparison with stroke to

become less favorable with additional risk factors, but I want to caution that this particular point estimate is based on a total of only 6 non-fatal strokes. So, as the confidence interval suggests, there is wide uncertainty around that point estimate.

If we use low dose aspirin as an indicator now for underlying cardiovascular disease, this slide shows the comparison of the relative risk for celecoxib versus NSAIDs again in the construct that we have shown before, and showing the relative risk in a non-aspirin cohort over here, on the left and the aspirin cohort, over here, on the right. Again, this is about 10-12 percent to the total population. Here we see that there are no significant differences in any of the endpoints of interest, with the exception of non-fatal stroke favoring celecoxib this time in the aspirin cohort. There is a noticeable change in the relative risk of cardiovascular death from the non-aspirin cohort to the aspirin cohort. But this again is shaped by very few events, as evidenced by the wide

confidence intervals around the point estimate.

Next, if we return to the CLASS trial and evaluate the composite APTC endpoint by aspirin or non-aspirin use in terms of a time to event analysis, we see nonsignificant differences in the two time to event curves by log rank test in either the non-aspirin cohort or in the aspirin cohort. Approximately 22 percent of the patients in the CLASS trial were taking low dose aspirin.

So, our conclusions concerning risk factors are as follows: The cardiovascular safety profile of celecoxib remains comparable to NSAIDs regardless of cardiovascular risk factors as determined by medical history or use of low dose aspirin.

Next turning to epidemiology studies, 7 epidemiology studies have now been completed and reported as full-length publications in peer-reviewed journals, and have evaluated cardiovascular risk of celecoxib.

Returning to the concept of the score card but this time just evaluating the epidemiology

studies in isolation, if you aggregate the studies together there was a total of over 30,000 myocardial infarctions in the studies for all treatment groups and over 1000 MIs in patients taking celecoxib. Both in terms of the number of events and in person-years, you can see that in terms of the total as well as for celecoxib users, these numbers are substantial in comparison to randomized, controlled trials.

I am going to review these studies individually very quickly, starting here with the study of Ray et al., published in 2002, in this study celecoxib at doses less than 300 mg daily or 300 mg or greater daily had a similar relative risk of hospitalization due to myocardial infarction or coronary death as compared to non-users. These results were very similar to the relative risk seen with ibuprofen and naproxen. In contrast, we see that the relative risk associated with doses of rofecoxib greater than 25 mg were significantly different than non-users.

The second study, published in 2003,

showed that there was basically no difference between celecoxib, rofecoxib, naproxen or any of the other NSAIDs in terms of the relative risk of hospitalization for MI as compared to non-users.

In a third study, conducted by Solomon and co-workers at Harvard, found that celecoxib at all doses combined or subdivided into low and high doses was associated with a relative risk for hospitalization for myocardial infarction no different than non-users. In contrast, in this study as in the first study, rofecoxib at doses of 25 mg or greater was associated with a relative risk of 1,58, significantly different from non-users.

Next we turn to the study published by Kimmel and co-workers earlier this year. In this particular observational study celecoxib was associated with a significantly protective effect with respect to the relative risk of myocardial infarction, as were all NSAIDs combine. Rofecoxib was associated with no such effect when compared to non-users.

Next we turn to perhaps the largest study conducted and published thus far. Here again we see, as in the previous trials that celecoxib was

associated with a relative risk of myocardial infarction or coronary death, this time to remote use of NSAIDs, that is no different in terms of remote use. In contrast, here again we see that the relative risk associated with high doses of rofecoxib were significantly elevated. In terms of the NSAIDs, the point estimates of relative risk ranged from 1.06 for ibuprofen to 1.60 for diclofenac. None of those point estimates were different from remote users.

Next, turning to the results of Shaya at al., these investigators used an APTC-like endpoint in their observational trial. They found that celecoxib alone, rofecoxib alone or the coxibs combined were similar in terms of adjusted odds ratio to non-naproxen NSAIDs in their study.

Finally, the publication of Levesque et al. reports the following, they show that celecoxib, subdivided into low and high doses, was

no similar to non-users in terms of the relative risk of MI. Here again we find the observation that rofecoxib at doses of 25 mg or greater was associated with a significantly elevated risk, and the NSAIDs were generally also similar to non-users.

These investigators also subdivided the evaluations of the compounds into non-aspirin users and aspirin users. We see that either in the non-aspirin cohort or the aspirin cohort the relative risk of celecoxib is similar to non-users. We find a significantly elevated risk in patients taking rofecoxib at doses of 25 mg or greater.

Trying now to sum all the previous observations into one trial, the results are shown here. They are subdivided by low doses and high doses of celecoxib and rofecoxib. We see that celecoxib at either low doses or high doses is similar to non-use with respect to risk of MI. In contrast, rofecoxib at high doses is systematically associated with an elevated relative risk of MI as compared to non-users.

So, our conclusions from that rapid review of epidemiology studies are that the risk of myocardial infarction with celecoxib as used in the

real-world population, that is at the doses that patients actually take and the duration for which they actually take them, is consistently similar to non-selective NSAIDs in non- or remote use of NSAIDs. These findings are in contrast to the increased risk associated with rofecoxib. The available data suggests that the risk of MI is similar for low and high doses of celecoxib.

So, turning now to a consideration of the topic of mechanism, a unifying hypothesis that would attribute cardiovascular risk to the coxib class only conceivably could explain the VIGOR results, the APPROVe results with rofecoxib and the APC results with celecoxib. But it couldn't explain the consistent comparability between celecoxib and the NSAIDs as viewed in the meta-analysis or versus non-use in the epidemiology studies, and could not explain the lack of effect of celecoxib in the PreSAP trial or other results

in the ADAPT trial where the non-selective naproxen was associated with increased cardiovascular risk, unlike celecoxib.

So, if we try to sum up all of the clinical observations to date, it would appear that the absolute cardiovascular risk associated with coxibs may be small in terms of the order of magnitude, but the risk may be different between compounds within the class, and that non-selective NSAIDs may carry the same risk. Therefore, that draws into question the clinical significance of the prostacyclin-thromboxane imbalance and its importance in leading to a prothrombotic state.

In support of the hypothesis, NSAIDs may not provide effective blockade of platelets even though thromboxane production is reduced throughout their entire dosing interval. This would be more or less a unifying hypothesis across both classes. It would unify the coxibs and the NSAIDs together if this was the case, to some degree.

Alternatively, what all these compounds have in common, which was discussed this morning,

is that they inhibit COX-2. But by doing so, they not only inhibit the formation of prostacyclin but they also inhibit the formation of other prostaglandins that are formed by COX-2 activity and subsequent enzymatic activity.

So, the data on this slide go back to point one on the previous slide. Here we are showing the effect of a single dose of ibuprofen 800 mg on platelet aggregation responses, over on the left. What you can see here is that following ibuprofen administration in normal health volunteers there is a significant reduction in the platelet aggregation response to arachidate, but that this effect is largely eliminated by 8 hours and the platelet aggregation responses return to essential control levels. This occurs despite significant inhibition of thromboxane-A2.

Over on the right-hand panel is the time course of the urinary excretion of the major prostacyclin metabolite, and here we can see that ibuprofen comparably inhibited the urinary excretion of this metabolite to a degree comparable

to that seen with celecoxib, and that the inhibition was significant even at the 6-12 hour time period.

As was mentioned this morning, this effect will vary from NSAID to NSAID, but using the example of ibuprofen, it is conceivable that, as again was mentioned this morning, mixed inhibitory, non-selective COX-1 and COX-2 inhibitors could act in terms of platelet function, in terms of vascular effects as selective COX-2 inhibitors during a portion of their dosing cycle.

Alternatively, COX-2, as I mentioned previously, in the vasculature has been linked to several cardiovascular disease states, and the up-regulation of COX-2 expression not only results in the production of prostacyclin, which would then lead to downstream beneficial effects on endothelial function and prevention of platelet aggregation, but has also been shown to increase the production of prostaglandin E2 which, again through a cascade, could result in reduction in plaque stability ultimately. Also, COX-2 could

lead to the formation of thromboxane-A2 which would obviously have effects opposite of those to prostacyclin.

That particular scheme would suggest that the results of COX-2 inhibition might be more complicated than just focusing on prostacyclin, and also that the clinical outcomes of such effects might be more difficult to predict than we would envision.

If we move this consideration of mechanism a step further and ask the question, well, if that may be the case in the coxibs and the NSAIDs are all alike, then what may account for the differences that are seen with rofecoxib as compared to the other agents in terms of cardiovascular risk?

We should not forget in this conversation, and this was brought up this morning, that each of these compounds has unique pharmacology, pharmacologic activity, unique pharmacokinetics and other properties that could mitigate or worsen a cardiovascular risk profile that is embedded in a

mechanism-based effect.

What we are showing on this slide is some of the recent work and so all these compounds may be characterized by that. Rofecoxib has been heavily studied in this respect, as has celecoxib. What has emerged from some of these studies is that rofecoxib and/or some of its metabolites may have pro-oxidant effect which could ultimately lead to increase in blood pressure or thrombosis. Do we know for sure that this is an overall effect of rofecoxib? No, but it is clear from the clinical literature that rofecoxib has been associated with elevations in blood pressure to a degree that are not seen with other agents, whether they be non-selective NSAIDs or celecoxib.

The most recent example of this is shown on this slide. This is the third of three studies now that basically confirm the same observations. So, at equal efficacious doses for osteoarthritis, that is, 200 mg of celecoxib once daily, 25 mg of rofecoxib once daily, or 500 mg twice daily of naproxen, we see that over both 6 and 13 weeks of

therapy with these agents in patients with osteoarthritis and treated for hypertension, as determined by 24-hour ambulatory blood pressure monitoring, that rofecoxib was associated with a significant elevation in systolic blood pressure at both the 6- and the 12-week time point, and was significantly elevated as compared to the celecoxib and naproxen treatment groups.

So, we know from outcome studies that reductions in this order of magnitude in terms of systolic blood pressure can have a significant impact on cardiovascular mortality and morbidity.

In summary then, it is not established that the prostacyclin-thromboxane imbalance contributes tot he effects observed for coxibs or NSAIDs clinically. Furthermore, the underlying pharmacology is more complex, involving other prostaglandins and pathways and raises the potential even for benefit for COX-2 blockade. And, there is emerging evidence for molecule specific mechanisms.

Finally some brief concluding remarks on

risk/benefit of celecoxib as it currently stands, just by way of recap, celecoxib in comparison to the NSAIDs in terms of GI safety within the randomized, controlled trial setting has a lower incidence of clinically significant GI outcomes, and in epidemiology studies has similar risk of hospitalization for GI bleeding versus non-users.

Celecoxib versus NSAIDs in terms of cardiovascular safety--the randomized, controlled trials indicate that there is a comparable cardiovascular safety profile versus the alternative therapies. The epidemiology studies indicate that there is a similar cardiovascular risk in celecoxib users as compared to non-users.

In conclusion, the overall risk/benefit assessment of celecoxib is as follows: In the currently approved arthritis indications the risk/benefit of celecoxib remains positive relative to NSAIDs. There is comparable efficacy that demonstrates a GI safety benefit, and it has comparable cardiovascular risk based on the data that we have currently.

There is shared uncertainty of the cardiovascular safety beyond one year of continuous treatment for all of these therapies. Thus,

further studies are planned by Pfizer to evaluate the longer-term GI and cardiovascular safety of celecoxib versus NSAIDs in arthritis patients. Thank you.

DR. WOOD: Thanks very much. Questions from the committee? Yes?

DR. DWORKIN Could you go back to the blood pressure slide, and do you have any data on what it would look like if you had 400 mg daily of celecoxib? I think you just showed 200 mg. I am sort of interested in 200 BID.

DR. VERBURG: We do not have a direct comparison of 200 mg BID celecoxib versus rofecoxib. We have done a 24-hour ambulatory blood pressure trial evaluating 200 mg BID of celecoxib relative to placebo, and we have found very minor differences in the blood pressure profile of celecoxib at that dose as compared to placebo. That is as close as I can come to that.

DR. WOOD: Curt?

DR. FURBERG: I think the focus of your presentation troubles me a bit. You really spent most of the time on comparative trials, and if you are really interested in safety comparing two active drugs is not the best way to go. You get

much better information by looking at the placebo-controlled trials.

I think we are here to answer two questions, is Celebrex safe? And I think what you talked about is not going to help us answer that question. We need to look at the placebo-controlled trials.

You answered the second question, is the safety of Celebrex different from the NSAIDs? Let's come back to the placebo-controlled trials. There is information in the briefing document from Pfizer that you did not bring out, and I would like to refer people to table 4 which presents a summary on the Celebrex experience in placebo-controlled trials, and it is showing risk ratios of 1.7, 1.8 versus placebo for thromboembolic events--trends

that are not too dissimilar to what we see in other placebo-controlled trials of the other COX-2s.

I think in addition to that, you did not address at all the issue of heart failure that we talked about earlier. We were informed that in the APPROVe study there was a 4-fold increase in heart failure in that placebo-controlled trial. For Celebrex, if anything, it is worse. If you look at your table 6, although there are small numbers, there is a 6-fold increase in heart failure, statistically significant, and that is not mentioned.

So, if you are going to talk about safety, my plea is that let's look at all aspects of safety, including the thromboembolic events and heart failure, and let's pay a little bit more attention to the placebo-controlled trials because, as has been said over and over again, we really don't know the safety profile of the various non-selective NSAIDs, and to compare to those drugs is not very informative. Thanks.

DR. WOOD: Do you want to respond to that?

DR. VERBURG: I think the only way to respond to that is actually review some of the data. Why don't we take a look at a couple of the

slides? So, why don't we go to slides C-112?

Going back to the meta-analysis, with the caveats that it is 11,000 patients and it is 6 weeks of exposure and it is roughly 31 events. So, we are shaping conclusions based on a very small data set over very small durations. The composite endpoint for placebo was 1.4 in terms of events per 100 patient-years as compared to 1.8 for celecoxib. In terms of cardiovascular death and MI, you can see that the results were lower with placebo and there was no difference in non-fatal stroke.

Indeed, if you plot these out in terms of relative risk, you find that the point estimate of relative risk for three of these endpoints favors placebo but the confidence intervals are fairly substantial, indicating very low precision around those points.

DR. WOOD: What was the exposure for that?

DR. VERBURG: Six weeks.

DR. WOOD: I think we should emphasize that. You missed that out. Just go back to the slide.

DR. VERBURG: This is 1.7 months of exposure.

DR. WOOD: As long as we have that on the

record.

DR. FLEMING: But in essence, if you are doing a non-inferiority, if you want to show you are not worse, there is a major issue of you are not giving very long exposure here as to whether you might be really underestimating excess risk.

DR. VERBURG: In our view, that is why we did not focus on these data in the presentation. We felt it was really non-informative and we would really leave the discussion of placebo comparisons over longer term to Dr. Hawk and Dr. Levin when they present.

DR. WOOD: Well, why don't we put up the Kaplan-Meier curve from the trial, the APC trial?

DR. VERBURG: Again, I don't have those data.

DR. FURBERG: For any myocardial thromboembolic events the relative risk is 1.77. So, I don't know why you have that discrepancy. You have much lower relative risks in your slide than in the briefing document that was sent to the committee members.

DR. VERBURG: I probably should step back, it is a little bit different construct in my presentation than in the briefing book, and it was

really based on our desire to get to what was a more meaningful endpoint and that was the APTC. I don't think that the differences between the analyses in any way change the overall conclusions.

DR. FURBERG: Well, we may disagree on that point. How about heart failure then?

DR. VERBURG: Sure. Let me just check my notes here. Can you bring up for me C-248? These are data that were provided in the briefing book I believe--

DR FURBERG: Correct.

DR. VERBURG: --comparing celecoxib to placebo in terms of reports of adverse events from

investigators, not adjudicate, hypertension and peripheral edema and cardiac failure, and celecoxib is associated with a significant increased incidence of all these events, as are all non-selective NSAIDs.

Let's go to the next slide.

DR. WOOD: What duration?

DR. VERBURG: Same duration.

DR. WOOD: Six weeks treatment?

DR. VERBURG: A mean of six weeks of treatment.

DR. FURBERG: So, the patients didn't even have a chance to develop heart failure. You raised their blood pressure and caused fluid retention and you followed them for a few weeks. They didn't have a chance to get into heart failure.

DR. VERBURG: So, let's step back. What we are doing is we are trying to determine some cardiovascular safety parameters from trials that were designed to test fundamentally the efficacy of arthritis.

DR. FURBERG: Sure.

DR. VERBURG: So, again, we have recognized all of the faults in what we are doing. There is no getting around that. But if we want to

see what the data look like in order to form some conclusions, this is what it looks like. We hear the criticism but, again, these are from NDA trial databases of 12-week, placebo-controlled trials to evaluate efficacy in arthritis. So, we are limited by the purpose of those trials.

DR. FURBERG: Yes, but these are trials that you designed and set up, and you are not providing the answers that we need to evaluate the efficacy and safety.

DR. WOOD: I don't understand the answer to the last question. You are telling us you don't have the data that you published in The New England Journal two days ago with you in this presentation of a placebo-controlled trial?

DR. VERBURG: I do not. That trial was conducted by the National Cancer Institute.

DR. WOOD: You are welcome to download a slide from The New England Journal. They have a

web site that let's you do that.

DR. VERBURG: And we will cover that topic later. I just don't have a slide with that in my presentation.

DR. WOOD: Any other questions? Byron?

DR. CRYER: Yes, throughout your presentation you suggested that there may be cardiovascular risk, specifically thrombotic risk associated with non-selective NSAIDs. You suggested this mechanistically with ibuprofen and with naproxen based upon the ADAPT trials from observations.

My sense and my understanding of the literature is that there are no good data with non-selective NSAIDs to suggest an increased cardiovascular risk when one looks at meta-analyses, specifically a meta-analysis published by Garcia Rodriguez as recently as 2004. The relative risk of ibuprofen was right at 1 and there was a relative risk for an overall reduction of events, albeit modest, associated with naproxen.

My specific question to you is that in the

ADAPT trial you stated that the increase in events with naproxen was significant. My question is do we, in fact, know whether that increase was statistically significant because my assessment of the math from the ADAPT trial, given the limited data that we have, is that it is mathematically unlikely that the increase in events with naproxen would be statistically significantly increased.

DR. VERBURG: We have not seen the data so I think it is speculation. My interpretation of what was put into the public domain is that there were significant differences, but without having the data to review I can't answer that.

DR. CRYER: But I think your wording is very important and somewhat misleading because you specifically say "significant" and many of us, when we hear the word significant, we are led to a conclusion that that is a statistically significant increase. And without having the data, as you just said, I think it is just a little misleading. All we can say for now is that there was a numerical increase which, if not statistically significant

with naproxen, could have been entirely due to chance.

DR. VERBURG: Point taken. Thank you.

DR. WOOD: Ralph?

DR. D'AGOSTINO: I just want to get clarification from you. Given the discussion we had previously with the APPROVe trial and waiting 18 months before you started seeing a separation of serious events, and so forth, how do you respond? I mean, your presentation was talking about six weeks, a year at most. So, how do I interpret your presentation? And I was going to ask about the placebo trials also.

DR. VERBURG: So, the purpose of my presentation really was to go back and review what we know about the cardiovascular safety of celecoxib in the approved indications for this drug, which are osteoarthritis and rheumatoid arthritis. We reviewed all of the data that is available to review the safety of that drug versus placebo or versus alternative therapies. Subsequent speakers I think will expand into other

indications that are currently being explored.

DR. D'AGOSTINO: So, your presentation would leave it that we really don't know what to make out of any long-term use?

DR. WOOD: Wait a minute. It is one thing to say you presented the data for placebo-controlled trials in the approved indications, but it is not reasonable to say you presented all the data in placebo-controlled trials. The largest placebo-controlled trial presented in The New England Journal you haven't presented and you say you don't have the data here. That just doesn't pass the laugh test. Here it is, do you want it?

DR. VERBURG: I have seen it.

DR. FECZKO: Just for clarification of this, the APC trial will be presented I think later on this afternoon by Dr. Hawk. It is sponsored by the National Cancer Institute. We were not part of that trial. We are not privileged to the data. We were just given some top-line commentary about the data. The same holds for the ADAPT trial. We were

not part of that data safety monitoring board or the results of that trial. I believe that is planned to be presented on Friday.

DR. D'AGOSTINO: My concern is the conclusions which we heard. I mean, you know something is coming down the line and why were these conclusions given as opposed to saying here is what we have at this point in time and walking away from it? It is a very positive presentation.

DR. WOOD: Dr. Manzi?

DR. MANZI: I think probably my questions can wait until they review the APC trial because it really has to do with the long-term issues.

DR. WOOD: All right, thanks. Dr. Shafer?

DR. SHAFER: One might think I am fixated on low dose aspirin here, and perhaps I am. But once again we have three bits of information on low dose aspirin. We have table 4 in the handout that Pfizer prepared or the document that Pfizer prepared which again shows that actually the risk factors that existed, in fact, got worse on low dose aspirin.

We have in the APC trial, which will be coming up, table 4 from those data, again showing that the risk factors maybe were ameliorated a

little bit but still with low dose aspirin the risks persisted. So, we don't have a protection, if you will, from low dose aspirin.

Then in your own slide 48, now in 48 it is not a placebo-controlled result and it is not blinded, but we can use the relative risks in the ASA versus non-ASA used for the other drugs to see that in the case of the high-dose rofecoxib group low dose aspirin conferred no protection.

Do these data, this sort of persistent signal that low dose aspirin provides no protection--are those data that actually pretty strongly support your contention that there are other mechanisms besides the COX-1 and COX-2 balance at play here?

DR. VERBURG: I am not sure that I follow where you are taking the question.

DR. SHAFER: You had suggested that perhaps there is something else besides the

COX-1-COX-2 balance.

DR. VERBURG: Right.

DR. SHAFER: If it is the COX-1-COX-2 balance low dose aspirin ought to make these COX-2 drugs look like non-selective drugs.

DR. VERBURG: Correct.

DR. SHAFER: The fact that low dose aspirin doesn't do that repeatedly would look to me to support your contention that there is something else going on, and that is what I am asking. Is this something that Pfizer has considered? Have you had more thoughts on that?

DR. VERBURG: Only to reiterate some of the thoughts that I think were brought up this morning, and that is that this would not necessarily obviate or alter any changes in blood pressure that might occur with these drugs. It might but it might not. Also, it sort of lends itself to is there other molecule-based pharmacology that could moderate or modulate the effects that one sees from one compound to another? But that is about the extent of it.

DR. WOOD: Garret, this keeps coming up. Do you want to address this?

DR. FITZGERALD: It is always difficult to

address a straw-man when the construct is laid out and the arguments are assembled. I find the aspirin story really straws in the wind as opposed to anything definitive. For example, a comment was tossed out about blood pressure. We have absolutely no information as to whether low dose aspirin impacts on the blood pressure elevation by COX-2 inhibitors by controlled experience.

I think as far as the mechanistic issues that we talked about this morning, we would only expect aspirin to have a diminishable effect as opposed to an abolitional effect on that type of hazard because, as I mentioned this morning, it isn't a prostacyclin-thromboxane yin-hang balance. Prostacyclin acts as a more general constraint on factors that transmit cardiovascular risk. So, I find the arguments unpersuasive.

As far as molecule specific effects are concerned, it is quite true that almost every drug

has multiple mechanisms of action that relate to dose-response relationships. But, in contrast to the mechanism we discussed this morning, the in vivo basis for the molecule specific effects are tenuous to non-existent and that includes the pro-oxidant effect of rofecoxib which is based on one paper in the literature using quantitative estimates of oxidative stress that those of us in the community view as highly questionable. Thank you.

DR. WOOD: I think your job, Garret, is to take Dr. Shafer for a drink and make sure that the two of you have sorted this out tonight! Dr. Domanski?

DR. DOMANSKI: I was just waiting for discussion of APC and I can wait a bit longer.

DR. WOOD: All right. Dr. Dworkin?

DR. DWORKIN: Yes, given the results that you allude to for the APC trial, suggesting that you don't really begin to see a difference until after a year, do you think it is going to be ethically possible, going forward, to do long-term

placebo-controlled trials of celecoxib? You were suggesting that we need to do that, but I am not sure how given the results that we have in The New England Journal.

DR. VERBURG: I don't but I really want to address the question of ethics. I think I will step back and answer the question as follows, the APC was not the only trial which you will hear today. There is also another trial that shows that there was no risk associated with celecoxib. What does that inform us about the true risk of celecoxib over the long run? Relative to placebo, the drug may carry a cardiovascular risk. That I don't think is something that is known entirely. If the risk is there it seems to be small because it is not seen on a consistent basis. You could throw in the ADAPT trial. The results there are shown to be the same.

So, our sense is that you know something about the long-term cardiovascular profile of celecoxib. You know nothing about the long-term cardiovascular effects perhaps of non-steroidals.

Yet, many patients would take them continuously. So, I don't know that it necessarily would be unethical. In fact, you might suggest that it would be mandatory for us to go and evaluate that. Patients have a need and a desire to know what risks they will be taking with their drug, not just in comparison to alternative therapies but what is the true risk if they decided not to select any therapy at all.

DR. WOOD: Allan?

DR. GIBOFSKY: Just a comment. I think it is important when we consider the safety issue to bifurcate the safety issue because there may be a dichotomy between how we are approaching it. I think some are approaching it with is the drug safe, while others are approaching it with is the drug safe for the intended use as prescribed in the label? I think those are two very different issues.

The test of whether a drug is safe or not, to test it across all indications is one thing. To test it across all other indications is something

else. So, I really think we need to discuss safety in the context of intended uses. Many drugs, when tested for unapproved uses, will turn out not to be safe, whereas they may very well be for the indications for which they are approved, and that is why I think we have to be a bit relative in our discussion as well as being absolute.

DR. WOOD: Dr. Friedman?

DR. FRIEDMAN: Two points, first, you touched briefly on the issue of blood pressure. Surely, there must be ways of getting some good data on what celecoxib really does to blood pressure. The data you have shown are from relatively small numbers of people, followed for a very short time, and we don't know anything at all about what other medications or how they were otherwise protected. Do you have any plans for getting better, longer-term information in a more consistent way?

DR. VERBURG: Well, I think what I would like to do is turn the discussion over to Dr. Welton who has been studying the blood pressure

effects of celecoxib and NSAIDs for many years. He can at least recapsulize for you what we have and perhaps also indicate what the future directions might be.

DR. WELTON: Thank you so much. Andrew Welton, from Baltimore. I have, I have to tell you quite frankly, been itching to get up here to the microphone to clarify at least the clinical aspects of the evolution of the blood pressure story because I do not think it has come across entirely clearly either this morning or this afternoon, specifically, the human component thereof.

So if you will bear with me for a moment, I will tell you, if I might have slide C2-42, that sequence, please? I would point out that this is a fascinating story that first came to our attention with NSAIDs in 1993. These were the observations of Janet Pope, who was then a first-year rheumatology fellow, who pointed out in this meta-analysis, published in The Archives of Internal Medicine, that, indeed, all NSAIDs, when compared with placebo, do distort blood pressure

and elevate blood pressure.

If I might have the next slide, the following year we learned something else in an additional meta-analysis. That was, once again, that NSAIDs disrupt blood pressure, the mean increase being 55 mm, but particularly learned that this dominantly emerges during the treatment of hypertension, which then set up the issue that maybe we are looking at an issue of drug-drug interaction.

If I might have the next slide, this was about the time frame with respect to the start of the first two coxib development programs and, therefore, we were very mindful of the importance of blood pressure as these drugs went into a human evaluation.

I show you here the data for the osteoarthritis studies as they were incorporated into the new drug application. You can see, scanning from left to right, that there really isn't much in the way of hypertension adverse events reported, and here we are at the mercy of

the investigators doing the trials. In the CLASS trial, as Dr. Verburg already pointed out, additionally not much in the way of blood pressure.

If I might have the next slide, taking exactly the same approach, using NDA osteoarthritis trials for the second of the coxibs, this then gave us the emergence of a very obvious dose-correlated increase in hypertension events but, again, at the mercy of the investigators doing the trials. This wasn't correlated with specific elevations in blood pressure.

Next one, please. It was at this point that I and my colleagues thought the only way to resolve this correctly is to do head-to-head, prospective, double-blind, randomized trials. And, the logical subset in which to do these studies is, in fact, patients who are being treated for hypertension because this was emerging now more as a story of disruption of blood pressure control rather than the genesis of new onset hypertension.

In brief, our first trial was powered to look for a 3 mm or greater difference in blood

pressure effects between the two coxibs using that because it is a guidance rule from our colleagues in the Cardiorenal Division of the FDA. The essence of it is it showed in treated hypertensives early disruption of blood pressure with rofecoxib, as seen on your left; continued for 6 weeks of observation; and not seen with celecoxib.

This was reasonably curious. Standard rule of thumb, make sure your observations are correct. So, on the right-hand side of the panel it shows repeating these studies in over 1000 people.

Next one please. The additional issue that emerged--

DR. WOOD: Try and get to the point quickly because you are answering a single question and we are running really short of time.

DR. WELTON: I understand. Mr. Chairman, I beg your pardon. Bear with me for a moment.

DR. WOOD: One moment.

DR. WELTON: Over 24 hours pressures are sustained. Next one. There are differences in the

antihypertensive drugs. There are differences seen in the responses of the drugs also at the doses that cause comparable efficacy.

Next one, please. Let me simply wind up. If I might have the next one, please. As you will see at the top right-hand side, what it shows is that if you shift in the population blood pressure by as little as 2 mm, on the right-hand side at the bottom, you can see the reduction and mortality. So, these small changes in blood pressure in large numbers of patients are very, very important.

I would end to answer the question of Dr. Nissen that he asked earlier on, if I might have C-28-3, and that, Mr. Chairman, is my final point.

DR. WOOD: It really is.

DR. WELTON: Here we are showing elevations of greater than 20 mm Hg and it does show between these two coxibs there are important differences in these big swings in blood pressure. I regret I cannot show you placebo results in this trial because we didn't incorporate them but that speaks to your earlier question, Dr. Nissen.

DR. WOOD: Thanks a lot. Curt?

DR. FURBERG: I just wanted to say for the record that we have some missing information.

There is a fairly large number of studies sponsored by the NIH that have information on cardiovascular outcomes. An effort was initiated to get that information together but no real follow-up. So, it looks to me like the NIH has dropped the ball and not provided the information that we need from those other trials.

DR. WOOD: Cardiovascular outcomes in what? In celecoxib?

DR. FURBERG: Yes, with Celebres, yes.

DR. WOOD: I see.

DR. FURBERG: So, I think we should request that information and, if necessary, even go to the director.

DR. WOOD: Tom?

DR. FLEMING: I commented earlier about how one struggles to try to interpret the data when there are such short-term interventions, the 41 trial meta-analysis that if you focus on the

placebo control you only have 6 weeks of treatment. It certainly tempts me to focus much more on the half a dozen studies that have longer-term follow-up.

You mention in slide 36, the CAESAR trial and the CLASS trial, although diclofenac is the control and, as Dr. FitzGerald said, is that Celebrex with hepatic side effects? What does it mean if there is not a difference? Interestingly though, when you look at the CLASS trial and the non-aspirin users there is also an ibuprofen arm and the summary that is given here is in atrial SAEs, anginal SAEs, MI and thrombophlebitis. There are four times as many events on Celebrex than ibuprofen in the non-ASA users.

If we go to the placebo-controlled trials, we have seen that in the APC trial there is a three-fold increase in the rate of CV death, MI and stroke. Another placebo-controlled trial that you didn't mention is the Alzheimer's trial, the 9702001 trial, that being placebo-controlled is of interest, and it had I think a doubling in the rate

of targeted events.

Then, the last issue related to this is the PreSAP and the ADAPT trials will also be very informative, and I am very confused in exactly what you do know. I think someone has already alluded to. On slide 821 it is written as though you know that these results will be neutral or favorable.

So, I have a multi-component question here, am I interpreting this--can you tell us more about the Alzheimer's 9702001 trial? And, what exactly do you know today about the PreSAP and ADAPT trials?

DR. VERBURG: Let me start with the second one first. So, the PreSAP results will be reviewed by Dr. Bernard Levin later this afternoon in full detail. So, those results will be disclosed to the committee. For the ADAPT trial I know no more than what has been published, what has appeared in the newspapers, nothing more.

DR. FLEMING: And what about the 9702001 trial?

DR. VERBURG: Right. So, let's go to

slide C-214. Let's talk about this for a minute. So, the Alzheimer's trial, study 001, was a small randomized trial comparing celecoxib 200 mg twice daily to placebo over one year of treatment. Notice that the randomization was 2:1 and that the mean patient exposure was on the order of about 10 months or so.

This goes back now to the concept that we used in the briefing book and we will update this in a minute, but for any cardiovascular event you can see that there were 3 events versus 11 events. There were 4 myocardial events in total. Two of those I believe were angina and 2 were MI. Cerebrovascular events are listed here and then further down.

Of course, these are based on investigator reports to us. Also, if we go back--

DR. FLEMING: Well, before you leave this slide, which I guess you have just done--is there data that you have on heart failure as well?

DR. VERBURG: I am sure we do. I just don't have that right at hand but we can certainly

get that for you. I just don't have that in my presentation.

I am looking for the background medical history in this trial. Do I have the wrong slide number? So, what concerned us a little bit about the results of the trial you can see here, again coming back to my comment earlier, when the purposes of the trial are not cardiovascular in nature, they can be heavily confounded because you are not controlling for distribution of patients by risk factor. So, what you see here is a trend for a higher degree of underlying risk in this patient population.

Also, I want to add one comment--

DR. FLEMING: Although somewhat modest I would say when you are looking a relative risks of 2 in the outcomes. A valid point, small numbers, but it doesn't explain a large part.

DR. VERBURG: So, we didn't entirely dismiss it there either so we took it one step further and, in fact, at about the time of the CLASS and the VIGOR results we did employ a blinded

adjudication process of all cardiovascular events, serious cardiovascular events that Dr. William White, who is with us today, conducted along with some of his colleagues. That trial was published several years ago.

Could I have slide C-217? That article that Dr. White wrote was targeted to arthritis patients. At the time, he and his co-workers also adjudicated the events from the Alzheimer's trial. Dr. White, if you would care to make a comment? I think you are most informed on these results.

DR. WHITE: Thank you. William White, University of Connecticut Cardiology Center. So, these were done in accordance with the other clinical trials that you have heard, using strict criteria between two blinded adjudicators. As you can see, there was a 2.9 percent incident rate in the placebo group and a 3.5 percent rate in the celecoxib group, which was not statistically different.

To answer the heart failure question, there were just too few cases of adjudicated heart

failure, not different between the two treatment groups.

DR. WOOD: So, these were adjudicated events that had already been reported? Or, where these prospectively defined?

DR. WHITE: Yes.

DR. WOOD: So, tell us what you did.

DR. WHITE: I am not sure what you are asking, were the cases prospectively defined when the study started?

DR. WOOD: Right.

DR. WHITE: No.

DR. WOOD: So, maybe somebody should comment on that. Richard, to you want to comment? Okay, well, we will get to that.

DR. FLEMING: For heart failure you said there were two adjudicated cases. They broke out in what manner?

DR. WHITE: i believe it was equal in each group. It was a very small number. There was either one and one or two and two. I can't recall, to tell you the truth.

DR. FLEMING: Why don't we check?

DR. WHITE: We will check.

DR. WOOD: Any other questions? Dr.

Shafer?

DR. SHAFER: This does not involve aspirin.

DR. WOOD: Thank goodness!

DR. SHAFER: One of the things we are looking at is overall safety, and you brought up the subject about alternatives, NSAIDs being the alternative. What data are there about celecoxib GI tolerability versus NSAIDs when combined with a proton pump inhibitor?

DR. VERBURG: I am not aware of any data that evaluate GI tolerability issues--

DR. WOOD: There is lots of data on that.

DR. VERBURG: There are data with respect to complicated ulcers, but with respect to whether patients stay on therapy longer with celecoxib alone versus the combination of an NSAID and, say, a proton pump inhibitor, I am not aware of any such data.

DR. WOOD: Do you want to take that, Steve? No? Actually, the last sponsor presented some of that data in their presentation.

DR. NISSEN: I want to explore with you for a moment the issue--you have several times used the term "equally effective doses" and this is

important. In several of the trials we see a relationship between dose and the amount of cardiovascular toxicity. It is particularly important because you have done a lot of blood pressure comparisons between rofecoxib and celecoxib and one of the arguments I have certainly heard is that the equivalent dose of celecoxib to 25 mg of rofecoxib is 200 mg BID, not once a day. So, I would be very interested in understanding that, particularly when you consider that there is a much shorter half-life and, you know, particularly if you do an ambulatory blood pressure study the effect of the drug may be gone toward the end of the dosing interval, which would tend to bias the study in favor of celecoxib. So, could you address any data that you have that indicates

that 200 mg once a day has the same effectiveness as 25 mg of rofecoxib? DR. VERBURG: 200 mg of celecoxib in terms of 25 mg of rofecoxib in terms of effectiveness?

DR. NISSEN: Yes, I want to know about efficacy, and then I would also like to know about any blood pressure comparisons of 200 BID to 25. I am trying to understand. You have made a case that the drugs have a very different effect on blood pressure and I am testing that a little bit with you to make sure that we got that right.

DR. WHITE: Do you want me to answer that?

DR. VERBURG: Yes.

DR. WHITE: Well, I have conducted two controlled clinical trials in this regard. The first one was done about three or four years ago in 178 patients treated with celecoxib at 200 mg twice daily versus placebo twice daily, specifically in hypertensives treated with an ACE inhibitor to bring out the worst-case scenario with regard to interference with the drug. The 24-hour systolic blood pressure difference was 1.3 mm Hg between

celecoxib at 400 daily and placebo, which was not statistically different. That was giving it BID.

Now, in the other realm, not placebo controlled but published two weeks ago in The Archives of Internal Medicine, was a 500-patient study in which patients with osteoarthritis of the hip or knee, plus hypertension, plus type II diabetes, also treated with a angiotensin blocker were then randomized to celecoxib 200 daily, rofecoxib 25 daily and naproxen 500 BID. At 6 and 12 weeks into the double-blind period a very formal cluster of arthritis efficacy assessments were made using the same standards for any arthritis drug, and they were, in fact quite equivalent using Womack and Visual Analog Pain Score and so forth.

So, from the patient perspective at 6 and 12 weeks, they were therapeutically equivalent. At those same endpoints as you already saw, there was a significant pharmacodynamic interaction between rofecoxib and perhaps the underlying treatment because there was very little salt and water retention, evident based on edema and weight gain,

with about a 4.2 mm increase in 24-hour systolic pressure. That was a sustained increase during the daytime.

With regards to naproxen and celecoxib, there was no such increase seen, yet, there was clinical equivalence with the regards to anti-inflammatory responses. That is pretty much what there is. There are no other studies like those.

DR. VERBURG: Dr. Simon, do you have a comment?

DR. SIMON: Yes, I was one of the authors of the hypertension study in the Archives. As a hypertension study and as a rheumatologist, why would I be involved in such a study? In fact, I was involved to ensure that the outcome measures for osteoarthritis, as measured by Patient Global and Womack, which is a functional outcome scale, and the VS scale for pain would then be the appropriate way to look at equivalence of benefit.

The data sets that suggest that there isn't equivalence in this kind of analysis of 200

mg versus 25 are really based on different ways to look at the evidence, such as night pain and other aspects of components of some of these outcomes. This was really a very robust way that is, in fact, typically used for approval at the FDA in determining efficacy of a particular therapeutic. And, we were able to demonstrate both at 6 weeks and at 12 weeks that there were equivalent benefits. But you are absolutely correct, differences in half-life, if you ask different questions will give you different responses.

DR. WOOD: Do you really want to say something because I really want to get to the next--all right.

DR. BRAUNSTEIN: Yes, I just want to show--

DR. WOOD: Be quick.

DR. BRAUNSTEIN: Well, I will show you actually the pharmacologic responses for COX-2 inhibition.

DR. WOOD: All right, go ahead.

DR. BRAUNSTEIN: This shows you the

average 24-hour inhibition of COX-2 for different doses of rofecoxib and celecoxib. This is a standard ex vivo PGE-2 inhibition assay. What you can see is that there is a dose response, as we know, for all NSAIDs to inhibit COX-2, and over 24 hours celecoxib 200 mg twice a day has the equivalent COX-2 inhibition of approximately rofecoxib 25 and celecoxib 200 once a day is roughly the same as rofecoxib 12.5.

May I have 233? These are the results of a clinical study looking at Patient Global Assessment in response to therapy, acetaminophen 4000, celecoxib, rofecoxib 12.5 and then rofecoxib 25. Without getting into an argument--although statistically rofecoxib 25 had the greatest effective, you can see that rofecoxib 12.5 is the dose that has the most similar efficacy to celecoxib 200 once a day, you know, similar to what you would expect based upon the pharmacologic and the pharmacodynamics.

DR. WOOD: All right, thanks. Let's move on to the next presentation, which is from the FDA

and is by Dr. Witter.

FDA Presentation: COX-2 CV Safety: Celecoxib

DR. WITTER: Good afternoon. I am going to try and push along here to make up some time. I am a practicing rheumatologist. I have been with the FDA for almost ten years.

One of the first drugs that I was given at its 30-day IND stage safety review was celecoxib. So, although I could say a lot about it I am going to limit myself to the topic of interest to day and I will try to move along as expeditiously as I can.

Just to remind everyone, and we have been discussing this but it factored into my historical perspective in terms of why we did what we did, or what kind of discussions went on, to remind everybody that there are different reasons for drug exposure which have been talking about, acute and chronic pain for example. I will be talking later about some acute pain issues so, to some extent, I have two presentations that are tied together. But, you know, in this situation you are a patient; you have a reason to be taking it because of the

pain. The issue of placebo control and how we might define placebo, and we can discuss that for quite a while, but in a short-term trial for example placebo control might generally be viewed as acceptable because there is rescue available. On the other hand, in a long-term chronic pain type study there are problems to deal with. It is not realistic; it is difficult, and that has impacted some of the ability for us and the sponsors to do the kinds of things we might want to have done.

On the other hand, if you are trying to prevent disease progression, such as the Alzheimer's and the polyps studies that we will be hearing about later today, one can classify them as subjects, not really patients, and so in this situation, again depending on the placebo, it may be more acceptable to conduct such studies.

So, having said that, let me just take this opportunity to thank the sponsors, past and present, be they from the industry or from the private sector or from government, for their efforts in this regard in this complex area and,

more importantly, to thank the patients and the subjects for the topics that we have been discussing and will be discussing in the next few days. This is a very complex area of medicine but very important. So, we have the privilege of seeing some data today that we didn't see back when I started. And one of the points, if you take nothing else from my presentation, is that we have had a paradigm shift in this area. It has been a dramatic shift in terms of looking at safety events and the kinds of data that we have. So, one of the themes I am going to try to develop is exactly that.

So, this slide is to remind us all that there are available OTC, some of the medications we have been discussing, be they ibuprofen or naproxen, that have been available for a while and available for the studies for the most part that we have been discussing. Although we try, and I know the investigators try to limit that exposure, it is also a factor that I think has to be remembered, particularly here as we think through these data

that we are looking at.

In preparation for the meeting then I also looked back--and not meaning to pick on any drug in particular but I went back to the diclofenac approval back in 1988 to try to give us all a sense of what were the databases available back then and how decisions were made.

So just very quickly here, we had some pivotal trials in OA that involved 97 patients for 56 weeks. We had patients in pivotal RA trials that went on for anywhere from 6-12 weeks. We had Phase I/II trials, which are the PK kind of trials for example, with 950 patients or volunteers. Those were mostly 2 weeks. There were some supportive trials that had 11 patients for 12 weeks. We had some long-term open-label trials that involved 252 patients for about 38 weeks. So, I had one of the statisticians do this calculation for me and that comes out to be around 224 patient-years. So, keep that number in mind as we move forward.

I would also like to point out that as I

was reviewing this I noted that there were two myocardial infarctions with diclofenac; none that I could see in the other comparators which, by the way, included aspirin and one of the adverse events that used to be looked at a lot was tinnitus and people would get evaluations for hearing loss. In any event, there were two MIs, one during double blind and one in the open-label trials. So, I just thought this might be of use as we think through where we are.

Part of my challenge here today is to present to you then a bit of a historical perspective and to try and merge some of the different approaches in terms how sponsors conducted the trials and how we subsequently analyzed the information.

So, I just want to step back just for a bit. I am presenting here the World Health Organization terminology that was used to define cardiovascular events in the celecoxib NDA base. These kinds of reporting systems have evolved over the years, as we all know, but just to give you a

sense of what were some of the terms that were looked at in the original approval for celecoxib, just a few of them are listed here.

Then just to remind everybody that we, for the most part, will be describing and discussing today--at least I will--mostly serious adverse events. There is a regulatory definition for that. Deaths are obviously the hard endpoint which will be also discussed. The point I think has already bee made that in the celecoxib NDA these were spontaneous investigator reported events. They were not prespecified or not adjudicated. In my subsequent presentation what I will do is give you some information about the adjudication process and how sometimes that is problematic. Also, in discussing CLASS I would like to point out that the GI endpoints, because that is what the trial was intended to do, were prespecified and adjudicated but, once again, the cardiovascular events were not prespecified and not adjudicated. These were spontaneous investigator reports but we look at all this information.

This is a slide that Dr. Villalba had shown earlier. I have just added one column here, and the only point I want to make from this is that

as we might look at events--and I am not going to talk about the various categories--these are different ways to look at cardiovascular events. We are all familiar with the APTC we are all familiar with. But I just wanted to make the point that as you look at the numbers and you make just a rough ratio comparison, they appear to be similar, leading one to make an assumption that the inferences that would be drawn by looking at any of these data sets, at least in a qualitative way, would be the same.

Turning specifically to Celebres, this is my reminder to you that this information is available on the web. It has been an effort that has evolved over the years. We have tried to put as much information as we can in our reviews so that all of you can have a chance to look at this information.

The original NDA was submitted on June 29

or 1998. It consisted of 51 studies. I have just listed them briefly here as to the types. There were 29 studies in Phase I. There were 14 studies that were arthritis patients either with OA or RA. There were 7 post-surgical analgesia studies. There was one long-term study which went out 2 years, study 024.

To remind everybody, although you probably weren't here, when we talked about the original approval of Celebrex at an advisory committee meeting, one of the things that I discussed in particular was this concept of dose creep, that patients tend to increase their dose if they are allowed to. I would also like to reemphasize the point that in any of these kind of long-term trials there is no controlling arm and that really makes it difficult to try and get a handle on how to interpret these events, particularly from a perspective of common events like cardiovascular events. So, in my own thinking anyway, you always want to have some kind of a controlling arm whenever you do long-term studies. Then, again,

with this particular type of drug how OTC medications may impact some of these results.

That is just a summary of what I will be talking out and I will just point out what I will be talking about, which is the ADAPT trial and two other trials which will be discussed a bit.

The reviewing process for an NDA and particularly for this one when it came in--it was a very large database and so this was really a team effort and that is one of the things I want to stress here. This data is looked at by multiple people with multiple talents for long periods of time. So, there isn't just one person looking at the data; it is done as a team effort. In this case, for example, I was the primary medical officer to look overall efficacy and then to come to an overall conclusion about safety. To assist me was a renal/cardiovascular consultant. We also had another medical officer who reviewed the data and also paid attention to the cardiovascular results. We had a GI consultant who served as a secondary medical reviewer also looking at the

safety data. Then we had people specifically looking at analgesic trials and the platelet safety trials. So, there really is a team of people who look at these results whenever they come in.

I am going to stick with just the OA and RA exposure because that is the most robust exposure that you have in here. What I am doing is displaying results from some of the consults that we had to the Division about these issues. I will be describing most of the results either in terms of patient-years or crude rates, and I will try and tie this together at the end to Kaplan-Meier approaches.

But just to give you a sense, in the original NDA in the controlled trials there was not a lot of information for exposure beyond 180 days, not surprisingly, but when you looked at the open-label trials we had a larger exposure. To the extent that these numbers make any sense, I am just pointing out a 16,208 patient-year exposure versus diclofenac, as I pointed out earlier, at 324.

Turning then to the cardiovascular

mortality in the NDA database for Celebrex, the comparisons here in the information that we had are against placebo, Celebrex itself and the NSAID comparators in two different ways. They don't differ that much; there was a slightly different definition. Then also in the long-term open-label studies. You can see that there were not many events. When you do the math here and divide it using the patient-years to get an estimate of the crude mortality rate, you can see the highest number comes out here for the NSAID comparators in both situations. It also is higher than what was found when looking at the all known cardiac deaths in the long-term open-label arthritis experience. So, there didn't appear to be any large signals when looking at this particular outcome.

Turning then to serious adverse cardiac and renal events, i have again here the columns of placebo, differing doses of celecoxib and the NSAID comparators. When you look at these events overall there were no important differences. In fact, they looked worse for the NSAID comparators and the

placebo looked roughly equivalent to celecoxib.

When you look at some of the individual events, and let me see if I can point to the particular events that have been discussed so far today, heart failure for example, there didn't appear to be any major differences between celecoxib and placebo; myocardial infarction, again there appeared to be no important differences between all the groups.

So, looking at this data in summary, there didn't appear to be any major clear signals that distinguished celecoxib as it appeared in the NDA database from NSAID comparators and, at least in some of these comparisons, from placebo as well.

Looking then at the data from the extension trial after the NDA in a bit different way, we configured the data to display the events of cardiovascular mortality based upon the last known dose that the patient had at the time of the event. So, that is what is displayed here. As you can see, you go from zero at 100 mg and up to 200 mg, 300 mg and 400 mg. When you do the math again

using patient-year of exposure, there certainly appears to be a trend here. As you go up in the dose, the cardiovascular mortality goes up. These are small numbers and, again, it was difficult for us to place this in context with no controlling arm.

For example, if an event had been adjudicated away, and we don't do this, it would bring the rates down to what I have given here just for comparison's sake. So, we are aware of this; didn't know what to do with it; difficult to make comparisons without some kind of a controlling arm.

I would like to turn then to the SUCCESS-1, which stands for Successive Celecoxib Efficacy and Safety Study. In terms of what we are discussing today, this was a short 12-week study in patients with osteoarthritis. It had two comparisons with celecoxib, two different doses, naproxen and diclofenac. It was a large study involving 39 countries, lots of centers, and it was really intended to evaluate the homogeneity of efficacy and safety around the world. it was not

intended as a cardiovascular outcome study. None of what I am discussing today was intended as a cardiovascular outcome study.

I have put up here a bit more of summary results to give you a sense--and these results were described previously at other meetings--between celecoxib, diclofenac and naproxen. What I have tried to do is highlight for you in yellow who has the most events. As you can see, for the most part with the exception of a small increase of cardiovascular events, there wasn't anything that in particular distinguished celecoxib from the other groups.

I have noted down here an update last month. There were, in fact, 8 myocardial infarctions in the 100 mg group; 2 in the 200 mg group; and 1 in the NSAID comparators. And, I have done the calculation for the rates to make some comparisons here. But as you can see, and I think the points are starting to emerge as we discuss more and more data, that when you look at the comparator NSAIDs they have their own sets of

problems which we were certainly aware of as well.

Turning to the CLASS trial, in case you don't know, it stands for the Celecoxib Long-Term Arthritis Safety Study. I have highlighted the term arthritis here because, again, this is for the indication of arthritis and that is where this was studied. This is a unique trial. It was intended to mimic a real-world setting. We have been hearing criticisms that trials were not extrapolatable and generalizable so what we were trying to do, and the sponsor as well, was to come up with a trial that was in a more realistic setting.

I should point out that the only trial that was available, large outcome trial, was the MUCOSA trial published in 1995. So, this was a unique trial at the time. A lot of discussions went on about how to design this trial. One of the things that we had been discussing was aspirin use if indicated. Patients had either OA or AR. As we will be hearing more about, RA, we know, traditionally increases the risk of cardiac

problems. In particular, there is something that just came out in Arthritis and Rheumatism this month which points out that RA doubles the risk of heart failure. This seems to be, according to the authors, an independent risk associated with the disease itself.

So, just to reiterate, this was designed as a GI safety study and it was intended to try and change the NSAID template regarding this particular outcome. This was not powered nor designed as a cardiovascular safety study.

This is a slide that back then, in 2001 when we discussed these particular CLASS and VIGOR trials and what we were bringing to the forefront at that point of time was this concept of 2X. So, let me just tell you a bit about the history of that. The X dose was intended to be the highest dose for the intended chronic indication. The idea of 2X was to give us some assessment of the robustness of the safety results. We have certainly heard, as somebody rolls in the door as an NSAID that, you know, we are safer. So, we

wanted to see the data. We were also skeptical of the surrogacy for endoscopic results and how that might translate into rigorous outcomes. So, it was that kind of thinking that impacted upon the design of these kinds of trials.

Again just to remind you, at the time--and this is still the language in the GI portion of the FDA warning label, it describes in terms of looking at GI ulcers, gross bleeding of perforation, that there is one percent of patients if treated for 3-6 months who experience this event, but this occurs in about 2-4 percent of patients if they are treated for one year. So, this is data that we had previously known from other NSAIDs. And, I saw this on a slide earlier today--the kind of information that we had available from other databases, suggesting that there were lots of hospitalizations and lots of deaths associated with this particular adverse event.

Some of the baseline demographics then in terms of looking at the CLASS trial, the mean/median age was about 60 years; 11 percent of

the patients were 75 years or older. These were mostly white females. Approximately 27 percent of the patients had RA; 10 percent had a history of GI bleeding or gastroduodenal ulcers; and about 21 percent were taking aspirin.

In terms of looking at the inclusion criteria and exclusion criteria, they were fairly open. Basically you needed to be able to give informed consent; that you required something like this kind of a medicine and that you were not pregnant. On the other hand, that you didn't have any active disease of any signals in terms of looking for hepatic events.

The aspirin use in CLASS deserves some comment. It was at less than or equal to 325 mg daily. Again, this was if patients needed for cardiovascular events. But the use was not stratified in the CLASS trial. The dose and the duration of use also varied. It wasn't a constant. So, I think this is one of the things that we had discussed back in 2001, that it was probably not a good idea to try and draw any firm conclusions from

the aspirin use from this trial, and that only observations and possible directions for future studies might be the most value for this particular study.

To give you a sense then of the exposure in the CLASS trial, it was again a large trial. In terms of making some comparisons here, this one trial to the extent that we believe, or you believe, patient-years of exposure and how adequately that assesses risk, there was three times more information in this one trial on diclofenac than we had in other trials, the point being that, you know, we had been very comfortable with much larger databases in this regard which is a good thing.

The exposure, in terms of looking at the durability and long-term, is listed here for celecoxib, diclofenac and ibuprofen. The patients who were exposed from 12-15 months, there were not many patients in the diclofenac group compared to the other two arms. This was a confounding observation and when we were trying to understand

some of the benefits in this trial we got into discussions of informative censoring, which I won't get into today, but this was a factor in terms of trying to understand and put some of these results in context.

Turning to deaths, I have listed here--and this is the same information I have talked about at other advisory committee meetings--there were 36 deaths overall, 19 in the celecoxib group, 9 i diclofenac and 8 in ibuprofen. I have calculated roughly the patient-years here for comparison. No important differences, at least to my eye. Most of these patients were 65 years or older. Most of these deaths were from cardiovascular events. There were 11/19, or 58 percent, in celecoxib and roughly the same in diclofenac, a bit more in the ibuprofen group.

In terms of looking at this data, and in spite of my own caution earlier about looking at aspirin versus non-aspirin, it is exactly what I am going to be doing to give us a sense of what the data look like. Again, here are the three

treatment groups. This displays all deaths and this displays the cardiac deaths, broken down this time into all patients, those that use aspirin and those that were not using aspirin. When you look at this data in terms of all-cause mortality, again, there do not appear to be any point differences. When you look at aspirin users there were more events in the ibuprofen group. When you look at non-aspirin users there were more in the diclofenac group. This pattern basically held through when we looked at the entire study for cardiovascular deaths. There was the same trend.

Turning then to serious cardiovascular events in the CLASS trial, here again is displayed a comparison between aspirin users and non-aspirin users. Looking at the groups, you can see then that there were not as many patients that did take aspirin so the numbers are smaller; the patient-years of exposure are smaller. But, nonetheless, here are the results. When you look in the aspirin users and at the issue of myocardial infarction you can see that there were more of

those in the ibuprofen group. When you look at the combined atrial endpoint, which was a combination of atrial fibrillation, bradycardia, tachycardia--I am not remembering one of them, anyway, it was a composite endpoint that we had come up with to get a handle on this. There were more events in the ibuprofen group. For combined anginal disorders, which was a combination of unstable angina and coronary-artery disorder, there were more in the diclofenac group.

Looking at the non-aspirin users and looking at the same types of endpoints, in this situation it looks different in that there are more events in the celecoxib group than in the other two comparators--small differences but differences nonetheless.

What I have tried to do in this slide is to put together some of this information in terms of looking at APTC-like events, recalling again that these were not adjudicated. I don't want to diminish the importance of APTC so I am calling it "like" events. So, I have just simply added up

cardiovascular deaths, MI and strokes to give us a sense of what this endpoint might look like if it had been done, and you can see in this comparison that there are more of these events in the ibuprofen group versus the other two.

This is Kaplan-Meier analysis that I took from one of the publications that I have listed up here, by Dr. FitzGerald, in Nature/Drugs Discovery, in 2003. There also was something by Dr. Strand and Hochberg in 2002 in Arthritis and Rheumatism. I put this slide up here to try and make some comparisons for us. This displays the Kaplan-Meier analysis for serious thromboembolic cardiovascular events, arguably in the most important population to look at, in the non-aspirin users, and as you can see from this particular analysis celecoxib appears to be between the comparators here. It might not be showing up well in the back. This is diclofenac; here is ibuprofen.

What I have displayed over here then is to give us some comparisons, if one looks at true rate comparisons with these number of events or

patient-years to tie back to earlier looks of the data, and again it is probably hard to see, this is 0.97, 0.7, 7.45 versus 1.78, 1.33 and 0.8. the point being is that there do not appear to be any important differences in the conclusions or inferences that are made no matter how you look at this data.

I would like to turn then to the Alzheimer's study, 001, which has been discussed a bit today. This was under an IND in a different division, Neuropharmacologic Drug Products. We were aware of this study. This information had been discussed previously.

This was a study that was started in 1997. It was a double-blind, placebo-controlled trial that lasted for a year. It was a comparative study of celecoxib for the inhibition of Alzheimer's disease. One of the results in terms of efficacy conclusions was that celecoxib did not limit progression in this situation.

There were other studies that were ongoing at the time, 004. This was an open-label study

looking at long-term safety. This study was terminated when the results of 001 were made available.

There was another study under this IND, 002, which was a placebo-controlled, long-term study. It had vitamin E co-use in it as well. This was intended to look at brain size by MRI and to look at Alzheimer's disease-associated proteins and inflammatory mediators to get a sense of mechanisms. This study was also terminated due to the results of the 001 study. So, the IND was inactivated in July of 2001.

As we have been preparing for this meeting it came to our attention, the following letter which I just want to bring to your attention regarding this particular study. I am just highlighting a few things here rather than showing the whole letter. But this was basically a letter from the DSMB that was involved in this particular study. What the letter points out is that the trial was conducted between 1997 and 1999; that there were, according to this letter, no adverse

events to support stopping the trial while it was ongoing, however, at final review there was an excess of cardiovascular-related and other risks but it was difficult to interpret, according to this letter, because of the small sample size which made relative risk and odds ratios unreliable. This was conducted in a frail and fragile population that had substantial co-morbidities and concomitant medications, making it difficult to know how to generalize these results. It was commented that there were indications of failure in randomization in baseline cardiovascular disease and cardiovascular medications, meaning in particular that there were more in the celecoxib group than in the placebo group.

The letter went on to state that the members were concerned that this data had not previously been made available, other than i an abstract form, and they were concerned about this because this may be the only information available in medically ill elderly populations with placebo control.

Looking then at cardiovascular events, I have summarized them briefly here comparing the Celebrex 200 mg versus placebo. I just summarized

the events. With the one exception of cerebrovascular disorder, there don't appear to be any differences in all the adverse events--deaths overall, cardiac deaths, serious adverse events, cardiovascular, and no matter how you look at it--congestive heart failure, atrial fibrillation and then I made another APTC-like calculation here, they all wind up on the celecoxib side of the ledger here.

This is also information that we had available to us in preparing for this meeting in terms of addressing the issue or randomization. These are results from the sponsor that you saw already. When you look at the Celebrex group there were imbalances in terms of hypertension, diabetes, those that had bypass surgery, those that had history of ischemia and those that had history of coronary-artery disease. Whether or not this, in a small trial, is enough to explain the results is to

be determined.

So, that is what I have to say today. Thank you.

DR. WOOD: Thanks a lot. You also have not covered the APC trial. Right? That is sort of surprising. Does the committee want to go on to the next two presentations and wait for questions to Dr. Witter at that point? Let's do that. Let's go on to the next two presentations.

DR. FLEMING: Could I have jut one?

DR. WOOD: Sorry.

DR. FLEMING: Just on slide 35 as you were presenting those 001 results, it is certainly noteworthy that there is a pretty consistent excess across all of these key categories for Celebrex. We talked, for example, about heart failure adjudication. It is kind of hard to adjudicate something in a blinded way when all the events are in the one arm. I don't know if the adjudication committee was aware of how the results broke out before they did their adjudication. In any event, we were told those broke out at 1/1 after

adjudication. They were 5/0 before. So, that seems difficult to justify as well. So, I look at this as one of a small number of placebo-controlled trials with a fairly long period or treatment exposures. So, this is of some relevance.

DR. NISSEN: Tom, did you attempt to do a p value there from those numbers?

DR. FLEMING: For which aspect of this?

DR. NISSEN: Well, say, APTC-like or just the serious AEs? Is that going to be significant?

DR. FLEMING: Probably borderline.

DR. WOOD: You know, the elephant in the room is the next trial so let's move on and see if we can get some of these questions dealt with afterwards. Let's go on to Dr. Hawk's presentation.

DR. WHITE: Do you mind if I make one comment, jut for cleaning the air? The adjudication committee was not aware of the results when they looked at the data at all.

DR. WOOD: Right. Let's come back to that point later because there are lots of problems with

that adjudication. Let's go on to the next two talks.

NIH and Investigator Presentation:
Celecoxib in Adenoma Prevention Trials:
The APC Trial (Prevention of Sporadic Colorectal Adenomas with Celecoxib)

DR. HAWK: My name is Ernie Hawk. I work at the National Cancer Institute, currently Office of Centers, Training and Resources. The study I will share with you was done while I was a member of the Division of Cancer Prevention, and it is the APC trial.

The story I would like to share with you over the next 20 minutes or so--I will be followed by my colleague from M.D. Anderson who led the Pfizer-sponsored PreSAP trial--the story I would like to share with you really has three important components. That is, the data that are available today; the data that I can't share with you today because they are still emerging. These two trials that I will discuss now are still ongoing. Drug administration was halted in mid-December with the

finding of the risk that I will share with you today, but the trials remain ongoing, looking at efficacy and other issues with regard to overall safety. Then, finally, one of context because while the discussion this morning and early afternoon is centered upon the usefulness of these agents in inflammation and pain, they have another very important potential indication in terms of cancer risk reduction, both in a preventive as well as a therapeutic context. And, I hope to bring a bit of that to your awareness.

Depicted here is the disease in which we are attempting to intervene. It is colorectal cancer. When looked at globally or within the United States, despite the availability, as we heard earlier, of effective approaches to this disease in terms of screening and risk modulation through things like polypectomy, we remain with a significant problem, with 145,000 new cases anticipated in 2005 and about 55,000 deaths, and obviously a much larger issue ii the worldwide scene. So, the National Cancer Instituted is

devoted to not only extending available techniques but exploring new areas to combat this disease.

I am trained as a medical oncologist and, therefore, my focus of attention and my training was to the right side of this slide, that is cancer. But cancer, as with most diseases, is actually a process--if only we had the tools to be able to identify it. Depicted here is the process moving from normal mucosa in the intestine through a variety of stages, intermediate polyps, adenomas, to invasive disease, invasive cancer.

This process is time dependent, taking typically years in most settings, and already this process is becoming the focus not only of cancer itself, but the process of cancer development has become the focus of clinical screening and surgical intervention when adenomas are identified, that is, they are commonly removed on identification. Because we are understanding the molecular pathogenesis of the disease, it provides opportunities to not only address at a pharmacologic level cancer itself but potentially

to address the development of cancer through targeting of a variety of the parameters that drive the process on a molecular level. COX-2 is one important target in this process.

Depicted on this slide is the talk I usually give over the course of about half an hour. So, I will summarize for you the really profound amount of data suggesting that non-steroidal anti-inflammatories and COX-2 selective inhibitors may be useful in terms of preventing and/or treating cancer. The data is most compelling in the intestine, particularly the large bowel, however, as you will see it extends to other organs as well. It is one of the reasons why the NCI has invested so heavily in this area and why we believe it still holds great potential to benefit patients living with cancer or at risk for cancer.

There are four lines of evidence here that I would like to share with you with, again, probably hundreds or thousands of studies underlying these points.

On a mechanistic level, non-steroidal

anti-inflammatories and COX-2 selective inhibitors have been shown to induce apoptosis of neoplastic clones, to reduce angiogenesis in animal models, to inhibit proliferation and to stimulate immune surveillance of neoplastic cells--all things which should retard carcinogenesis.

In vivo, in the intestine alone there are more than a hundred animal studies now published, 90 percent of which roughly show profound benefits in terms of reducing intestinal carcinogenesis, as depicted by reductions in cancer incidence, multiplicity in these animal models, delays in time to progression, reductions in advanced characteristics of tumors.

In terms of epidemiology, there are now more than 35 studies--retrospective, prospective, nested case control studies--which pretty consistently, with the exception of two studies, show 30-40 percent reductions across the spectrum of intestinal neoplasia, that is, reductions in adenoma incidence, cancer incidence and cancer-associated mortality.

So, we believe, based on the observational animal and mechanism data, that changes in adenomas will ultimately in the longer term translate into

improvements in later outcomes such as colon cancer incidence and mortality, at least with this class of drugs, again, because of the really profound database. The epidemiologic studies alone amount to several million individuals involved in those studies.

Finally, there are now three published randomized, controlled trials of aspirin in the peer reviewed literature that suggest 30-40 percent reductions in recurrent adenoma. They were designed very similar to the APC and PreSAP trials that I will share with you in greater detail.

So, based upon this abundance of literature with its great consistency, we believe that non-steroidal anti-inflammatories and/or coxibs may very well reduce the risk of colon cancer. Importantly, what we learn in the colon may very well extend to other organs as well.

There are similar sorts of evidence, not

nearly with the volume nor the consistency necessarily but suggesting that COX-2 is a relevant target to carcinogenesis in a variety of other epithelial organs, and that these agents may very well reduce risk of cancer development and/or be useful in cancer therapy.

I will point out that already these agents are used not only with the hope of preventing or treating cancer but also in treating many important conditions in cancer patients, such as pain and inflammation. coxibs are particularly useful because they tend not to interfere with platelet function, an important parameter in cancer patients because so many of our other therapies actually suppress bone marrow production, and we are faced with the situation where, with thrombocytopenia, we need to try to identify agents that are useful in those populations for other indications.

I won't belabor this point. You already know the safety concerns with traditional NSAIDs that are established. The question is what others lie out there still to be discovered because,

indeed, as you have heard several times this morning, we don't believe that there are the same sort of information databases that we have now with celecoxib and, as we heard earlier, with rofecoxib with traditional NSAIDs.

We embarked on this effort to explore non-steroidal anti-inflammatories and coxibs specifically back in the late '90s when the data based upon the relevance of COX-2 to cancer development became apparent with the growing body of data I summarized two slides previously. So, we joined a collaborative relationship, a clinical trial agreement, with Searle, Pharmacia, Pfizer--a migration of companies over time--to evaluate celecoxib in a cancer prevention setting based upon the lines of evidence summarized here.

Our first attempt to do that was in a very high risk situation, that is, patients with familial adenomatous polyposis. I won't belabor this point greatly. This is a surgical specimen in the upper left and an endoscopic view of the intestinal burden of precancerous polyps in

individuals born with this germline condition with defect in the APC gene. It is a relatively rare condition but confers essentially 100 percent lifetime risk of cancer if not mitigated by surgery or other maneuvers. So, typically these patients are subjected to a variety of standard care procedures involving genetic screening, endoscopic screening, surgical prophylaxis--actually removal of all or part of the colorectum, as well as standard surveillance for any remaining segments. Despite that standard of care, these individuals, compared to age matched controls in a landmark study done at St. Marks, one of the leading institutions for care of these patients, had a three-fold increased risk of death, mostly from cancer.

So, this led us to do a trial of celecoxib in which we showed efficacy. At the moment it is the only approved pharmacologic adjunctive therapy for this condition. However, earlier randomized, controlled trials had documented solidex efficacy as well, although that is not an approved

condition.

These are the data that led to that approval under the Subpart H guideline, with further definitive trials required and those are ongoing and planned. This is with 6-month intervention involving 83 patients in a differential randomization, 1:2:2. This is endoscopic parameters. This is worsening below the line. Here is endoscopic improvement. What we see here, focused on the colorectum, is no mean change in the placebo group; a slight improvement at the 100 mg twice a day dose; and a substantial improvement at 400 mg twice a day.

Importantly, as someone pointed out earlier, individual activities are probably important because, clearly, some patients respond quite dramatically even to lower doses of celecoxib, although clearly you have a more profound and robust improvement at the 400 mg twice a day dose. Just as an example of what was seen, this is a non-selected patient. This is before. This is after 6 months of exposure, only 6 months

of exposure with reductions in the intestinal tumor burden.

Importantly, these folks are at risk for duodenal cancer as well and we assess that in a variety of ways and feel that there is a suggestion of benefit in the upper GI tract as well, but it is certainly something that requires subsequent confirmation because that was not statistically significant.

That trial then led us to consider the possibility that celecoxib, as with aspirin and other agents that have been tried for adenoma prevention, may be useful in adenoma prevention in a cohort at moderate risk due to prior sporadic adenomas.

So, the NCI and Pfizer-sponsored APC trial was initiated. It involved 2035 patients with prior sporadic adenomas who were randomized in a balanced manner to celecoxib 400 mg twice a day, the dose that was effective in FAP patients, administered over 36 months versus 200 mg twice a day, a dose that had previously not been

interrogated in oncologic settings versus placebo. It was conducted with a baseline colonoscopy, a colonoscopy after 12 months and after 36 months, evidencing adenoma recurrence, with collection of all adenomas while on trial.

The study was a major effort and really I should note the dedication of both the practitioners in the study team but also the patients involved, involving 91 sites, English speaking, most of those in the United States but with participation in Canada, Australia and the U.K. Accrual began in late November and extended to March of 2002.

Well, the trial moved forward with careful monitoring by the standing data safety monitoring board, and was largely unchanged until September of this year when, following the Vioxx announcement, the data safety monitoring board convened and recommended the initiation of a dedicated effort. Previously safety was a specified secondary endpoint but not cardiovascular safety specifically. So, they recommended to the steering

committee that we initiate a process of cardiovascular adjudication and analysis focused on CV serious adverse events. So, that was done by drawing upon the expertise of a group of cardiologists and statistical team that is outlined here, based at Brigham and Women's, with the clinical endpoint committee involving two individuals who conducted the adjudication process in a blinded manner, created a database specifically focused on cardiovascular risk, and handed that off to a cardiovascular review committee, again with representation from Brigham, University of Glasgow and Dr. Wittes doing the statistical analysis.

The process of that adjudication, which we think is terribly important in this sort of trial that didn't up front specify cardiovascular endpoints, involved three steps. First of all planing. The team put together standardized definitions, hierarchical analytic categorization scheme and a statistical analysis plan.

Next, the data were compiled, verified and

adjudicated. All SAE forms were reviewed along with source documents. Sites were queried to supply supplemental data focused on cardiovascular events. The events were adjudicated in the prespecified manner and a database was created for those events, handed off to the analytic team who then obtained randomization codes and relevant baseline data and analyzed the data according to intent-to-treat principles, and presented the data back to the data safety monitoring board in December.

Now to move to the data which has just been published on-line within the last 24 hours, I believe, on The New England Journal of Medicine web site. This slide depicts the baseline characteristics of the patients involved in the APC trial split out by treatment arm. What we see is that randomization worked quite well in terms of distributing these factors: Age roughly 60 years of age was the mean. About 70 percent of the cohort was male. About half of them had a history of some form of cardiovascular event that, of

course, mainly being represented by hypertension in approximately 40 percent; diabetes in about 10 percent. Importantly, aspirin use and lipid-lowering drug use in this cohort was on the order of 30 percent and was balanced across arms.

When we come to the hierarchical characterization of cardiovascular endpoints--I had a heart attack when I saw the earlier presentation and different numbers were presented, but I realize that they were presenting the death from cardiovascular causes or myocardial infarction or stroke. That is the third line on this slide, not the fourth line which is the one that the steering committee and the safety assessment team chose to focus upon, which includes cardiovascular death, myocardial infarction, stroke or heart failure because we feel these are all clinically relevant and important outcomes that could be considered together.

Although the events are quite infrequent in this 2000 patient, 3-year study we see a differential occurrence regardless really of the

categorization you are looking at when you are looking across treatment arms, whether expressed as number or percentage of patients or the rate per 1000 patient-years, there is a consistent increase in risk moving from placebo to 200 BID to 400 BID.

I will make a point that these are expressed as hazard ratios, that is relative to placebo, and again with all the various categorizations, and this really moves from the hardest endpoint, cardiac-associated death at the top, down through progressively felt to be more subjective assessments of cardiovascular risk to the bottom where you are dealing with cardiovascular death, myocardial infarction, stroke, heart failure, angina or need for a cardiovascular procedure. You will notice that the risk decreases as you move toward a broader categorization of cardiovascular events. But when you focus more specifically--again, I will highlight the blue line, the one that is highlighted in the manuscript--we see a 2.3 increased risk at 200 mg twice a day compared to

placebo and a 3.4 increased risk compared to placebo at 400 mg twice a day. I will note that the lower number of 2.3 percent in the 200 mg group is marginally statistically significant but clearly significant at most assessments in the higher dose group.

If we focus, instead of that sort of assessment, on death, we see that there was a difference, not statistically significant per se from cardiovascular causes perhaps, but that death from non-cardiovascular causes does not follow the same trend. Indeed, when we look at death from any cause, overall mortality, there is really no significant difference across these arms, with the 200 mg group and placebo being equivalent in this study.

Similar to the discussions we have heard earlier, we considered a variety of cardiovascular risk factors based upon baseline characteristics at this point, and we evaluated age, gender, CV risk factors, diabetes, aspirin use and use of lipid-lowering drug use at baseline. We saw no

statistical evidence, assessed by interaction terms, looking at the risk factor and treatment to suggest a differential hazard by any of those baseline factors. Of course, the analyses are limited by few events and, therefore, limited power.

If we look at a time to event analysis, with the Y axis including all 2000 patients and 3 years of follow-up, we see relatively slow event rates. However, if we then change the Y axis to focus specifically on a probability up to 5 percent we see the diverging curves similar to what was seen previously with rofecoxib, but the divergence coming somewhere arguably around 12-14 months. Importantly, these are intent-to-treat analyses.

I want to conclude with just a couple of points. you have already heard alluded to by Dr. Furberg the possibility of compiling a larger set of data from NIH-sponsored trials. Indeed, we have been very busy over the last several months trying to get this data in shape for presentation here from these two dedicated trials. I will point out

that although the PreSAP trial is specifically sponsored by Pfizer alone, they shared their data with us and the adjudication and analysis process I described was applied to both the NCI-sponsored APC trial as well as the PreSAP trial, and funded by the NCI.

So, that was our first effort at an across trials analysis. You will hear in a moment from Dr. Levin that the analyses from PreSAP are not completely mature yet so we have a plan of doing this across the two that we have done as well as four others that we know exist that are NIH-funded, and it is simply a matter of trying to do this in an expedient manner at this point.

These are the six trials that we feel have long enough exposure. That is, these are defined by at least 2 years of exposure and we generally try to shoot for sizeable trials, all placebo-controlled, because we felt these would be informative to the question at hand.

I will point out that the last study down there, the NEI study, is very small but a very high

risk cohort and, therefore, they state they have a significant number of events, on the order of 20 events in just 86 patients.

Finally, I have tried to highlight for you that these agents may very well have a unique set of contributions to make to patients living with cancer or at risk for cancer, and we believe that strongly holds true and needs further investigation.

This study, with the caveats mentioned earlier this morning--this is an unpublished study but has come to our attention recently because we have investigators interested in looking at traditional NSAIDs given now the cardiovascular risk that has been identified with coxibs. What we see in a cancer relevant population, that is, patients with oral cancer in a closed population-based nested case control study in Scandinavia, is that the risk in this small study, unpublished yet, may extend to other NSAIDs. I think this, combined with some of the other observational data and the experimental data from

the National Institute's of Aging study, may very well raise questions about other NSAIDs, and we think it is terribly important to answer those questions given the potential opportunity thee agents present for patients with cancer.

I will close with this slide, just stating that with most good research you are left with more questions than answers. Indeed, I think that is the case here. We believe that there are many issues still to be answered about this cardiovascular risk and what it means for patients with or at risk for cancer. I will leave this really to Dr. Levin to come back to at the conclusion of his talk, and turn it over to him at this point.

NIH and Investigational Presentation: The PreSAP Trial (Prevention of Colorectal Sporadic Adenomatous Polyps)

DR. LEVIN: Thank you very much, Dr. Hawk. Mr. Chairman, committee members, it is my honor to present a summary of the data in the PreSAP trial. My co-principal investigator, Dr. Nadir Arba, in

Tel Aviv University, and I have been aligned with this trial since its birth with Searle, Pharmacia and Pfizer.

In this trial, depicted here are 1561 patients with sporadic adenomas who were randomized in a 3:2 manner and stratified by aspirin use and clinical center into celecoxib 400 mg daily for 36 months and placebo for 36 months. Colonoscopy was performed after 12 and 36 months of exposure evaluating recurrence, and collection of all pathological endoscopic information.

As you have already heard from Dr. Hawk, some of this information is still in a preliminary status. This study involved 106 clinical research sites in 32 countries. Patients were enrolled from March, 2001 and completed approximately one year later.

The cohort characteristics at baseline are shown in this slide, somewhat similar to the APC trial in terms of age and gender. What is different is that the smoking status is higher, 25 percent, and baseline aspirin use is lower. Some

of this data may still be in a preliminary format so I am not going to discuss it significantly further.

Depicted here, and somewhat similar terms to that which Dr. Hawk showed, is the incidence and hazard ratio of the hierarchical cardiovascular composite endpoints. Again, the blue column that is highlighted reflects the death from cardiovascular causes--myocardial infarction, stroke or heart failure. I would draw to your attention the placebo rate of 6.4, approximately double that in the APC trial, and a hazard ratio of 1.1.

Similar to the APC trial, the cardiovascular events examined by baseline subgroups were somewhat similar in age, gender and baseline cardiovascular risk. There was no statistical evidence of a differential hazard ratio by baseline risk groups. Of course, there are few events and it has limited power.

Depicted here on this Kaplan-Meier estimate, one can see that the number of events is

low, and when this is magnified, similar to what Dr. Hawk showed, the curves are essentially similar.

There are a number of issues which arise from these two trials. Perhaps the most important one which concerns us as the investigators, apart from the safety, is the efficacy and we don't have that information yet. We have some idea with the signal from the Vioxx trial about which you heard earlier. It is tantalizing. That will help us to make risk/benefit assessments for future.

We have to take into consideration in any of those discussions the relative gastrointestinal and cardiovascular safety referent to other non-steroidal anti-inflammatory drugs. Overall toxicity and safety, of course, are prime concerns when it comes to asymptomatic individuals and the public, and we don't have any information in these trials yet on gastrointestinal ulceration.

The cross trials meta-analysis that Dr. Hawk alluded to will also provide a great deal of information. What, of course, is most tantalizing

to everyone involved is why is there a difference in this trial compared to the APC trial? At this point, all we have to go on is the frequency or the schedule of administration of celecoxib. We don't have any other information from the patients enrolled in this trial on other possible factors.

In this trial there was no increased risk of cardiovascular adverse effects, but one overall would want to consider whether one could mitigate any increased risk by better clinical management if that were necessary.

Some of the differences, but that doesn't really apply to this trial, might be in metabolic polymorphisms but there is no evidence for that and we don't have that information.

So, for future research there are many questions that are of great importance. COX-2 remains a relevant oncology target and, as Dr. Hawk already presented, we want to consider the possibilities that there are other pharmacological targets besides COX-2 in the prevention and therapy of cancer. We already have some information on

that, the effect of these agents, and they don't all do the same, on 15-lipoxygenase-1 and also on the modulation of PPOD delta.

But primarily what we are interested in now is establishing efficacy or determining efficacy in these two trials and that information should be forthcoming in the next few months. Thank you for your attention.

Committee Questions to Speakers

DR. WOOD: Thanks very much. Any questions? Dr. Farrar?

DR. FARRAR: If you could show the PreSAP cohort characteristics slide, which I guess is your second or third slide, I would ask my colleagues to look on page 6 of the presentation of the study and if you just compare the baseline characteristics, I was struck by the fact that you said that what was different in the trial was the rate in the placebo group. There are, in fact, several major differences in the two groups. The age is the same. Male distribution is approximately the same. Cardiac history is the same. But if you look at

diabetes, there is more than twice the rate in the PreSAP than there is in the APC. The smoking rate is substantially higher. The baseline aspirin use is half. The lipid-lowering drugs are remarkably lower. I don't know what that means, but Dr. FitzGerald suggested this morning that this whole system is very complex and I would simply posit that, in fact, there is probably an interaction there that may be very informative. We need a lot more information about your trials. Obviously you are working hard to do that and I think there is a lot of information to be gathered there.

DR. LEVIN: If I might answer that?

DR. WOOD: Go ahead.

DR. LEVIN: Yes, Dr. Farrar, I agree entirely. I didn't want to highlight these differences which suggest that this is potentially a higher risk group to begin with, distributed in countries where the prevalence of use of lipid-lowering drugs would be anticipated to be lower. But some of this data is still a little bit preliminary so I didn't want to hark on it but I

think your point is very well made. Thank you.

DR. WOOD: Dr. Shafer?

DR. SHAFER: Yes, you showed a slide which, from my perspective, was somewhat unwelcome because I was trying to understand these things. That was the slide about the risk of the other NSAIDs which was based on unpublished data. I actually went looking for such data and had some trouble pulling it up. Are there published studies, or are there data that you are aware of, because this is relevant to the discussions that we are going to be having on Friday, suggesting cardiovascular risk from the other standard NSAIDs?

DR. WOOD: And while you are doing that, can you comment on the increased risk in that study of aspirin?

DR. SHAFER: I tried to avoid mentioning aspirin in my question.

DR. WOOD: I will do it for you, Steve!

DR. HAWK: The only other data that I am personally aware of is the study done in the Kaiser-Permanente database that we saw alluded to

in an earlier presentation. I am not aware of other data. I put this up with all the caveats, and I believe I mentioned that this preliminary and so it violates some of the rules that we heard this morning. But it is particularly relevant to the Cancer Institute because, again, we have applicants suggesting that they should move now to traditional NSAIDs and that is a very important question to answer but we don't think the answer is there, that is, the absence of evidence doesn't necessarily prove that they are safer and I think that is an important context issue, at least for us.

DR. WOOD: But in commenting on that, the second line, it shows aspirin increases the risk of cardiovascular.

DR. HAWK: I wish that John Baron were here because John Baron did one of the three aspirin trials in adenoma prevention that I alluded to. I didn't have time to show the data but if you go into that study--it is published in The New England Journal of Medicine--he studied placebo versus aspirin at 81 mg versus 325 mg, and if you

look at the adverse event table you see that the aspirin groups actually had more events in a dose-dependent manner than did placebo. I don't know what that means but it is very similar to the sorts of information we have from the APC trial. But, again, you know, there are a lot of long-term placebo-controlled trials showing that aspirin prevents cardiovascular risk in other settings. So I don't want to use that to impugn aspirin. I am merely stating what is published.

DR. WOOD: Dr. Hennekens?

DR. HENNEKENS: Dr. Hawk, I would make a comment that leads me to a question. The totality of evidence for aspirin from 135 trials for the treatment of secondary prevention shows a highly statistically significant and clinically important 15 percent reduction in cardiovascular mortality. In contrast, in 5 trials of primary prevention with 55,180 or so patients, with much lower endpoints, there is not a statistically significant benefit of aspirin but the confidence intervals are still compatible with that. We need more data on this.

So, with that as a background, as a chair or member of various data safety monitoring boards, I try to follow the principle of early stopping

based on proof beyond a reasonable doubt that is likely to influence clinical practice, with some asymmetry in that you have greater concern about safety than efficacy but, nonetheless, included in this algorithm is the statistical stopping guideline whether you follow the teachings of O'Brien and Fleming or Land and de Mets or Peto and Haybittle. Intrinsic in this is that during the course of a trial, if you reach a statistically extreme p value then there is a high likelihood that by the scheduled end of the trial that p value will at least be at 0.05. But if you fail to achieve that extreme p value, then it is highly likely that by the end of the trial you may find no significant difference.

So, one of the questions is what were the considerations in stopping this trial, and is the play of chance a likely explanation for the findings?

DR. HAWK: I would say that the trial was still blinded to efficacy and broader issues of safety. The data safety monitoring board still exists so I am not privy to all of their closed session discussions and deliberations. What I can tell you is that this trial was about three months

away from the last patient going off of it. We were told that there was a cardiovascular risk and it was the considered opinion of the data safety monitoring board that it would be the better part of valor to halt drug administration in this trial and continue to follow patients for relevant outcomes. That is what we did and that is my level of insight into the issue.

DR. WOOD: Dr. Furberg?

DR. FURBERG: Yes, I would like to make a plea that we are not making too much out of the findings from the PreSAP trial. For the combined outcome the hazard ratio is 1.1. The 95 percent confidence interval is very wide. So, the PreSAP findings are consistent with a 40 percent benefit and a 2.34-fold increase in risk. So, the trial

doesn't add much to our knowledge.

DR. O'NEILL: You may not have this information right now but I notice the APC trial had 72 sites in the U.S. and the PreSAP trial looked like it had 132 sites. What is the relative U.S. versus non-U.S. distribution in those two trials?

DR. HAWK: In the APC trial there were 70-some sites in the U.S.

DR. O'NEILL: No, I mean denominator-wise, subjects. I am trying to see whether the placebo rate differs inside or outside U.S. in the two trials.

DR. HAWK: That is a very good question and I don't have those data.

DR. O'NEILL: Yes, I think that would be useful to have.

DR. WOOD: Byron?

DR. CRYER: I understand that in your APC trial results you haven't yet analyzed the potential polyp reduction effects of celecoxib, but you pointed out a couple of very real observations,

that aspirin is an effective agent for the reduction of polyps, associated with a 20-30 percent reduction of recurrent adenomas, and we heard earlier in the APPROVe trial that rofecoxib was associated with a 24 percent reduction of recurrent adenomatous formation.

So, assuming, let's say, that celecoxib achieves a result that is in the same realm, let's say 20-30 percent and given that aspirin, as Dr. Hennekens pointed out, is such an effective agent for prevention of cardiovascular events, I was wondering if you could postulate as to potential reasons for us to use celecoxib for this indication over aspirin, assuming a similar endpoint.

DR. HAWK: Sure, i would be glad to. I think the answer will come with the data. What I am going to say is conjecture. In animal models aspirin is one of the least effective of the traditional NSAIDs. Celecoxib was one of the most effective in traditional animal models. So, we had reason to believe, both on the basis of an improved efficacy profile in animal models as well as

potential for an improved safety assessment that existed at the time of the initiation of the trial, that in both ways we could improve the therapeutic index.

I think we don't know if these cardiovascular events are occurring in patients that have efficacy or in the group that don't have efficacy. We don't know the level of efficacy here. So, it is very difficult to answer you question in a scientifically rigorous way. I can tell you the premise but I can't tell you the data because I don't yet know whether this drug is efficacious at all.

I will say that in FAP settings there was a small Japanese trial done with rofecoxib which showed I believe something on the order of a 10 percent reduction in adenoma burden. We saw about a 30 percent reduction in our randomized, placebo-controlled trial. That is a suggestion that in a different patient cohort celecoxib may be more efficacious but it is really speculation and what we really need are the data from these two

trials in order to be able to answer your question accurately.

DR. CRYER: Just to reiterate, you pointed out data from animals and the human data with aspirin is quite good with respect to prevention of recurrent adenomatous polyps.

DR. HAWK: We were hoping for better.

DR. LEVIN: I think, Dr. Cryer, I might answer your question as well. It is valuable to look at the two studies. In particular, one study showed that there was, as you quote, approximately a 30 percent reduction. But what was particularly interesting was the effect on advanced adenomas, a 49 percent reduction. So, I think we don't have these data but the question will be, in my opinion, very relevant to what will be the impact of this or any other kind of they on the more significant lesions that have an enhanced propensity to develop into cancer. That might be an important differentiation between aspirin and rofecoxib or any other agent.

DR. WOOD: Dr. D'Agostino?

DR. D'AGOSTINO: Curt already raised the issue I was going to. I don't think the two studies contradict each other.

DR. WOOD: Peter?

DR. GROSS: I wonder if one of the factors to be considered is that when celecoxib is given once a day the suppression of prostacyclin and whatever else is going on does not last for 24 hours, whereas when celecoxib is given twice a day you get more sustained suppression.

DR. WOOD: All right. Dr. Nissen?

DR. NISSEN: I was going to echo what Curt had to say and also Ralph, but then I had a question. Clearly, the confidence intervals for these two trials, for virtually every endpoint, overlap. But because they are so similar in design, long before you have all the trials in this list you could combine APC and PreSAP and look at an analysis of the two combined which would give us more stable estimates of the hazard ratio. I think it might be useful. I am going to guess somebody has done that and, if you have, I sure would like

to know about it. Maybe Tom has already done it on the back of an envelope. I can see him shaking his head. But I am trying to get a more stable estimate, particularly for the non-super-therapeutic dose, the 400 mg dose which was common to both trials--try to get more stable estimates for what the hazard ratios really are.

DR. HAWK: First of all, I want to highlight that the "super-therapeutic" dose is based upon our frame of reference that is different than the indication where we are applying it here, in cancer prevention. Here the only effective dose we have is 400 mg twice a day. So, I take your point but please take mine as well.

In terms of the combined analysis, that has been done based upon preliminary data that were analyzed back in December. Since that period of time we have confirmed all the events so that we can do the intent-to-treat analysis that was discussed here as well. So, I don't think it has been done yet on the mature data. Janet Wittes is in the audience. Janet, can you speak to that?

DR. WITTES: It is not done on very mature data but I am sure that if you calculate, you can do it by hand.

DR. SEIBERT: Dr. Hawk, perhaps I can clarify. Karen Seibert, from Pfizer, pharmacologist. We have evaluated 400 mg once daily versus 200 mg twice daily looking at the exposures. The total exposure as an AUC is about equivalent. As you might expect, the C-max for the 400 is about 30 percent higher. The C-min at 12 versus 24 hours for the 200 and 400 is about 20 percent different. The total exposure is the same. And we believe that the C-mins which are achieved at steady state still exceed that which is necessary to inhibit COX-2. We are happy to provide those data to this committee but we don't see a clear differentiator there in the dosing regimen.

DR. WOOD: Other questions? Richard?

DR. PLATT: I would like to circle back to Dr. Shafer's question. Were you asking if there are data about the other non-selective NSAIDs?

Because in Tab S of our book there are a couple of articles that speak to that. They are observational studies but they seem to be saying that there doesn't appear to be excess risk.

DR. SHAFER: That is what I was wondering about, finding one that shows excess risk.

DR. PLATT: There does seem to be some literature that looked and didn't find it.

DR. WOOD: Dr. Fleming?

DR. FLEMING: Well, I have been, just out of curiosity, doing a back of the envelope calculation to see what it would look like on the primary endpoint, if we take the primary endpoint to be CV death, MI and stroke, and the standard error is the square root of 4 over the number of events, so just using that without doing a formal stratification, I would come out with a relative risk of about 1.82. So, one study says 10 percent increase; the other study says a relative risk over 3, and it is just barely over the statistical significance. So, it is borderline statistical significance in the meta-analysis with an estimate

of about 80-85 percent relative increase.

DR. WOOD: So, they would be compatible, in other words. Any other questions? Yes?

DR. DANNENBERG: My name is Andrew Dannenberg, Weil Medical College, Cornell University. I am here today as a consultant for Pfizer, but I am one of the would-be authors of the data demonstrating an increased risk of cardiovascular death in those taking non-selective NSAIDs versus acetaminophen. That NIH-funded research is based on the following hypothesis: It is known that COX can activate tobacco carcinogens and convert them to mutagens. We, therefore, were interested in the possibility that NSAIDs could protect against tobacco smoke-induced oral cavity cancer.

To be enrolled in that trial, which was led by a group in Norway and M.D. Andersen, a retrospective study, one had to smoke 15 pack years or more. We observed a significant decrease in the risk of oral cavity cancer in those taking NSAIDs but not acetaminophen. However, when we looked at

life span there was no apparent increase in life span despite the reduction in risk of oral cavity cancer.

That led us to interrogate the data set to look at all causes of death. We noted a hazard ratio of 2.06 in those taking NSAIDs from the standpoint of death due to cardiovascular disease. By contrast, acetaminophen did not impact on the risk of cardiovascular death. So, that is a more complete description of the rationale for the study and how we arrived at interrogating the data set.

DR. WOOD: Thanks very much. Let's move on to the next presentation, which is also by Dr. Verburg.

Sponsor Presentation:

Cardiovascular Safety and Risk/Benefit Assessment of Valdecoxib and Parecoxib

DR. VERBURG: Thank you very much. I will be brief. The next 25 minutes or so are focused on the cardiovascular safety of valdecoxib and the parenteral prodrug of valdecoxib, parecoxib, and brief risk/benefit assessment.

Just by way of some quick background, valdecoxib was approved in the U.S. for the indications of osteoarthritis and rheumatoid

arthritis in November, 2001. The approved dose is 10 mg once daily. In terms of the NDA database, over 15,000 individuals were studied, which was roughly comparable to that which we supplied for celecoxib. Since the approval we have been focusing this drug in terms of its effects in acute pain as well as other non-arthritis chronic pain conditions.

Our overall assessment or position of valdecoxib is stated on this slide. First, it is our view that valdecoxib remains a viable treatment alternative for patients with osteoarthritis and rheumatoid arthritis. We have data to suggest that valdecoxib provides improved GI safety compared to NSAIDs. The valdecoxib cardiovascular safety database is smaller than celecoxib at present, however, the emerging CV safety profile of valdecoxib appears similar to alternative therapies in arthritis patients, that being non-steroidals,

for up to 6 months. And, the cardiovascular signal in the CABG surgery setting, therefore, does not appear to extrapolate to the arthritis population based on the data at hand.

Just as with celecoxib, we have shown that valdecoxib exhibits the properties expected of a selective COX-2 inhibitor. That is, as shown on the left-hand portion of the slide, it provides efficacy--in this casein a trial of osteoarthritis patients--that is superior to placebo treatment and in every way comparable to patients treated with naproxen at a full therapeutic dose. At the same time, over the same 12-week period we see that the rate of endoscopic ulcers, with valdecoxib doses ranging from 5 mg to 20 mg once daily, were similar to placebo and in contrast, again, to the results seen with the non-selective agent naproxen.

In our prespecified, predefined way, we also evaluated 8 of the randomized, controlled trials with durations of 12-16 weeks in the NDA database, and also evaluated the same in 3 open-label studies up to 1 year. This was done

according to prespecified definition, prespecified protocol and by a blinded events committee.

What we see here is that the incidence of ulcer complications, that being GI bleeding, obstructions and perforations, were significantly higher in the combined NSAID group, that being comprised of naproxen, ibuprofen and diclofenac, as compared to placebo treatment. No such difference was seen in the valdecoxib treatments as compare to placebo at doses ranging from 5 mg up to 80 mg daily. We also see that in long-term exposure at doses of 10 mg to 80 mg daily out to 1 year in nearly 3000 patients the event rate seen with valdecoxib looks similar to that which we saw in the more short-term but controlled settings.

As I have mentioned before, there are more limited safety data than with celecoxib and the analysis is largely confined to the randomized, controlled trials in arthritis at present, as well as some short-term acute pain studies alone or valdecoxib in combination with parecoxib. There are no completed epidemiology studies to report,

although we are aware of three that are ongoing.

In the meta-analysis of valdecoxib there were 19 randomized, controlled trials included, with a total of over 12,000 patients. Again, the majority of the patients were osteoarthritis and rheumatoid arthritis patients, with a smaller minority of patients with chronic low back pain or chronic cancer pain.

The distribution of patients is shown here. The study duration ranged from 2 weeks to 12 months, and 11 of the 19 studies were 3 months or longer in duration. We evaluated all doses of valdecoxib in the meta-analysis.

In terms of exposure, 50 percent of the patients treated with valdecoxib were exposed to the drug for periods of 3 months or longer; 22 percent for 6 months or longer; and 4 percent for 1 year or longer.

Here we show the distribution of events, as well as the event rate, comparing valdecoxib at doses of 10 mg or higher, in other words, it is full therapeutic dose and super-therapeutic doses

that were tested as compared to a combined NSAID category. We find here that for the composite endpoint of cardiovascular death, non-fatal MI or stroke valdecoxib compares with a somewhat lower rate than that seen with the NSAIDs. There are very few events to shape this comparison, 21 in total. But as we go down to the various components of that composite endpoint we see essentially the same kind of pattern.

If we translate that into a relative risk comparing valdecoxib to NSAIDs, we see that the point estimates of relative risk all lie under 1, or the large confidence intervals do not allow any strong conclusions to be drawn at this point.

On this slide we break down the comparison of valdecoxib to the individual NSAIDs, as well as compare it to placebo. Again, this is in terms of a composite of these 3 events. We see for placebo that the risk estimate is 1.26 but not significantly different. Then breaking out the comparison between naproxen and diclofenac, we see that again the point estimates are below 1 but not

significantly so. No comparison could be done against ibuprofen. There were no events in either the valdecoxib or ibuprofen patients in which to do so.

Again, we have very limited information to establish any type of dose-response relationship or relationship of dose to cardiovascular safety with valdecoxib. The data that we do have are shown here. At 10 mg and 20 mg the point estimate compared to the NSAIDs is below 1, not significantly so. We noticed the point estimate moves to favoring NSAIDs at a 40 mg dose, however, when we move up to 80 mg there were no events in either treatment group in which to shape a conclusion. Again we are moving to very small numbers of patients as we begin to subdivide the meta-analysis for valdecoxib.

In terms of the incidence of cardiorenal events, as was the case with celecoxib, there are significant differences in the incidence of adverse events--these are investigator reports now--as compared to placebo. But comparing valdecoxib at

doses of 10 mg or greater to NSAIDs, we see that there are no significant differences for either hypertension, edema or cardiac failure in over 7000 patients in this particular evaluation.

There is one other safety issue that we need to bring up with valdecoxib, that being the reports of serious skin reactions. Spontaneous reports of serious skin reactions, that being Stevens-Johnson syndrome, etc., received approximately 6 months after the launch of valdecoxib in the U.S. This rate appears to be higher than celecoxib or rofecoxib and, as a result, a black box warning was added to the prescribing information for valdecoxib or Bextra in November of last year.

In brief then to summarize the conclusions, valdecoxib shows efficacy that is similar to NSAIDs, and there is emerging data to establish that GI safety benefit is superior to NSAIDs and the CV safety profile is comparable to NSAIDs.

The added warnings allow physicians to

choose appropriately based on the evidence of rare although severe skin reactions.

The future plans for valdecoxib are very similar to those proposed for celecoxib. Longer-term studies are planned to evaluate the GI safety and the cardiovascular safety of valdecoxib in the arthritis patient population.

Now briefly a discussion of parecoxib. Parecoxib is the water soluble prodrug of valdecoxib. Its water solubility allows it to be administered parenterally either by intravenous or intramuscular injection. Parecoxib itself does not have any inhibitory activity at the COX-2 enzyme but, once administered, it is rapidly converted to valdecoxib. In fact, there is nearly total conversion within 30 minutes following administration.

So, the choices of parenteral therapeutics for the treatment of acute pain, whether it be post-surgical or other conditions, are fairly limited. As a result, there is an additional need to provide agents that improve the postoperative

pain control or other acute pain situations with parenteral therapy.

As we have seen from various reports, inadequate postoperative pain is one of the most important factors in prolonging hospitalization and also in progression of acute pain to chronic pain following surgery.

Postoperative analgesia at present is traditionally provided by opioids but we all are aware of the complications of those therapies, and also opioids do not provide adequate analgesia upon movement and, of course, both of these issues also prolong the post-surgery recovery course.

There has been an increasing move towards the use of multimodal analgesics, that is, drugs from two or more classes, to minimize the adverse effects of the drugs alone by reducing the dose, or to improve the ultimate efficacy output. In terms of the addition of agents to opioid therapy, therapy are very limited at present for parenteral therapy and basically limited to ketololac which has issues of its own in the post-surgical setting

but, nonetheless, when studies are done this allows for early oral intake, ambulation and hospital discharge. The net comment on this slide is in the box here, which is that parecoxib is intended to provide significant analgesia, while sparing opioids without the GI and bleeding risks of parenteral NSAIDs.

This is just some data that illustrates the point that I made on the previous slide. These are two studies taken from the ambulatory surgery setting. On the left is a study of nearly 4000 patients who were asked to evaluate their pain one day after surgery, and we can see here that over 25 percent still had moderate to severe pain despite being treated with standard of care opioids.

Over on the right-hand portion of the slide is a much smaller study, conducted in patients undergoing laparoscopic surgery or hernia repair, and what we can see is that patients struggle to return to their pre-surgical functional status after surgery. Although the time course of recovery is somewhat dependent on the type of

surgery they undergo, there is still significant functional disability several days after ambulatory surgeries.

So, by way of background, parecoxib was approved for the short-term post-surgical pain in Europe in March of 2002. At this point in time over one million patients have been treated. The parecoxib NDA is currently under review in the U.S. for the management of acute pain.

In total, the clinical registration program for parecoxib looks as follows: There are 64 studies completed. Of these, 26 were analgesia studies. In total there were about 10,000 patients randomized to one of the three treatment groups shown here; 1670 patients received treatment for 3 or more days with parecoxib and over 1000 patients received treatment for 10 or more days with parecoxib and then transitioned to oral valdecoxib therapy.

One of the earlier studies that we performed in the program was in a high risk surgical population to gauge the overall safety of

parecoxib. We chose the CABG surgery population to perform such an analysis. This was a 2-treatment arm, double-blind, randomized, controlled trial. Patients were randomized in a 2:1 fashion to active treatment. Following CABG surgery they received parecoxib at 40 mg IV Q 12 hours for a period of at least 3 days, and then once they were able to transition to oral treatment they received valdecoxib at the same dose.

The other treatment arm received placebo treatment throughout the course of the 14 days. Both treatment groups received as needed supplemental analgesia in the form of morphine during the parenteral treatment period or oral acetaminophen codeine during the oral treatment period.

It is important to note that prior to randomization or receiving study medication all patients were to receive 80-325 mg daily of aspirin. Approximately 89 percent of these patients underwent CABG surgery with cardiopulmonary bypass, and about 11 percent of the

patients were off-pump cases.

Here we show the results that emerged from the first CABG surgery trial. We had put in place an endpoint committee to adjudicate the events in this trial according to prespecified definitions and, of course, they were blinded to study treatment. What we see here is that if you look at the composite endpoint made up of these various components, we see that over the course of the entire trial there was an increase in the incidence of any thromboembolic cardiovascular event in the parecoxib/valdecoxib treatment group. This result was driven primarily by this imbalance that we see here in stroke or TIAs, although those incidence rates and differences between the treatment groups did not achieve statistical significance.

In light of those results, we elected to evaluate the cardiovascular safety of parecoxib and valdecoxib in a larger CABG surgery study. The study design is outlined on this slide. In total, this was a trial of over 1500 patients. Following CABG surgery the patients were randomized to one of

three treatment groups. They either received parecoxib as a 40 mg IV loading dose and then 20 mg IV Q 12 thereafter, transitioned to valdecoxib after a period of 3 days, and then for an additional 7 days of oral treatment.

The second treatment group received placebo during the parenteral period and then was transitioned to valdecoxib during the oral treatment period. The final treatment group received placebo throughout both the parenteral and oral treatment periods. Again, patients were able to receive parenteral supplemental analgesia as required. As in the previous CABG trial, all patients were to receive aspirin at doses of 75-325 mg daily per protocol. In this trial all CABG cases were performed with cardiopulmonary bypass.

We used a slightly different adjudication scheme in this trial as compared to the first trial, and we were focused in this trial on myocardial events, cerebrovascular events, peripheral vascular events and pulmonary embolism.

Here we show the results of the CABG

surgery trial in terms of the overall composite endpoint of all adjudicated thromboembolic cardiovascular events. This is broken down to the intravenous, oral and entire study period. If we look at the entire study period which, by the way, included not only the 10 days of treatment but also a 30-day post-surgery follow-up period, we see that parecoxib/valdecoxib was associated with a significantly higher incidence of thromboembolic cardiovascular events as compared to patients who received only placebo. Patients who received only valdecoxib had a numerically higher incidence of thromboembolic cardiovascular events. This difference did not achieve statistical significance. Also, as you scan up here you can see that actually 3 of the events in this treatment arm occurred in patients prior to the point that they ever received valdecoxib.

Similar to the results seen in the evaluation of the crude incidence rates, here we show the time to event analysis for the parecoxib/valdecoxib treatment group, valdecoxib

only and the placebo group, again, out to 30 days post last dose of study medication, as stipulated per protocol. Again, we see that based on log rank test the parecoxib/valdecoxib treatment group was significantly different from the placebo group. No significant differences were seen between the placebo and the valdecoxib only treatment groups.

If we now break down the composite of cardiovascular events into its components and quickly look at the various components, we see again, as we saw in 035, that a major driver for the difference overall is the CVA or TIA category, as well as cardiac arrest and cardiovascular death which tended to occur later in the treatment of parecoxib/valdecoxib, while the strokes were clustered quite closely to the post-surgical setting.

By the way, I should probably state that as a result of those findings we quickly went to those countries, those regions of the world where parecoxib is currently marketed and have modified the product labeling in those areas to

contraindicate parecoxib and valdecoxib in CABG surgery or in other revascularization procedures since those types of settings have not been studied.

We have also taken the step in the U.S. of including a contraindication for the use of Bextra of valdecoxib in the CABG surgery setting or revascularization setting even though Bextra does not carry an indication for acute pain.

I just want to go back to the CABG surgery setting and make some concluding remarks. Again we are faced with limited data to really evaluate the effects of parecoxib and valdecoxib as compared to NSAIDs in this treatment setting. There is very little data with respect to NSAIDs.

The mechanism for the increased cardiovascular risks with parecoxib and valdecoxib is not known. We did risk factor analyses but, as you can appreciate with the small number of events, that didn't prove to be too fruitful.

We do know that patients that undergo CABG with coronary bypass pump result in activation

platelets, leukocytes and endothelial cells; that aortic cross-clamping results in ischemia, re-perfusion injury and emboli formation. There is a complex time course of changes in prostacyclin and thromboxane-A2 that have been reported following CABG surgery. And, as Dr. FitzGerald mentioned this morning, this patient population is also characterized by a high degree of platelet aspirin resistance. So, the constellation of all these factors obviously in some manner contributed to the results that were observed with parecoxib and valdecoxib, but the importance of all of these factors in that respect cannot be sorted out with the current study. What we do know though is that some of these are isolated exclusive to the CABG surgery setting.

At the same time we conducted a study in CABG surgery patients, we also undertook a study in general surgery patients. This was basically an all-comers trial. Only patients undergoing transplant surgery, intracranial surgery, revascularization procedures or partial liver

resections were excluded from the trial.

The doses tested and the duration of the trial are very similar to the CABG trial. The same endpoint committee was employed. Events were adjudicated in the same manner, according to the same definitions as the CABG trial. This was a 2-arm trial evaluating parecoxib followed by valdecoxib versus placebo and, as in the previous trials, patients could receive additional analgesic medication as required.

So, if we look at the incidence of adjudicated thromboembolic events in the general surgery trial, we see that the event rates--these were crude event rates--were one percent in the placebo group and one percent in the parecoxib/valdecoxib treatment group. This study also had a 10-day treatment window as well as a 30-day follow-up period. Again, we see that the distribution of events is scattered through the components of the composite with no clear patterns established.

The time to event analysis is shown here.

Again, no differences were seen in this analysis by log rank test.

We have also expanded our evaluation of the cardiovascular safety of parecoxib to all the surgical trials that we have performed with this drug. Here we are showing such an analysis, excluding such minor surgeries as third molar extraction, etc. We are really focused here on the more complicated surgeries, whether they be orthopedic, etc. We had about 1900 patients in the placebo group; over 2600 in the parecoxib treatment group. Again, we saw no differences in the incidence rates. We tried to collect as much information as we could over the entire parecoxib registration database.

Very quickly, just a brief word on the benefit that we see with parecoxib. I want to turn to the general surgery trial, first showing you the analgesic results that were observed with parecoxib and valdecoxib in this trial. We saw significant reductions in pain across the entire treatment period with parecoxib/valdecoxib as compared to

standard of care alone. In fact, these reductions were fairly impressive. They were on the order of 25 percent or more. Those improvements in analgesic efficacy came in the face of significant reductions in overall morphine or opioid requirements to control pain. There was a 35 percent reduction overall in the use of requirement of morphine across the trial in the parecoxib/valdecoxib treatment group as compared to placebo. You can see that most of that effect occurred during the parenteral treatment period. With that also came an improvement in opioid-type side effects but also, perhaps as importantly, it also came with improvements in functional status of the patients following surgery.

Here we show the Modified Brief Pain Inventory Functional Questionnaire, and you can see that there is a significant improvement in function in the parecoxib/valdecoxib treatment groups as compared to patients who received standard of care opioids only.

Finally to sum the risk/benefit of

parecoxib, parecoxib appears to offer unique benefits over existing parenteral analgesic medications and has a favorable risk/benefit ratio in surgical settings, other than CABG or revascularization procedures. Because parecoxib is a parenteral, it is administered in controlled settings under physician observation. This risk/benefit assessment is also shaped by the cardiovascular risk that is found in the CABG surgery setting but no in other surgical settings. Again, the caveat is that we have no evaluated the drug in other revascularization procedures and have no assessment of safety in that regard.

At this time I would like to turn the podium back over to Dr. Feczko for some concluding remarks.

Concluding Comments

DR. FECZKO: Thank you, I will be brief. I would like to thank the panel and the FDA for the opportunity given to Pfizer today to show the data that demonstrates the cardiovascular safety profile of our COX-2 inhibitors, both Celebrex, Bextra and

parecoxib.

Patients with chronic inflammatory arthritis pain have few therapeutic alternatives. While there has been a lot of debate about the placebo-controlled trials in the treatment of arthritis, placebo is really not an alternative. So, we did focus today's presentation predominantly on relative risk versus traditional non-selective non-steroidal anti-inflammatory drugs.

We know about the GI risks of older non-selective NSAIDs, but how much do we really know about their long-term cardiovascular safety? I think it is a question that needs to be answered. Part of the problem we had, as noted in the CLASS trial, was the high dropout rate associated with diclofenac over the dosing period. Given these unanswered questions, all the data suggests that Celebrex and Bextra probably have an important role to play in treatment of patients with rheumatoid arthritis and osteoarthritis.

As you heard, there is an extensive body of clinical trial and observational data with

Celebrex. We believe that this data shows that the cardiovascular safety of Celebrex is at least on a par with therapeutic alternatives such as the non-selective NSAIDs.

Pfizer is committed to doing the right studies with the appropriate study population and the appropriate study hypothesis to confirm what we believe is the preponderance of data we have seen today that Celebrex cardiovascular safety is comparable to the non-selective NSAIDs.

The Celebrex protocol is currently filed with the agency. We have had one review with a number of outside cardiology consultants. We are awaiting, however, the outcome of this advisory committee to determine whether or not the protocol, in conjunction with the FDA, is the appropriate model to be used for long-term evaluation of Celebrex.

We are committed to also continuing the evaluation of Celebrex in the prevention and treatment of cancer, as outlined by Dr. Hawk and Dr. Levin. We also agree with Dr. Hawk, and as Dr.

Furberg mentioned earlier, that I think there is a large body of evidence right now at the NIH that has already had a number of patients treated for well over two to three years, mainly in the cancer setting, mainly in placebo-controlled trials. I think it is imperative that we look at that data as soon as possible.

While the data for Bextra is definitely smaller, it is growing and in the treatment of rheumatoid and osteoarthritis we believe has not shown any increased risk in cardiovascular risk. The extrapolation from the CABG studies has been taken as evidence that there is a problem with Bextra overall. We actually don't see that right now, however, I will be the first to say that the database is much, much smaller.

We are also committed to looking at Bextra in a long-term trial in our arthritis patients as appropriate to evaluate the relative risk associated with Bextra. I think this is important because I do think rheumatoid and osteoarthritis patients do need treatment options and I will be

getting to that in a second.

Parecoxib, as was just mentioned, is an injectable drug, approved and marketed in some 40 countries around the world. It has found a place in those countries in the perioperative analgesia setting. It is found to be highly effective in relieving postoperative pain and in morphine sparing and, therefore, sparing the side effects associated with morphine in the postoperative setting, such as ileus and respiratory depression.

It has shown no evidence of the increase in severe AEs in the general surgery setting or the outpatient surgery setting. These seem to be confined right now to the post-CABG setting and, as Ken mentioned, this is already in the labels in all those countries in which it is currently being used and is still on the market.

In conclusion, I continue to be confident that Celebrex and Bextra have important treatment options for arthritis patients. I actually believe that there is no effective treatment for arthritis patients that is safer than Celebrex. I agree

though that we do need to do the long-term evaluations of both Celebrex and Bextra to really see their place in the therapeutic armamentarium.

For arthritis patients, and here I include myself because I also am on chronic therapy for osteoarthritis--arthritis patients need safe and effective treatment options. Not everything works for everyone. Patients do try different therapeutic options and do not tolerate some and it is not really clear why. We discussed this fact earlier on about dyspepsia, people stopping therapies, people trying various proton pump inhibitors to suppress the dyspepsia or related GI effects and these don't often work in people. Arthritis patients do need safe and effective treatments and they need the to move, to work and to make the most out of each day.

So, with this, I want to thank the committee and the FDA and we will throw this open again to questions for Ken and anybody else who can answer them. Thank you.

DR. WOOD: I have a number of questions.

In the general surgery study, there are a lot of issues about that that you didn't present. There is the same number of patients in that study as in the CAB study but many of these were women. They were much younger patients and the chance of seeing events in that study was extraordinarily small, don't you think?

DR. VERBURG: True. The underlying risk factors and risk factor status in the general surgery population was lower.

DR. WOOD: So, the general surgery study shouldn't give us any confidence to overrule the CAB study. Correct?

DR. VERBURG: I would not suggest that it would overrule the CB study. I would take note of the fact though that the cardiovascular events that occurred in the general surgery trial occurred at about an incidence of one percent. That was in the range of the incidence that we saw in the CABG surgery trial which ranged from 0.5 to 2 percent. So, although it doesn't completely put the issue to rest about to what degree the drug has a

cardiovascular risk associated with it in the general surgery population relative to standard of care alone, the trial that we have conducted, we believe, moves us down that road considerably.

DR. WOOD: What percentage of the general surgery patients were women?

DR. VERBURG: I believe that was 60 or 70 percent female.

DR. WOOD: And they were getting minor gynecological surgery largely?

DR. VERBURG: Actually, the largest percentage of surgeries was gastrointestinal, followed by orthopedic and then gynecological.

DR. WOOD: And do you recall the age difference between the two groups?

DR. VERBURG: No. I can find that.

DR. WOOD: I think it is about 10. I think it is more than 10 years.

The other issue that we are here to address is the total safety of these drugs. I wonder if you can show us Table 3 from your paper in The New England Journal, or perhaps you can go

through it? It is the one that shows the incidence and risk ratio of your predefined adverse events in the CAB study.

DR. VERBURG: I don't have that on a slide.

DR. WOOD: You are the author on that though, right?

DR. VERBURG: That is correct but I don't have a slide.

DR. WOOD: Well, let me help you. Every one of the predefined adverse events has a relative risk of greater than 1, and not all of them significant but every one of them greater than 1. So, I was sort of intrigued by the slide that said there was obvious benefit of this drug in surgical patients. Tell me how I would recognize the benefit given these predefined adverse events.

DR. VERBURG: I would like Dr. Nessmeier to come up and make some comments. Dr. Nessmeier was also an author of the CABG surgery paper, and a practicing anesthesiologist.

DR. NESSMEIER: I would just like to say

that the selective COX-2 inhibitors I think are potentially an important tool in the armamentarium from the standpoint of an anesthesiologist for treatment of postoperative pain, given that the alternatives also have side effects. Right now we have, obviously, the opioids and the narcotics cause dose-dependent respiratory depression and cause, you know, excessive sedation that is also dose-dependent, as well as nausea and vomiting, ileus, urinary retention. One has to wonder if morphine, for instance, would be approved if it were subjected to intense scrutiny today.

In addition, we have the non-selective non-steroidal anti-inflammatory drugs as potential therapy for postoperative pain, but they also are not without side effects. The one that is most commonly used by anesthesiologists in the perioperative setting would be ketololac and that has, as you know, the potential that surgeons worry about for post-surgical bleeding problems, the potential for gastric ulceration and also renal dysfunction.

So, given that the alternatives also have side effects, it is I think reasonable to continue the study of this drug, and it has been approved in

over 40 countries. I know my colleagues elsewhere are very favorably impressed with its analgesic potential, you know, primarily in relatively low risk patients. Certainly we have demonstrated that it should be avoided in patients undergoing coronary re-vascularization. I would certainly extend that, just based on common sense, to any other revascularization procedures. But that does not apply to the majority of general surgical procedures, gynecologic surgical procedures, orthopedic surgical procedures. We have no evidence that any of these concerns apply right now to the lower risk patients who are undergoing the vast majority of surgical procedures worldwide.

DR. WOOD: But, Nancy, if you look at your table, greater than one confirmed adverse event, that includes everything you have predefined and that is presumably what we are looking for, and the relative risk was 1.9, with a p value of less than

0.01. And, the events were not all cardiovascular--renal failure, upper GI events, every one of them--surgical wound events, every one of them, death even, has a relative risk of more than 1. So, I agree there may be an advantage but, in the absence of demonstrating that advantage and in the presence of clear risk, I don't see where the advantage is here.

DR. NESSMEIER: Well, the risk is well demonstrated now in coronary-artery bypass grafting population. It just hasn't been seen in any of the other studies, including the large general surgical study that was just completed and that we are in the process of writing up. That was over 1000 patients. But there are these 19 other smaller studies and it hasn't been seen in any of them in the other populations. I certainly agree that further study is needed because it is a vast population we are talking about, and the power to demonstrate absolute safety is also vast.

DR. WOOD: Tom?

DR. FLEMING: I have a very parallel set

of observations. I thought the final conclusion on B-36 was very strongly worded, unique benefits over existing analgesic medications and a favorable benefit to risk when, in essence, the general surgery study has ten events and you have four times that many events in the two CABG trials. And, you were referring to The New England Journal article. We can also go to the background material at Tab Q, page 18, and we see a very similar, striking global safety profile when you look at the SAEs in the 035 trial. There is a doubling in SAEs from 10 percent to 20 percent. When you look overall at GI SAEs, it is 0 against 7; cardiovascular renal SAEs, 7 against 33; cerebrovascular events, 9 against 1; thrombophlebitis, 3 against 0; atrial fibrillation, 2 to 1; MIs, 5 to 1. Now, the events that we saw, 15 to 2 just had 1 to 1, but I think the reported before adjudication events were 2 against 9. Then, pulmonary postoperative, 5 against 37. So, a very striking increase across a wide array of different SAE categories in the CABG setting for both of the

trials.

DR. WOOD: Curt?

DR. FURBERG: Well, I am troubled by something else. I am troubled by some inconsistencies that I have found in the briefing document from Pfizer. I would like to just briefly go over some of them. On page 55 there is a summary from acute pain studies. It says here are the safety data from 18 clinical studies. On page 76 in the summary it says here are the safety data from 20 completed studies.

I just wonder what happened to the other two trials. They disappeared. Any suppression of information or is it just an error?

DR. VERBURG: We will check on that.

DR. FURBERG: The other thing relates to the overall findings from these summary studies, the 18 studies. In Table 19, on page 60 for acute myocardial infarction it says placebo, 0; valdecoxib, 3. In the following table for myocardial infarction it says 1 versus 3. So, there is an internal inconsistency in two tables

after each other.

What is even more striking is that when you start looking at the individual studies that contributed to the summary statistics for the 18 studies--I just looked at two of them, the study we just talked about, the general surgery study. In terms of myocardial infarction, depending a bit on how you define it, there were 3 and 2. If you include cardiac arrest and sudden cardiac death it is 6 to 0. The summary statistic was 0 to 3 or 1 to 3 and here I have 6 in one study. I add in the data from one of the bypass surgery trials and I get additional numbers. So, just by combining the bypass surgery trial 071 and the general surgery for MI I have 0 to 8 or 1 to 9; not 1 to 3. And how about the other 16 studies? That is troubling.

I also find that they included in the summary statistic one of the bypass surgery trials but not the other one. Why? I mean, the other study met the same definition. If you put that in the numbers get even worse. So, there is clearly an under-reporting of events the way I interpret

it, and I have to say that we all make mistakes, and most of them are honest. Honest means that sometimes you benefit from your mistakes and sometimes you are hurt. But here all the inconsistencies tend to go in one direction. So, I just raise the question whether these are honest mistakes. It has made me wonder how much trust I can have in the information that we have received.

DR. WOOD: Dr. Hoffman?

MR. HARRIGAN: Excuse me--

DR. WOOD: All right.

MR. HARRIGAN: This is Ed Harrigan from regulatory affairs at Pfizer. We would like to have ten minutes. We are not prepared at this point to go through table by table to look at the questions that you have. We would like ten minutes tomorrow to do that and I think we will quite readily answer all the questions you raised.

DR. WOOD: Okay, that is helpful. Dr. Hoffman?

DR. HOFFMAN: I would like to just raise some questions that are extrapolations from the

CABG study where your explanation for why there may have been increased events is both provocative, interesting and perhaps, in fact, true. But what if this is a phenomenon that does not have to do with just perturbation of endothelium and cross-clamping, etc.? What if the patients going through a CABG in fact are going to CABG because the lesion that they have represents a generalized high plaque burden, unstable plaque? We would all agree then that, if we were to extrapolate from that, we would not give perhaps any drugs in this class to people at considerable cardiovascular risk that we knew of.

But the problem in chronic therapy for patients with RA and OA is that many of them come to us with perhaps moderate to even severe coronary-artery disease that is clinically silent. Even with extensive screening we may not be able to pick up those patients. We can only postulate that those patients will be the tip of the iceberg that may have events because of the physiologic effects of COX-2 inhibitors and perhaps Bextra in

particular because of what the data is that you have reviewed with us.

So, I am concerned that you would advocate, given these unknowns, the use of Bextra still in patients who have OA and RA and might be taking that drug for years, given that we don't have data that goes significantly beyond six months to a year long term.

DR. VERBURG: Would you like me to respond? Our position is that, again, we are shaped really by a lack of understanding about how other agents would act in the CABG surgery setting. I think your point is a good one. You do not know whether patients are entering CABG and the result is because of their history, the procedure or some combination of the whole. So, we are left with a lot of unknowns and we are left with trying to shape conclusions based on the data we have in the arthritis populations, being mindful of the concern that you raised.

DR. HOFFMAN: A follow-up to that but not directly related to that is, while you have shown

good efficacy for analgesia postoperatively and have provided a caution about why you would not use Bextra postoperatively for not just cardiovascular disease but vascular surgery in general, do you have any data from animal models that tells us anything about wound healing after vascular surgery in animals given Bextra and not given Bextra?

DR. VERBURG: Not that I have information specifically about wound healing following vascular surgery, we have done wound healing experiments with Bextra and the other agents. If you would like a quick synopsis of those, we can do that. Dr. Seibert or Dr. Kahn, can you make some comments in that respect?

DR. SEIBERT: Dr. Seibert, pharmacologist for Pfizer. We have looked directly at wound healing, looking at incisional wound repair, tensile strength and seen no effect at super-therapeutic doses of compounds like valdecoxib, celecoxib. If wounds are infected there may be some delay in that wound healing process. We are aware of that. We have no direct

evidence that there is a direct effect on wound healing in an incisional setting. We have no direct experiments looking in a vascular setting at this point.

DR. PLATT: It seems to me that in addition to having to make decisions without having all the information we would like, we have to make decisions around data that are internally not consistent with one another. That is, a lot of different studies come from a lot of different place and say things that can't all be fit into a single coherent framework. For instance, I take your point that the observational studies of Bextra seemed to show no real increase compared to other non-steroidals. On the other hand, there are observational studies of other non-steroidals that seem to show that they don't have increased risk compared to no drug and, yet, there is a good placebo-controlled study of valdecoxib that shows quite a lot of risk.

So, I don't know a way to them all together. It seems to me--this is a statement to

my colleagues on the committee, we have a tough job of saying not only is there a lot we don't know but we are going to have to decide which pieces of the information we do have to put the most weight on. Just to sort of herald the discussion that I know we will have, the question is what is the cautious way to proceed while acquiring the additional information that we need to have? How important is it to think about the way these drugs are used while the additional information is being collected?

DR. WOOD: Agreed. Dr. Paganini? No? Was there somebody else down there? Go ahead.

DR. FRIEDMAN: Sometimes vascular surgery, cardiovascular surgery in particular, has to be conducted on an emergency basis. How do you deal the case of people who may have been on Bextra, for example, and then need surgery? Do they have to be off for a period of time, or what policy are you advocating?

DR. VERBURG: Bextra is not approved for acute pain so if we are talking about placing a

patient perioperatively on Bextra--

DR. FRIEDMAN: No, no, I am talking about people who may have been on it for arthritis but then need emergency surgery.

DR. VERBURG: Well, I don't know that I have any specific recommendations on that. I haven't really envisioned that. I do know that patients undergo surgical procedures with selective COX-2 inhibitors routinely without discontinuing medication due to the fact that they do not result in excess bleeding. But I don't know that anybody has really thought through the implications of the scenario that you just brought up.

DR. WOOD: Dr. Nissen?

DR. NISSEN: I am going to suggest a conclusion from this study and I want to see if you agree with it, that what we learned from the CABG study is that a sufficiently high dose of a potent COX-2 inhibitor, given for only ten days to a group of people also taking aspirin, is capable of producing a highly significant increase in cardiovascular thrombotic events.

What is unique about this study from my perspective is the rapidity with which the events occur with relatively short-term exposure. So,

doesn't it tell us that the potential exists for potent COX-2 inhibitors to produce events quickly even in patients taking aspirin? I mean, I think that is something we haven't talked about with this study. Everybody got aspirin, as I understand it. So, this is a pretty rapid emergence of the problem. We heard about an 18-month delay in another study and everybody was talking about, well, is there an inflection point and so on? This is only ten days of therapy. So, isn't that the proper conclusion from the study?

DR. VERBURG: I would tend to agree. The onset was obvious by the time to event curves. All those rapid events tended to be stroke events in both trials, which is also somewhat puzzling and a little bit different from the types of events that we have been seeing in other settings.

DR. WOOD: Any other questions?

DR. FLEMING: Just one thing to add to

what Steve is saying, and that is just the absolute increase. We have seen that in terms of a relative risk increase this is a multi-fold increase but these are frequently occurring events. So, in the 035 trial when we are looking at the denominator of 311 people we are talking about cerebrovascular accidents in 9, an overall event rate increase from 1.3 to almost 5 percent. So, it is a tripling in the overall rate but to an absolute occurrence of 1/30 persons treated.

DR. NISSEN: You are suggesting sort of the number needed to treat in order to get an event is relatively small. DR. WOOD: Steve?

DR. ABRAMSON: I think it also speaks to the fact that, because aspirin was present, perhaps the importance of COX-2 in this acute event of cardiovascular insult but because aspirin was present it simply says if you inhibit COX-2 to a high degree you may get this result. It doesn't say that it is a highly selective COX-2 agent that is necessarily responsible. It may simply be the process of inhibiting COX-2. So, I think we have

to separate whether this is a selective COX-2 effect. The presence of aspirin basically says it is not a selective COX-2 effect; it is the importance of COX-2 derived prostaglandins in this setting that one is aborting.

DR. SEIBERT: I could just add--I know it is late in the day but, you know, I think that is exactly one of the points we want to raise, that the setting that we see these results in, in CABG, seems quite different, as Dr. Nissen pointed out, from what it takes in very chronic exposure in the arthritic patient. In fact, that evokes quite possibly very different mechanisms or very, very different places in the continuum.

What we really don't know is the effect of an NSAID in the same CABG setting because we haven't seen direct comparator studies performed, and we would not be interested in doing them at this point. We have conclusive evidence.

But this is quite different than the mechanism that we try to unify around the NSAIDs and the coxibs like celecoxib in the chronic

setting, where we believe hypertension is the driver there. And, if rofecoxib stands outside of that with unique properties then perhaps it does. So, we are really believing that we are working with very different hypotheses and mechanisms here.

DR. WOOD: Well, would you take it if you were at high risk of a platelet-driven problem?

DR. SEIBERT: I am sorry, I don't know where the question came from.

DR. WOOD: Here. I mean, given that CAB is a model of platelet-derived problems, would you take a drug if you had some other problem that looked like that?

DR. SEIBERT: Well, I would get right to the issue of risk/benefit and what your alternatives are.

DR. WOOD: And the benefits from Bextra in clinical trials like VIGOR or what?

DR. SEIBERT: I guess we would have to get right to the issue of risk/benefit here and, you know, perhaps that is best addressed in terms of that risk/benefit in that setting by our clinical

consultant.

DR. STRAND: May I answer you--

DR. WOOD: Sure.

DR. STRAND: --as a practicing rheumatologist, and I teach at Stanford. Bibica Strand. I think all of our patients to not respond uniformly to one non-steroidal. Similarly, they don't respond to COX-2 uniformly. Thus, we need multiple agents, and we have a group of patients with chronic OA, rheumatoid arthritis, even motor vehicle accidents who need anti-inflammatories on a regular basis. Would I recommend that a patient with high cardiovascular risk be taking one of these agents at the present time based on the data we just discussed, the answer would be no. But I think that there is a risk/benefit profile here that is positive in terms of understanding that these patients need treatment for their chronic pain. In fact, there is a GI benefit and, in fact, except in this setting which may be confounded somewhat from aspirin in terms of the CABG studies, we don't yet see an increased risk with Bextra. It

does not have an increased risk for hypertension or edema until you get to 40 or above, and the doses are 10 in clinical use.

I think the other point to be remembered is that in this CABG study, and of course it is confounded and one cannot say that there is absence of evidence and presence of safety, but many of those cardiovascular events also occurred either on placebo or more than five half-lives after the drug was stopped in the period of time of follow-up when we are not clear with aspirin was continued or not.

So, I think it is very difficult to understand what happened with many of the delayed events. If we look simply at the valdecoxib and placebo arm versus placebo, we don't see the same signal. So, from that point of view I would argue that we still need this alternative for the patients who need chronic pain relief.

DR. WOOD: Well, we are lurching towards conclusions here perhaps by Friday. What you are saying is that the patients you would see it in are patients who have failed other therapy?

DR. STRAND: I see it in patients who have high GI risk but, in fact, most of our OA and RA patients already have increased risk and many of

them have already had GI bleeds because they have tried chronic non-steroidals for a long period of time. I see it in patients who have not already responded to celecoxib or may have been forced to discontinue Vioxx.

DR. WOOD: Let's move on to the next speaker and, hopefully, that will be our last for tonight, you will be sorry to hear.

FDA Presentation: COX-2 CV Safety: Valdecoxib-Naproxen

DR. WITTER: What I am going to try and do is bring back some of the discussion I had earlier and specifically try and set some of this into some kind of a context. I was the primary reviewer for parecoxib. I was not the primary reviewer for valdecoxib so I have had to rely on reviewing reviews for the information I have here.

In terms of valdecoxib, the NDA came in on January 15 of 2001; 60 studies and I have listed

them here again. We like to focus on the arthritis studies. There were 10 of those. There was a long-term exposure included which I will talk about briefly. I would just note again, as we have been discussing, that there has not been conducted a long-term outcomes type study. So that we are complete here, the original approval for valdecoxib did not contain a sulfonamide warning. That was addressed by subsequent label changes and "Dear Healthcare Provider" letters.

To give you a sense of comparison then from earlier studies, the patient-years are described here for OA and RA. You can see that the numbers are smaller than what we were describing earlier for example with celecoxib.

Turning to the deaths in the NDA database, there were 22 deaths and 17 of thee occurred during the double-blind studies, 4 in the CBG trial. So I will discuss that when I talk about parecoxib. Two of those were cardiovascular related. There were 8 deaths in patients receiving valdecoxib. Half of those were cardiovascular related. There were 3 in

patients receiving NSAIDs; 2 were cardiovascular related. There were 2 non-cardiovascular related deaths that occurred in the cancer pain trial. During the open-label studies there were 5 deaths, 3 were cardiovascular related.

So, taking that information and looking at the number of deaths and patient-years and trying to give you some sense of comparison between my prior presentation, you can see that the highest mortality rate is in the group of valdecoxib plus the CABG patients at 4.7 percent. Recall that it was 3.7 percent; it was the highest from the prior discussion. If we exclude the 2 cases in CBG we come down to a rate of 3.5 percent. In the open-label studies the rate calculates out to 1.4 percent.

There were a couple of analyses that were conducted, special analyses that are listed here to look at the NDA for valdecoxib. This was to address the rate of serious thromboembolic cardiovascular events. They were in two patient populations, one that was described as high risk

and the other was at risk. So, the high risk patients were those that had a history of angina, myocardial infarction, coronary-artery disease and cerebrovascular accident, while the at risk patients were described as those patients who had hypertension, hyperlipidemia or smoking.

The endpoints as defined by the NDA at that point for this special analysis were MI, myocardial ischemia, unstable angina, cardiac arrest, sudden death, CVA, TIA, pulmonary embolism, venous thrombosis, embolism in general, peripheral gangrene and peripheral ischemia.

Looking then at the high risk group and looking at cardiovascular safety in this group, you can see that there are small numbers of patients that fit into this category in particular when looking at the placebo arm here. When you look at the incidence rates of the events per 100 patient-years, you can see that there doesn't appear to be a consistent dose effect across the various doses. Valdecoxib doesn't appear to be any different than the NSAID comparators. The result

here, looking at placebo, certainly appears to be a spurious result based upon the small number of patients and the event rates there.

Looking at the at risk patients, there are more patients in this category. It gives us more patient-years to look at. The number of events is small. Again, calculating the incidence rates and the events per 100 patient-years, once again there doesn't appear to be any strong dose-response correlation here between the increasing doses of valdecoxib but they don't appear to be any different or any greater than what was seen in the comparator group.

As I mentioned, there was a study that was conducted at the urging of the agency to give us a better idea of the long-term cardiovascular events. This was study 047. This was a 6-month study that was conducted in patients with OA and RA. It was basically naproxen 500 BID against two doses of valdecoxib, 20 mg and 40 mg BID. I have listed here the percentage of patients who completed the 26-week trial, 43 percent naproxen and about 50

percent in both of the valdecoxib arms.

I would like to draw your attention to worsened blood pressure. There was a statistically significant, at p less than 0.05, increase in worsened blood pressure in the 40 mg BID group compared to naproxen. In general when you look at this data there was a dose trend against valdecoxib for all the events, with the exception here of palpitations. It was comparable across all the groups.

Turning then quickly to parecoxib, as we heard it is an intravenous/intramuscular formulation. One of the questions is why would we want to develop or anybody want to develop something like this? So, what I have done here in trying to help answer that question is the label that was in the toradol label--this was Table 3. What this table represents is a postmarketing study of 10,000 patients non-randomized, looking at the issues of incidence of clinically serious GI bleeding after 5 days on increasing doses of toradol, ranging from, in this case, less than or

equal to 60 mg up to greater than 120 mg. There are two age categories here, less than 65 and greater than or equal to 65 years. The patients are broken out into those either without or with a history of perforations, ulcers or bleeds. As you can see and I have highlighted here, and that was one of the points of having this included in the labeling, is that as one increases the dose you increase the number of events. A quarter of the patients in fact had these serious GI bleeds. There also is an increase as you go through the categories of increasing event rate with age. So, I think this is part of the answer to the question as to why one we want to develop an intravenous or parenteral formulation of a COX-2 inhibitor.

Just to review quickly, parecoxib has a half-life of about 15-30 minutes. It breaks down into valdecoxib. What this does, and this is what we were concerned about, this allows exposure to different patient populations that have differing risk factors. The trials, however, were intended to address the issues in analgesia and we have some

analgesic experts on the panel here. For example, the concept of multimodal analgesia is very much in the popular press these days. It is established that COX-2 has a role in all forms of pain, but there are also studies that looked at parenteral analgesia and opioid sparing and certain of these studies were conducted in concert with valdecoxib which you have heard about, the CABG trials, and I will just briefly review those too.

The original NDA for parecoxib was submitted on September 11 or 2000, 36 studies. They had a variety of studies, as I listed here. Just drawing your attention to the post-surgical analgesia trials, there were 8. There were 4 preoperative or preemptive analgesic trials, and there were 2 studies looking at opioid staring. The CAB 035 was one of those. The long-term safety is what I have already described in the valdecoxib 047.

This was CABG-I. The first CABG 035 as we know, was 2:1 randomization in terms of parecoxib to the placebo. I just want to point out the

placebo in this case really refers to standard of care so this is patient controlled analgesia and opioids. The study was broken up into two phases, as we heard. The first 3 days was the IV/IM formulation and then when patients were able to take medicines by mouth they were transitioned into the valdecoxib, same dose, 40 mg twice a day or every 12 hours up until 14 days. Aspirin was a requirement for the study at less than or equal to 325 mg. Patients were studied to 30 days for events, which I will point out in a second.

This was a first of its kind study. This was a study to address the concerns that we had in the agency about this particular drug going into a high risk population. There were a lot of concerns. We were certainly aware of the various hypotheses and issues that are out there with COX-2s. So, we challenged the sponsor to come up with a study in a high risk population. This was the agreed to design of the CABG study but, as I alluded to here, it was a complex study not only because of the patients but because of the

procedures and the co-medications.

So, to help address this there were blinded committees that were established to verify that the adverse events met established criteria to help figure out dates and attribution, and this is what was called then CRAEs, clinically relevant adverse events. As has been pointed out just earlier, there were no active controls in this CABG or the other CABG trial, and the discussion we had, which is what you are having, is would that have been an appropriate control in the first place given the risk factors associated with toradol for example?

The exposure, just to give you a sense, was more than 7 days. The bulk of the patients achieved that endpoint. To give you a sense of what the CRAEs were, they were defined as deaths, cardiovascular events, pericarditis, congestive heart failure, renal failure/dysfunction, TIA event, major non-GI bleeding requiring transfusion and infection which required institution of antibiotics and pulmonary complications.

What I would like to do is just briefly talk about some of these and give you a sense of the adjudication and what was actually looked at,

pointing out once more that events were followed up to 30 days post last dose of study drug.

Looking at myocardial infarction in terms of a CRAE, to qualify into that definition you had to have two of the following four criteria as I have listed on this slide. For example, chest pain that was typical, not relieved by rest or nitrates; you had enzyme elevation as I have listed here, CK-MBs, LDHs, troponin levels. You had new wall motion abnormalities or you had EKG changes looking at ST-T and Q waves, as I have indicated on this slide. So, you had to meet two of the four criteria to be qualified as having an MI.

Turning to the events then and to some extent repeating the results you have seen but just to go over it again, there were the two groups, placebo and the parecoxib 40 mg BID group. I have listed here the intravenous for the first three days and the entire study. Looking at any event,

you have a statistically significant, at p less than 0.12 by Fisher's exact test--the number of CRAEs in the entire study as compared to the placebo arm. When you look essentially at all of the adverse events as defined as CRAEs, just going down the list here, most of these are against parecoxib and valdecoxib. I would just draw your attention to some interesting ones. The MI, for example, there was only 1 event that fit the CRAE definition in both of these. On the other hand, there were 9 events that fit the CVA definition in the parecoxib/valdecoxib group.

Looking at the issue of MI adjudication, I just want to make this point, that there were 13 possible MIs. There were 11 that were in fact sent to the committee. These were 9 events in parecoxib and 2 in the placebo. Of these events, only 2 MIs survived the adjudication process so there was 1 that was listed for parecoxib and 1 placebo, which is what I just described in the prior slide. I note here that one of the rejected events was in the parecoxib group which resulted in death,

probable MI of the patient.

What this brings up is the difficulty that we had on both sides trying to, you know, adjudicate these events relating to the timing of the drug. As I have suggested before, this was a complex setting. There wasn't a lot of experience in looking at this. So, that was a factor. Nonetheless, these results factored into my recommendation that this drug not be approved. It also was not approved because there was essentially limited information in terms of efficacy. It was essentially single dose information.

So, there was discussion that ensued with the sponsor in terms of thinking through these events and understanding a way forward. I am sorry, let me just describe the deaths for a second in parecoxib. There were 4, as I said before. There was one in a 58 year-old male who died of a duodenal ulcer. There was one in a 69 year-old female who died on day 19 of a probable MI. There was one in a 56 year-old male who died of septicemia, pneumonia. There was also one in a 62

year-old male who died of an infarct in the left cerebellum.

Given what I just said before, the issue was that perhaps the dosing was too high in that study. There was consideration that adjudication of events on the day of surgery and giving the drug on the day of surgery was not a good idea so that dosing for parecoxib would be delayed until the day after surgery. Then there was an attempt to try to get a handle on whether these events were occurring during the intravenous phase or during the oral phase, or both. So, that was part of the explanation for the repeat study, CABG-II, 071.

This then also had the CRAE definition, again studied for 30 days looking for events. This was a larger study. The groups this time are fairly balanced in terms of the numbers so you have placebo/placebo here; placebo for the first three days; valdecoxib to finish out the study; and then parecoxib/valdecoxib.

When you look at any of the CRAE events in either group that contains the COX-2 agents, there

is a statistically significant difference compared to the placebo arm. When you look at all of the events of the CRAEs, for the most part they trend against the COX-2 selective agent, with the notable exception of DVTs. There was one in the placebo group and none in the other group.

I should just comment because there was a comment about it before, in CABG-I as well as this there were issues of wound healing and wound complication which was, to some extent, an unexplained finding. I should also just go back and remind everyone that there was an issue of hypotension that we noted, particularly in CABG-I for which still to this day there isn't, to my mind, a good explanation for.

The deaths in 071 included in the placebo group an intestinal perforation. The placebo/valdecoxib group included cardiac arrest, pneumonia and cardiac failure. The parecoxib/valdecoxib group included cardiac arrest, pulmonary embolism, myocardial infarction and ventricular fibrillation.

The question then ensued would the concern about what had happened in 035 in the at risk population extend to other patients, so there was

study 069 that was designed which was meant to look at more general surgery with basically the same doses that we had seen in 071, in the second CABG trial. So, there was a 40 mg loading dose followed by 20 mg BID. These were more general surgical patients which included a mixture of orthopedic, GI, GYN, thoracic and a small amount of others.

Looking at the CRAEs in this study, and I have just then listed here for the entire study. Again, the groups are exactly balanced in terms of the numbers. When you look this time at the number of events the results look different in the sense that there tends to be more of these events in the placebo arm than the parecoxib/valdecoxib arm. With the exception of looking at MI, cardiac arrest and cardiac death, there are more events ion the parecoxib/valdecoxib arm than there are in the placebo arm.

This trial was included, as was indicated,

in the current label for valdecoxib, as is study 071 which I didn't mention.

The deaths in 069 for the placebo included a cardiac failure, carcinoma, a mesenteric vein thrombosis and a cardiac arrest. In the parecoxib/valdecoxib group it included GI hemorrhage, MI and pulmonary embolism.

I will skip these slides and just make the following point, that as we think through safety for NSAIDs and COX-2s, what we have been hearing is, you know, think about the data that we have but I think we need to worry about the data that we don't have. As others have said and I am just reinforcing it here, the absence of evidence is not evidence of absence. So, there is a lot there that we still need to know. Thank you.

DR. WOOD: Great! Let's move straight on to the next presentation, and that is our last presentation for tonight. Then we will have the questions after that, if anyone is up to it still; hopefully not.

Bayer and Roche Joint Presentation on Naproxen

DR. BAUM: Good evening. My name is Len Baum. On behalf of Hoffmann La-Roche and Bayer HealthCare, I would like to thank the advisory

committee and the FDA for allowing us to come before you today to talk about naproxen.

Roche and Bayer would like to share what we know about the issues and provide information on the large body of data that can help the FDA and the advisory committee in their review. We also would like to help reassure consumers and healthcare professionals about the safety of naproxen.

Today we will provide a summary of the information from our briefing book and we will quickly go through some of the information that both Roche and Bayer jointly submitted. The information comes from over 30 years of clinical and marketing experience. We will provide a very brief overview of the history of the product, and we will quickly go through some of the properties of naproxen since a lot has been covered today. I will briefly touch on the ADAPT trial and then

spend most of the time on the safety evaluation that has been conducted.

Along with me today is Dr. Martin Huber who is the Vice President and Global Head of Drug Safety and Risk Management for Hoffmann La-Roche. We also have a number of people from each of our companies to assist us should we have any questions at the end of the presentation. And, a couple of outside experts also, Dr. Kay Brune and Dr. Ian Grainek who could also assist should there be questions at the end of the presentation.

Naproxen has been available for over 28 years now. The prescription was approved in 1976 for a number of indications that you see up here on the board. It is available by a number of manufacturers today for the treatment of rheumatoid arthritis, dysmenorrhea, bursitis and the other indications that are listed.

In 1994 Aleve was approved as the over-the-counter version. That came before an advisory committee who looked at the data and then was ultimately approved by the FDA via an NDA. The

indications are listed up there and it is currently marketed by Bayer HealthCare for the temporary relief of minor aches and pains, and also for reduction of fever.

I wish to note here that naproxen is safe and effective for these indications when used according to the labeling directions.

Quickly going through this and just to lay the groundwork for the rest of the presentation, we did talk today extensively about the class of NSAIDs, and naproxen has its anti-inflammatory, analgesic and anti-pyretic properties. It is also known to inhibit platelet aggregation, as we heard, with the major differences between the members of the class being potency and pharmacokinetics, and this includes duration of action.

Just to set the stage and to remind everyone, the class of NSAIDs is fairly large. The one thing I would like to point out is that coxibs as well as the propionic acid class are listed as part of the NSAID class. We have heard a lot today of NSAIDs versus coxibs but this is a large class.

Within the class of the propionic acids is naproxen under the form Aleve also for over-the-counter, ibuprofen, Advil, motrin. So, there are a large number of products that we use every day for both Rx and OTC.

What is the relevance of what we are looking at with naproxen? This compound has been well documented with a long history. It is referenced, as you have heard today, for many analgesic clinical trials. Naproxen as well as other selective NSAIDs are important treatment options for a broad range of patients and conditions. As we look at this data, we must also consider not just the safety data but also the efficacy, as has been mentioned a number of times today.

The data that has been submitted in our briefing document covers a considerable amount of patient exposure and experience. I am going to draw upon our safety discussion today, information from clinical trials, observational studies and postmarketing information. From the Rx side we

will draw from over 110 billion patient use. From the OTC side, over 550 billion, and this is courses of therapy. We have listed this as 2 tablets a day for 10 days.

When we look at the totality of the data, we have not seen any safety signals related to myocardial infarction, cerebrovascular events, and as we look closely now at ADAPT, what I am going to do is just highlight a couple of the points, and I do this more to let you know how this fits into the spectrum of the data that we have been presenting and will discuss today.

One point is that it is an NIH-sponsored trial. Bayer provided product, naproxen, for investigational use. It was a 3-arm study comparing naproxen celecoxib and placebo. The patient population included 1200 patients. We don't know the exact breakout of these but I want to point out that it was a 2:1 placebo to the investigational drug examination. So, it is not 2400 patients on any one drug. Patients were 70 years of age and older, and it was being looked for

as the prevention of Alzheimer's disease. The study began in 2001 and was planned for 7 years. It was suspended after 3 years. One thing about the patient population I would like to point out is that these patients did have a familial history of dementia or Alzheimer's.

What is on this slide are events that have been publicly reported leading up to the suspension of ADAPT. On December 10 the data safety review board did not recommend stopping the ADAPT trial. In fact, the same safety board reviewed the data at least twice over the past three years and each of the times did not recommend stopping the trial.

On December 17 the APC trial was suspended due to an indication in cardiovascular/cerebrovascular risk of celecoxib versus placebo. Although there was no significant risk for celecoxib, the ADAPT trial was suspended in part due to the APC findings and this was released as part of the NIH statement. So, on December 20th the NEI announced the ADAPT trial suspension. This information was released to the

public by the study group and it was based on preliminary findings, not through the peer reviewed journals.

Some of these data may be discussed on Friday by the NEI. We do not have that information and will not be covering that in our presentation. I put this up to at least bridge into the data that we will be covering on the safety analysis, and to help put that into its perspective.

In summary, at this point naproxen is a non-selective COX-1 and COX-2 inhibitor. It is widely used, with over 22 million patients using the product each year. It has an established safety profile with over 30 years of both clinical and marketing experience. It is used as a reference standard for many of the trials we have heard about, and the unadjudicated preliminary findings of ADAPT, and for that matter the final findings of ADAPT, will need to be put into the context of the wide body of data that is available on naproxen to date.

At this point I would like to introduce

Dr. Martin Huber who will review the totality of the safety data that supports the lack of myocardial infarction and cerebrovascular signals with naproxen.

Safety Data

DR. HUBER: Thank you, Len. Good afternoon. I will try to go through this in a little abbreviated form as I will be repeating data that has been summarized by other speakers.

What we looked at was we did an evaluation of the available data to us, looking at the question of myocardial infarction and/or stoke based on the preliminary findings that were reported for the ADAPT study. This evaluation included an overview of the clinical pharmacology, the clinical studies from both the NDA for the OTC as well as prescription filings. We also looked at our postmarketing safety data. Furthermore, we looked at the large randomized postmarketing clinical studies that were available in the literature, and finally spent some time on the observational studies.

With regard to the pharmacology, I think we have heard enough about COX-1 and COX-2 today to last most of us a lifetime so I am not going to

spend any time, other than t remind you that it is a known property of naproxen to inhibit platelet aggregation and this has been substantiated by studies demonstrating an increase in bleeding time, etc.

With regard to the clinical trials in the NDA, I would just like to briefly touch on that. There have been more than 500 patients treated in the original NDA for naproxen, of which more than 300 were treated more than 6 months.

In addition, a little more than 4000 patients were in the OTC NDA--limited duration of treatment for these patients but in each of these data sets there was no signal for either myocardial infarction or stroke.

Furthermore, we reviewed the postmarketing data available in the Roche safety database which goes back to the launch of the product in the early '70s and in that, with over 100 million patients

exposed globally, we saw no signal for either MI or stroke. A similar review in the OTC postmarketing surveillance data did not identify a signal.

I an going to skip over this. We did some disproportionality. These are some internal signal checks we do. It is in your briefing package and the basic message is we didn't see a signal even going back retrospectively. If you have questions I will be happy to discuss this.

What I would like to focus on are some of the large randomized, postmarketing clinical trials. The selection criteria we looked at here were that they needed to be published. They had to have naproxen in them and they also had to have prolonged exposure. We weren't looking at short term. There are hundreds of trials looking at very short-term use of these agents.

The first trial is the VIGOR trial. I think this has been discussed extensively and I will not spend any more time on it. I would like to spend a little more time on TARGET. This study has not really been discussed in detail today. Our

colleagues, I am sure, from Novartis will be spending more time on this tomorrow, but just to quickly go over a few findings with relevance to naproxen. I am not here to discuss lumiracoxib but to focus on naproxen.

Of note, this is really two studies; it is two sub-studies. One of these studies was lumiracoxib versus naproxen and another of lumiracoxib versus ibuprofen. So, this offers us somewhat of an interesting opportunity to potentially look at naproxen in relationship to another non-selective non-steroidal in a large randomized clinical trial.

In the first sub-study which was looking at naproxen versus lumiracoxib, with regards to stroke which included ischemic and hemorrhagic, as well as for acute MI, naproxen had a lower incidence of both of these events compared to lumiracoxib.

On the other hand, when we looked at the sub-study looking at ibuprofen, ibuprofen actually had a higher rate than lumiracoxib. What makes

this a little tricky though is that if you look at lumiracoxib in the two arms it is not comparable. There was actually a higher rate in the second study the naproxen study. The authors of the publication attribute this to a higher cardiovascular baseline risk in the second sub-study. But for our purposes today, what we would like to emphasize is that we have to be careful in these comparisons that if you use lumiracoxib as a common reference arm--the doses, schedule, et., I understand to be the same in both sub-studies, you have ibuprofen higher than lumiracoxib here; naproxen lower than lumiracoxib here.

The other study, as noted, was the Alzheimer's trial. This is not the ADAPT study. This is a study that was done in patients with mild to moderate Alzheimer's disease, published by Aisen, in JAMA in 2003. This was a randomized trial between placebo, naproxen and rofecoxib. These data are based on the publication. Essentially what we see is that in the placebo arm

there are 111 patients and what we have is death, MI, stroke and TIA. These data are the serious adverse event data as reported in the paper. We are not aware of any specific adjudication or any further analysis.

There has been extensive discussion of the trials with celecoxib. The only reason I bring this up is it is part of White's meta-analysis. There were 2000 patients treated with naproxen. There are 4 events that were noted in that meta-analysis, 1 fatal stroke, 2 fatal MIs. The rate of these events for naproxen was comparable to the other groups of celecoxib and placebo as part of that meta-analysis. We did not see in this publication evidence of an increased risk of myocardial infarction or stroke compared to either celecoxib or placebo.

Given the lack of large long-term randomized, placebo-controlled studies, I would now like to review the observational studies. We recognize some of the limitations of observational studies but I would like to spend a little time

emphasizing that there are some positive attributes of these studies as well.

First of all, these studies can be done in a fairly short period of time. I think all of us have noticed that since this question has been raised, there are multiple publications, 2002, 2003 and actually in fact even 2005, because you can do an investigation of chronic or prolonged exposure but by going retrospectively get the data in a relatively short period of time.

They also offer a tremendous opportunity to look at relatively rare events. You can say a one percent adverse event is not that rare but when you try to look at a 20-30 percent change in the risk of an event that is of one percent frequency in a clinical trial, all of you are aware of the limitations of sample size. Looking at 10,000 patients is easy to do, or relatively easy to do in an observational study.

Maybe more importantly, it is real-world use of the drug. These are heterogeneous populations. There are concomitant medications;

there are concurrent illnesses. I think what is the most important thing when we look at observational studies, we have already started to see isolated reports of limited observational data. Every observational study has intrinsic limitations, the database, how you identify the patients. We can have epidemiologists spend most of the afternoon or evening if they want in debating that, but at the end of the day there are limits. What is the real value of these studies is what do you see when you do multiple studies across multiple databases? Do you find a consistency of the finding?

These represent the observational studies that have been published for naproxen and myocardial infarction. That is the topic that was covered here. This was recently summarized in a meta-analysis by Juni et al. in Lancet in 2004, and there weren't any other ones out there besides these so we kind of borrowed the figure from Juni.

There has been a huge discussion in the literature regarding the validity, the strengths,

the weaknesses of the meta-analysis which showed that the overall risk was 0.86, but I am not going to spend a lot of time on that. What I would rather focus on is just to briefly update the committee on the weight of these studies.

Each study is represented here. What you can see is one is in the center of the axis here, and this would show that there was essentially an equal risk of MI between naproxen and whatever the control group was for the study. This direction favors naproxen having a lower risk than the control. This direction favors the control.

What we find is most important about this data is there are 11 studies and 10 of them show the risk either equal to 1 or less than 1, which is striking consistency. There is one study which had an increased risk. This is the Graham study which was recently published in Lancet, which showed a 14 percent increase in risk. Of note, in the publication in Lancet the lower limit of the confidence interval here did hit 1.0.

What we think is the important message

here is not to spend time going through each of these but rather focus on the relative consistency of the findings. Based on these data, we do not see evidence of an increased risk of MI with naproxen.

A criticism of this analysis is that it includes multiple studies from the same database. It seems pretty intuitive that if you do multiple studies on the same database you will get similar findings. So, we did a sensitivity analysis where we took only one study from each database. The ones we excluded are here. If you look at the pooled relative risk it stays at 0.87. Remember, the original analysis was 0.86. The confidence interval gets wider, but you would expect this because there is a fewer number of observations. So, we see no material change in the conclusions of Juni et al.

In summary, a review of the observational studies shows no increased risk of myocardial infarction with naproxen. A review of the postmarketing data also showed no signal for MI or

cerebrovascular events. The published clinical trials do not provide evidence of an increased risk of MI or cerebrovascular events. And we would urge caution that the unadjudicated preliminary findings of ADAPT are inconsistent with the known data and pharmacologic properties of naproxen and need to be carefully considered in your deliberations.

In conclusion, the vast majority of data, collected over 30 years, indicates no signal for naproxen and myocardial infarction or cerebrovascular accident. We believe that naproxen, both prescription and Aleve over-the-counter remain safe and effective and that they remain important treatment options for patients. Thank you.

Committee Questions to the Speakers

DR. WOOD: Great, and thanks for going through that so quickly. Kimberly tells me that the committee on breast implants went to eleven o'clock so we have a bit to go yet before we beat them. Anyway, we will take questions for the last group of speakers. Curt?

DR. FURBERG: A couple of comments, one regarding Bextra. I applaud the FDA in the effort to standardize myocardial infarction, but to apply

the standard criteria of myocardial infarction to patients undergoing bypass surgery doesn't make any sense because you are opening the chest so the whole criterion about pain doesn't make sense.

The other one is that many of them have increases in their enzymes. You cannot apply the regular criteria to myocardial infarction to the population. So, I just think that reclassification is not valid.

The second point is related to the ADAPT. you can add to your list of limitations of the study that there is no prespecified outcome for cardiovascular events. The investigators looked at a number of them and it is not clear which one they decided to put their money on. And, there is no adjudication of the cardiovascular events. They were all self-reported--very, very soft data.

DR. WOOD: Nancy?

DR. NESSMEIER: Well, just a comment about

the CABG study, the criteria were different in that it was diagnosed either by autopsy or by CK-MB level of more than 25 ng/mL within the first 72 hours after CABG, or an excess of 10 ng/mL if more than 72 hours had gone by, or a peak troponin of more than 3.7 mcg. So, those are more rigid criteria than would be used for a non-surgical study.

DR. WOOD: Right, and there was a control group so it should have shaken out. Right?

DR. NESSMEIER: Correct.

DR. WOOD: Yes, Dr. Hennekens?

DR. HENNEKENS: I have two comments and a question. First of all a comment about the CABG surgery data, in terms of benefit to risk assessment, I would believe that a priori any drug, regardless of its class, that would increase blood pressure, fluid retention and risk of heart failure, if given during or after CABG, would pose very difficult research and clinical challenges. I would say to Dr. Shafer, regardless of the mechanism that is proposed, this is far beyond the

powers of aspirin.

The second comment to Dr. Huber as regards his reassurances from the observational comparisons, I am concerned that for small to moderate effect there are biases confounding by indication, and uncontrollable confounding inherent in all case control cohort studies, no matter how large or how well designed, as well as their meta-analysis. They can either produce false evidence of benefit or harm or false evidence about lack of benefit or harm. I just think the randomized data are far more important, which leads me to my question to Dr. Huber. In VIGOR, do you believe the overall randomized findings are attributable to a hazard of rofecoxib, benefit of naproxen or some combination of the two?

DR. HUBER: I don't know.

DR. WOOD: That is a surprise! Other questions? Dr. Shafer?

DR. SHAFER: I just want to re-echo what Dr. Nessmeier said. The CABG population is very different, very much a pro-inflammatory population.

In anesthesia we do very poorly at treating postoperative pain, particularly in the first 24, 48. Multimodal therapy is what we are looking for and certainly if you say the CABG population is very different and you look at the data in the acute surgical setting--brief administration--it is an area where we do need improved therapeutic options and I would just encourage the committee to keep that in mind.

DR. WOOD: Other comments? Yes, Tom?

DR. FLEMING: Just looking at the nature of the data that we have been provided here, slide 10 where we looked at naproxen exposure data with millions of doses and the sponsor basically said there is no safety signal for cardiovascular events or MIs. I guess if we were looking at rare events, Stevens-Johnson's rash or something like this, this kind of evidence could be reassuring. But how is reassuring when we are looking at MIs and strokes where you expect to see a certain rate of these in natural history? How do we rule out a doubling? So, essentially it leads me to really wanting to

focus on the randomized trials as having a sense.

Looking at slide 17, I am worried about how little of this information is longer term exposure. So, if I am understanding correctly, we really have TARGET and VIGOR and ADAPT as maybe the best bases for making an assessment over a longer term in a truly controlled fashion for effects on cardiovascular-related major events--cardiovascular death, strokes and MIs. Two of those, VIGOR and TARGET, we don't have a placebo control. The questions that were just raised I think by Charlie Hennekens are in VIGOR--basically how do you make an assessment there without a placebo control? ADAPT is a placebo control.

We heard just now that the data monitoring committee specifically didn't stop the trial on 12/10/04. By my notes earlier this morning, I thought we were told that the data monitoring committee on that date did stop the trial due to naproxen GI bleeds, cardiovascular and cerebrovascular events. So, I am a little confused about what actually did happen. Is it true at this

point though that we don't have first-hand access to what the data actually are in ADAPT?

DR. HUBER: Let me answer your first comment about the randomized clinical trials. Basically what you said was that the TARGET and the VIGOR studies are the large randomized, comparative trials. There is also the Alzheimer's study which is obviously much smaller but it is one-year follow-up.

With regard to the postmarketing data, we recognize the limitations. We were just wanting to reassure you that there hadn't been numerous case reports out there. Also, when we look at disproportionality there is really no signal there. It is something we use in postmarketing surveillance.

I would be careful on the observational studies. Recognizing the limitations as stated, that does give us a large number of patients who have been exposed to naproxen and gives us some, we believe, important data. There are 80,000 exposures in that series of observational studies.

So, we do believe there is some weight to that evidence. It shouldn't be completely put aside.

DR. FLEMING: And the weight you are placing on that is you are reassured about what specific outcomes?

DR. HUBER: That for MI, for myocardial infarction with 11 observational studies, we see a consistency of finding that is at 1 or lower.

DR. FLEMING: But doesn't the fact that we have 11 of those give us a more precisely biased estimate? How do you know that all 11 aren't in fact subject to the same type of systematic bias and under-detection?

DR. HUBER: Well, we use multiple databases. There are different comparisons. There are past users in several of the studies. I guess the question is if we take that approach, then we have to question should we even do observational studies for any issue?

DR. FLEMING: Not necessarily. It depends on what you are looking for. My comment was if you are looking for MIs and strokes, which are events

that would in fact occur in natural history, unless you are looking for a ten-fold increase, isn't it really difficult for that type of outcome to truly be able to rule out a relative risk of 1.5? I would argue, yes, it is. While there are other things that were reassuring, if we wanted to be reassured about stroke and MI, this is where it is intrinsically the most difficult.

DR. HUBER: I agree you. I don't think we should rule things out on the basis of the observational data, but I think what is important is when we looked at this a priori based on mechanism of action, etc., the data was telling us there was probably not an increased risk. So, when we take that as the first line of evidence and then we put on the additional lines of evidence, at this point in time the only data suggestive of an increased risk, to our knowledge, is the release of the preliminary findings of ADAPT.

DR. FLEMING: Can you clarify that? Because I believe we heard something different this morning about what actually has been stated. Can

you clarify what actually has been stated?

DR. HUBER: What we are talking about is the NIH press release. I believe there were approximately 70 cases, and what was stated about it was that there was--I can't remember the exact wording of the text, but it was an increased risk of stroke or MI.

DR. WOOD: Well, we are going to hear about that on Friday morning.

DR. FLEMING: So, we will hear about it on Friday?

DR. WOOD: Yes, unless we keep talking until then, I guess. It is down for 8:10 on Friday morning. Other questions? Yes?

DR. MORRIS: Dr. Huber, while you are there, did any of the observational studies stratify by time on drug? And, was there any different finding by length of time on Naprosyn?

DR. HUBER: I am going to have to look to my epidemiologists? Dr. Thacker is the epidemiologist for Roche.

DR. THACKER: We did an extensive

literature review of all the studies that were published up to December, 2004. None of the studies really gave us any data on duration of use.

DR. WOOD: Other questions? Yes?

DR. WITTER: I just want to make the point that in the ADAPT trial naproxen was the OTC dose.

DR. WOOD: Any other questions or are we finally getting exhausted? Yes, Ralph?

DR. D'AGOSTINO: Just because we are exhausted, that doesn't mean that what was presented is, in fact, something we can buy. I think the comments that Tom is making are very important. We have all this meta-analysis. We don't know anything about those studies. So, I think we have to wait until we hear from the NIH.

DR. WOOD: Right. Dr. Seligman has something to say?

DR. SELIGMAN: Just a very brief announcement to the Drug Safety and Risk Management Committee. We would like to meet in the lobby at eight o'clock and all go out for dinner if you are still willing.

DR. WOOD: Before we break, do the FDA have any final comments or questions? No? In that case, we will meet promptly at eight o'clock and

start dead on time. See you tomorrow.

(Whereupon, at 7:30 p.m., the proceedings were adjourned, to reconvene at 8:00 a.m., Thursday, February 17, 2005.)

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