DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

CARDIOVASCULAR AND RENAL DRUGS

ADVISORY COMMITTEE

September 10, 2004

8:31 a.m.

Holiday Inn
Versailles Ballrooms
Bethesda, Maryland

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

Dornette Spell-LeSane, M.H.A., NP-C, Executive Secretary

Jeffrey S. Borer, M.D., Acting Chairman
Steve Nissen, M.D.
Alan T. Hirsch, M.D.
Thomas Fleming, Ph.D.
Maria H. Sjogren, M.D.
Jonathan Sackner-Bernstein, M.D.
John R. Teerlink M.D.

Susanna L. Cunningham, Ph.D.
William R. Hiatt, M.D.
Beverly H. Lorell, M.D.
Thomas Pickering, M.D.
Ronald Portman, M.D.

Paul Watkins, M.D., Ph.D.
Jose Vega, M.D.

FDA Participants

Dr. Mark Avigan
Dr. Florence Houn
Dr. Joyce Korvick
Dr. Kathy Robie-Suh

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

DR. BORER: It's 8:30 and I'm going to call the meeting to order. This is the Cardiovascular and Renal Drugs Advisory Committee meeting, and we will discuss New Drug Application (NDA) 21-686, proposed trade name Exanta (ximelagatran) by AstraZeneca, for the proposed indication of the prevention of venous thromboembolism in patients undergoing knee replacement surgery, the prevention of stroke and other thromboembolic complications associated with atrial fibrillation, and the long-term secondary prevention of venous thromboembolic events after standard treatment following an episode of acute venous thromboembolic event.

We'll begin by introducing everybody at the table. In this meeting, the Cardio/Renal Committee actually is advising the GI Division as well as Cardio/Renal, in fact, primarily the GI Division, so we have more people at the table than we sometimes do. Maybe we can each say our name and what we're doing here, and we'll start with Dr.

Vega on the far side.

DR. VEGA: I'm Jose Vega. I'm the industry representative on the committee, and I'm from Amgen.

DR. PICKERING: Tom Pickering from Columbia Presbyterian Hospital in New York.

DR. PORTMAN: Ron Portman from the University of Texas in Houston.

DR. HIATT: Bill Hiatt, University of Colorado.

DR. LORELL: Bev Lorell, Harvard Medical School, and also Guidant Corporation.

DR. SACKNER-BERNSTEIN: Jonathan Sackner-Bernstein, North Shore University Hospital in New York.

DR. CUNNINGHAM: Susanna Cunningham. I am the consumer representative on the committee, and I'm from the University of Washington.

DR. NISSEN: I'm Steve Nissen. I'm a cardiologist at the Cleveland Clinic.

DR. WATKINS: Paul Watkins. I'm a hepatology consultant from University of North

Carolina-Chapel Hill.

DR. BORER: Jeff Borer, cardiologist, Weill Medical College of Cornell University.

MS. SPELL-LeSANE: Dornette Spell-LeSane, Executive Secretary for the committee.

DR. TEERLINK: John Teerlink, University of California-San Francisco, and San Francisco VA Medical Center.

DR. FLEMING: Tom Fleming, University of Washington.

DR. HIRSCH: Alan Hirsch, cardiologist and vascular medicine specialist at the University of Minnesota and Minneapolis Heart Institute.

DR. AVIGAN: Mark Avigan, Office of Drug Safety at the FDA.

DR. STOCKBRIDGE: I'm Norman Stockbridge, the Acting Director of the Division of Cardio/Renal Drug Products at FDA.

DR. HOUN: I'm Florence Houn. I'm the Office Director for Drug Evaluation III.

DR. KORVICK: Joyce Korvick, Acting Director, Division of Gastrointestinal Coagulation

Drug Products.

DR. ROBIE-SUH: Kathy Robie-Suh, Acting Deputy Director, Division of Gastrointestinal and Coagulation Drug Products.

DR. BORER: Thank you very much.

We have many people at the table. I'm going to remind everyone that when you speak, you should press the button on your microphone, and when you're done, turn it off, please, unless you want to say something because that's the only way I'm going to know that you want to if you press the button and I see the light.

We'll go on to the conflict of interest statement. Dornette Spell-LeSane, the Executive Secretary of the Cardio/Renal Drug Advisory Committee, will present the conflict of interest.

MS. SPELL-LeSANE: Good morning. The following announcement addresses the issue of conflict of interest and is made part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda and all financial interests reported by the committee

participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting, with the following exceptions:

In accordance with 18 U.S.C. Section 208(b)(3), full waivers have been granted to the following participants. Please note that all of the consulting and speaking activities waived are unrelated to Exanta and its competing products:

Dr. William Hiatt for consulting for two competitors for which he receives less than $10,001 per year per firm;

Dr. Thomas Pickering for serving on a competitor's advisory board for which he receives less than $10,001 per year;

Dr. Ronald Portman for consulting for a competitor for which he receives less than $10,001 per year;

Dr. Thomas Fleming for consulting for four competitors, he receives less than $10,001 per year per firm;

Dr. Sackner-Bernstein for consulting for the sponsor and a competing firm, he receives less than $10,001 per year per firm. Also, for his Speaker Bureau activities for a competitor, he receives less than $10,001 to $50,000 per year;

Dr. Jeffrey Borer for serving on a steering committee for a competitor, he receives less than $10,001 per year;

Dr. Alan Hirsch for lecturing for the sponsor, for which he receives less than $5,001 per year. For lecturing for three competing firms, he receives less than $5,001 per year for serving on two Speaker Bureaus, and from $5,001 to $10,001 for one Speakers Bureau. Two consulting agreements for two competing firms, he receives less than $10,001 per year for one consulting, and from $10,001 to $50,000 per year for the other.

In accordance with 18 U.S.C. 208(b)(3), a limited waiver has been granted to Dr. Paul Watkins for serving on two advisory boards for a competing firm. He receives less than $10,001 per year for one and greater than $50,000 per year for the

other. Under the terms of this limited waiver, Dr. Watkins will be permitted to participate in the committee's discussion of Exanta. He is, however, excluded from voting.

Lastly, in accordance with 18 U.S.C. Section 208(b)(1), full waivers have been granted to the following participants for interests unrelated to Exanta and its competing products:

Dr. John Teerlink for speaking for two competitors, he receives less than $10,001 per year from one, and from $10,001 to $50,000 per year from the other. Also, for his consulting for a competitor for which he receives between $10,000 to $50,000 per year;

Dr. Maria Sjogren for consulting for a competitor for which she receives less than $10,001 per year.

A copy of the waiver statement may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building. 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 participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

We would also like to note that Dr. Jose Vega has been invited to participate as an industry representative acting on behalf of regulated industry. Dr. Vega is employed by Amgen.

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

Thank you.

DR. BORER: Thank you very much, Dornette. That was about the longest conflict of interest statement that I can remember.

But we still are five minutes ahead, Norman, so we'll hear a welcome and comments from Norman Stockbridge, the Acting Director of the Division of Cardiovascular and Renal Drug Products.

DR. STOCKBRIDGE: I'll see if I can keep us on schedule. Good morning and welcome to what promises to be an interesting meeting on behalf of the Divisions of Cardio/Renal Drug Products and GI and Coagulation Drug Products. I want to thank members of the Cardio/Renal Advisory Committee, consultants, and the sponsor for their participation.

I do need to acknowledge retirement of four members from the Advisory Committee: Alan Hirsch is here today, a couple of chairs down to my left; Steve Nissen is over at the middle of the table there; Paul Armstrong would be here today except that Homeland Security discovered that he's a Canadian.

[Laughter.]

DR. STOCKBRIDGE: And, finally, there is our Chairman, Dr. Jeff Borer. Dr. Borer's service to the committee began in 1977, an era in which members still sported powdered wigs.

[Laughter.]

DR. STOCKBRIDGE: I can't quite tell from

the records where he cast his first vote, but in that year, the committee heard arguments on potassium and atropine.

As tokens of our appreciation, Ms. Spell-LeSane has for each of you some actual certificates signed by our Acting Commissioner and some virtual plaques that look just like this one. So on behalf of Cardio/Renal, the Food and Drug Administration, and a grateful nation, thanks to you all.

[Applause.]

DR. NISSEN: Norman, I'm not from Canada, but I'm from Cleveland, and it's really close to Canada. Will you please not tell Homeland Security about me?

DR. BORER: Thank you very much, Norman, and thank you for staying way on time because we are now 17 minutes ahead of schedule, which is good. The sponsor has a 90-minute presentation. We'll try to allow you to move along as well as we can, but undoubtedly there will be some clarification questions. We ought to try to hold the

questions that we ask to clarification issues during the presentation, if we can, and we can get into the meat of the substantive discussion afterwards.

The presentation will be introduced by Dr. Cameron, the Vice President of Exanta.

DR. CAMERON: Thank you, Mr. Chairman, members of the committee, ladies and gentlemen, good morning. I'm Dr. Hamish Cameron, the Vice President of Exanta at AstraZeneca, and with my colleagues we're pleased to present ximelagatran, a new oral anticoagulant.

After a 20-year journey to discover and develop this new medicine and half a century without significant innovation in this area of therapeutics, we believe ximelagatran, the first oral treatment in the new drug class direct thrombin inhibitors is a real advance in oral anticoagulation.

Ximelagatran has a mechanism of action that's quite different from the vitamin K antagonists like warfarin and can provide the first

oral alternative to warfarin, today's only option for long-term anticoagulation.

Anticoagulation is the major approach to both the prevention and treatment of thromboembolic disease, a disease that's the final common pathway for many life-threatening conditions, like stroke, myocardial infarction, and pulmonary embolism. And it's the commonest cause of death and disability in America today.

At the outset we must ask: Given the widespread availability of the vitamin K antagonists like warfarin, why is there a need for a new oral anticoagulant? Warfarin is a highly efficacious anticoagulant and one of the top ten most prescribed drugs, used in nearly every medical specialty by 3 million patients in the U.S. involving 32 million prescriptions every year. But it's been in the top five, sometimes number one, in the lists of drugs associated with significant interactions, medication errors, serious bleeding, and hospital admissions.

Warfarin's profile of unpredictable

kinetics and dynamics; food, alcohol, and multiple drug interactions; together with its acknowledged narrow therapeutic index--too little warfarin, and there's the risk of residual clotting; too much, and the risk of bleeding--all these drive the need for a lifetime of INR coagulation monitoring and never-ending individual dose titration.

To put it simply, you don't get the benefit of warfarin from just taking the tablet. Its overall effectiveness is highly dependent on how it's managed. And it's this fact that frames the innovation of ximelagatran.

Many patients and doctors fear the risk of bleeding that comes with unpredictable anticoagulation. This fear tends to result in under-treatment, quite paradoxical in high-risk elderly patients, or in about half the overall patients eligible for warfarin, little or no treatment at all.

We started a discovery program targeting thrombin in 1985. We sought to develop a new oral anticoagulant, an alternative to warfarin, with a

profile that would allow fixed dosing without coagulation monitoring, further supported by a low potential for food and drug interactions.

We looked for a rapid onset and offset of action to simplify turning anticoagulation on and off, which is one of the challenging aspects of warfarin treatment. And all this had to be achieved with an acceptable bleeding profile.

Today, we believe these objectives have been met by the Ximelagatran Development Program, involving 82 clinical studies and enrolling over 30,000 subjects. More than 17,000 people received ximelagatran with 3,500 patients dosed for over a year. And our longest patient exposure has now reached five years.

Here are the three proposed indications in the current NDA, spanning exposures from days to several years. The first is the long-term secondary prevention of venous thromboembolism, VTE, after standard treatment for an acute episode. Treatment of acute VTE involved six months of anticoagulation with warfarin, but at the start of

this development in 1999, it was unknown whether longer treatment would be beneficial. And so a placebo-controlled study, THRIVE III, was conducted. As you'll see, this study demonstrated a highly significant reduction of VTE during longer-term prophylactic treatment. And as a placebo-controlled study, it provides the strongest evidence of ximelagatran's antithrombotic efficacy.

The second indication is the prevention of VTE after knee replacement surgery. Patients without anticoagulant prophylaxis run a high risk of DVT and pulmonary embolism, and in the U.S., warfarin is the most widely used drug, started late on the day of surgery to reduce this risk. In two warfarin controlled studies, EXULT A and EXULT B, we've shown a significant reduction of VTE risk for ximelagatran compared with warfarin.

The third indication is the prevention of stroke and other thromboembolic complications associated with atrial fibrillation. Here with the large SPORTIF III and V trials, we've shown the efficacy of ximelagatran to be comparable to

well-controlled warfarin.

Across these pivotal, mainly outcomes-based studies involving independent endpoint adjudication, we've demonstrated ximelagatran's antithrombotic efficacy and recorded a favorable leading profile, equivalent to and in some cases better than the comparator. We detected a signal of raised hepatic enzymes with chronic treatment, and so we've conducted a very detailed analysis, consulted with experts, and believe the risk can be adequately managed.

I should highlight that in your briefing packs and our safety presentation, we've included data from two other large studies in other indications, not for consideration today, but which contribute nearly 4,000 patients. The THRIVE treatment study is the first pivotal study looking at initial VTE treatment, and the second study is soon to start, while the ESTEEM trial is a Phase II dose guiding study in the post-acute coronary syndrome setting.

These data enrich the overall safety

assessment, including patients from very different clinical settings and a wide range of characteristics, and we're going to review all the key data in the presentations that follow.

We believe ximelagatran with its predictable anticoagulant effects and favorable bleeding profile has a positive benefit/risk in the proposed indications, provided it's used properly. And part of that proper use is the introduction of an appropriate risk management program directed towards the hepatic risk.

We made an initial proposal with our submission which had been developed with extensive external consultation and field testing, but we fully recognize, following the deliberations of this committee and further discussions with FDA, the program will need to be developed and strengthened further before an approach can be finalized in the best interests of patients. We are committed to working with FDA to achieve the most appropriate risk management program to ensure the safe use of ximelagatran because patient safety

is, has been, and always will be AstraZeneca's top priority when we introduce new medicines into clinical practice.

Since 1998, we've met repeatedly with FDA throughout ximelagatran's development--in end of Phase II meetings, a pre-NDA interaction, and there's a meeting coming up to discuss the nature and extent of the risk management program. The NDA was submitted in December 2003.

I should add that all the same data are now being reviewed in Europe by the French agency before a mutual recognition procedure. But there's one difference worth noting. Given the quite different clinical practice regarding anticoagulant prophylaxis in orthopedic surgery, separate developments were conducted in the U.S. and Europe. The European program, reflecting local practice and starting treatment much closer to the time of operation, was the subject of a separate earlier regulatory submission and completed the mutual recognition procedure in May this year. And the first orthopedic launch was in Germany in June.

Now, you have the data on this program in your briefing packs, but with the significant timing, comparator, and formulation differences, our presentations today will largely focus on the data directly relevant to the NDA orthopedic surgery application.

Here's the agenda for our session. Dr. Troy Sarich will review clinical pharmacology; Dr. Jay Horrow, efficacy; and Dr. Sunita Sheth, safety; allowing an overall evaluation of ximelagatran in the three requested indications. Dr. Jonathan Halperin from Mount Sinai Medical Center will then give his views on the benefit/risk of ximelagatran in clinical practice. And throughout our presentations, we hope to cover for you all the specific comments raised by the agency in their briefing document.

In addition to Dr. Halperin, we're also joined by other consultants: Dr. Gerald Faich, Dr. Lloyd Fisher, Dr. Peter Kowey, and Dr. James Lewis.

In summary, then, ximelagatran is a new oral anticoagulant that provides the first

alternative to warfarin after 50 years. We believe a total review of the available clinical data supports a positive benefit/risk in each of the proposed indications. Ximelagatran can enhance health care delivery in America and throughout the world to help prevent a range of debilitating and life-threatening thromboembolic diseases.

Thank you. Now I'd like to introduce Dr. Troy Sarich for clinical pharmacology.

DR. SARICH: Good morning. I'm Dr. Troy Sarich, Director of Clinical Pharmacology at AstraZeneca. I'll now present an overview of the clinical pharmacology of ximelagatran in which we have performed both the traditional clinical pharmacology studies and population pharmacokinetic analyses.

Ximelagatran is an oral direct thrombin inhibitor. It's rapidly bioconverted to the active form, melagatran. The bioconversion, which is Cytochrome P-450 independent, involves both de-esterification and a reduction that occurs throughout the body.

The exposure to melagatran is linear across a dose range from 5 to 98 milligrams ximelagatran. The pharmacokinetics are predictable over time with repeated dosing, and the elimination half-life of melagatran is approximately 4 to 5 hours in patients. Once formed, melagatran is primarily eliminated from plasma by a glomerular filtration.

Thrombin is a key enzyme in the coagulation cascade. It converts fibrinogen to fibrin, activates platelets, and induces its own generation. Melagatran directly inhibits thrombin as a classic competitive and reversible-binding enzyme inhibitor. There's a direct relationship between the pharmacokinetics and pharmacodynamics of ximelagatran. Its active when present in plasma, and once eliminated from plasma, its effect is gone.

Preclinical investigations indicated an antithrombotic effect of melagatran at approximately 0.05 micromolar, with increasing effect up to approximately 0.5 micromolar.

In humans, ximelagatran prolongs clotting time assays. The thrombin time assay shown here was prolonged in a linear manner at concentrations as low as 0.05 micromolar. In addition, melagatran prolongs in a concentration-dependent manner the activated partial thromboplastin time, although it is less sensitive.

Additional investigations using pharmacodynamic models in humans demonstrated evidence for inhibition of thrombin generation indicated by concentration-dependent reduction and thrombin-antithrombin complex levels and platelet activation indicated by concentration-dependent reduction in beta thromboglobulin levels at melagatran concentrations at or near 0.05 micromolar. All together, it was clear from these data that direct inhibition of thrombin by melagatran resulted in the intended anticoagulant activity in humans.

After oral administration, the inactive pro drug ximelagatran is rapidly eliminated from plasma as it is biotransformed to melagatran, shown

in blue, with peak melagatran concentrations occurring approximately 2 to 3 hours post-dosing. Melagatran plasma concentrations greater than 0.05 micromolar are achieved early after oral ximelagatran, indicating a rapid onset of action which simplifies the initiation of oral anticoagulation. Concentrations remain above 0.05 micromolar throughout the dosing interval, supporting a twice-daily dosing regimen.

And as shown here, the rapid onset of action of oral ximelagatran is not altered when co-administered with food. Although there's an approximately one-hour delay in the time to C-max, there is no effect on the AUC or Cmax of melagatran.

Warfarin's well-recognized drug interaction profile is largely related to its metabolism by the Cytochrome P-450 system and its high plasma protein binding. Ximelagatran is not metabolized by and does not inhibit the major Cytochrome P-450 enzymes listed here. It also has low plasma protein binding, and along with the

majority of melagatran eliminated from plasma by glomerular filtration, this leads to an inherently low potential for drug interactions.

Our investigations have identified pharmacokinetic interactions with erythromycin and azithromycin. Erythromycin results in an 80-percent or less than twofold increase in melagatran plasma levels, with a smaller, 40- to 60-percent increase with azithromycin.

These changes are within the overall range of melagatran exposures in patients, and as outlined in detail in your briefing document, investigation into the potential impact of this pharmacokinetic interaction found no signal for increases bleeding events or increased ALT elevations in the approximately 230 patients receiving ximelagatran and macrolide antibiotics in the long-term studies. These data do not suggest an important clinical impact of these pharmacokinetic interactions.

We have conducted many other interaction studies where we've found no significant

pharmacokinetic interactions. As shown by the mean melagatran AUC ration and the 90-percent confidence interval within or slightly outside the 0.8 to 1.25 no interaction interval. The drugs investigated include alcohol, common cardiovascular medications, an NSAID, a sedative, and several antibiotics. These results are consistent with population pharmacokinetic analyses indicating a lack of interaction with commonly used comedications in the patient studies. Taken together, these data suggest that ximelagatran has a low potential for drug interactions.

Melagatran is primarily renally eliminated from plasma, and so we've carefully investigated the impact of renal function on the pharmacokinetics of ximelagatran. In the three patient populations under consideration today, melagatran exposure increases as calculated creatinine clearance decreases. For this reason, severe renal impairment, a calculated creatinine clearance less than 30 mLs per minute, was an exclusion criteria for our clinical studies, and we're currently

investigating an alternative dosing strategy in that population.

It's notable that we've gathered considerable experience with ximelagatran in patients with mild to moderate renal impairment as approximately 45 percent of the Phase III patient population had a calculated creatinine clearance between 30 and 80 mLs per minute. The median exposures in these patients are about 1.5 to 2.5 times higher, respectively, than patients with normal renal function, but there's considerable overlap in melagatran exposure between groups, suggesting dose adjustment was not necessary.

We've also studied the potential effects on the pharmacokinetics of ximelagatran within other special populations, and other than differences in renal function between groups, we have not identified other important effects of age, gender, race, obesity--as measured using body mass index--or body weight on the pharmacokinetics of ximelagatran.

The agency has suggested there should be a

dose adjustment for ximelagatran in patients with renal impairment given the higher levels of melagatran in these patients. But I'd like to show you why a fixed dose, as used in our clinical studies, is appropriate across the patient populations studied.

We do agree with the agency's assessment that there's no need for dose adjustment in orthopedic surgery patients and that there was no increased bleeding related to melagatran exposure in VTE secondary prevention patients. We do acknowledge an association between increasing melagatran exposure and increasing incidence of major bleeding in atrial fibrillation patients. But this relationship appears confounded by the correlation between melagatran exposure and the age-related decrease in calculated creatinine clearance.

Shown here from the SPORTIF trials is the relationship between calculated creatinine clearance and major bleeding. As you can see, major bleeding increased with declining renal

function whether patients received ximelagatran or INR-controlled warfarin. This suggests the increase in melagatran concentrations in patients with renal impairment is not associated with increased bleeding versus INR-controlled warfarin.

It's also important to note that stroke risk increased with decreasing calculated creatinine clearance, and the vast majority of these strokes were ischemic. So there's a possibility that a dose reduction in renally impaired patients intended to decrease bleeding may increase the risk of stroke in those patients at highest risk.

We should also consider the hepatic findings, as will be presented by Dr. Sheth, and we have examined the possible relationship between melagatran exposure and ALT elevations. As pointed out in our briefing document, we have observed an association between increasing melagatran exposure and increasing ALT elevations greater than 3 times upper limit of normal, but this relationship is very weak. And as shown here, the relationship

between melagatran AUC and peak ALT elevation in individual patients, while statistically significant, does not suggest a clear relationship between melagatran exposure and ALT elevations.

In addition, we agree with the agency's conclusion that, aside from the ALT elevations noted with ximelagatran, there is no difference in the overall adverse event profile between ximelagatran and comparators in the long-term dosing study pool.

Factoring in the occurrence of major bleeding, stroke and systemic embolic events, ALT elevations, and the overall adverse event profile, the observation of increased plasma melagatran concentrations in renal impairment does not appear to justify a dose reduction in these patients. We believe our data support a fixed dose of ximelagatran in the patient populations studied.

Now I'd like to show the steady-state plasma concentrations of melagatran in atrial fibrillation patients receiving a fixed dose of 36 milligrams ximelagatran twice daily. There are

four key points here.

Plasma concentrations fluctuate during the dosing interval, remaining largely above 0.05 micromolar and infrequently exceeding 1 micromolar.

Mean trough melagatran concentrations after 36 milligrams are approximately 0.2 micromolar. So should a patient miss a dose of ximelagatran, the 4- to 5-hour half-life of melagatran means that low but pharmacologically active concentrations remain for up to 24 hours post-dosing. And the effect of melagatran is gone once it is cleared from plasma by the kidneys.

This emphasizes the importance of maintaining good diuresis in the management of bleeding. And while there is no specific antidote, if needed, melagatran can be dialyzed.

And, lastly, the APTT is prolonged in patients and may help identify a residual anticoagulant effect.

A critical aspect of oral anticoagulation is maintenance of a stable effect over time, and we have confirmed the long-term stability of oral

ximelagatran. Shown in yellow are the plasma concentrations of melagatran in atrial fibrillation patients in the Phase II study, SPORTIF II. We remeasured plasma melagatran concentrations in a subset of those same patients between 13 to 16 months later in SPORTIF IV, a long-term continuation study of SPORTIF II.

The mean plasma concentrations of melagatran are completely overlapping, and the variability in exposure within individual patients was low, with a coefficient of variation of 25 percent, indicating that oral ximelagatran results in stable and reproducible plasma concentrations of melagatran with long-term repeated dosing. This stability enabled us to conduct our clinical studies using a fixed dose without coagulation monitoring.

So we can conclude from this extensive clinical pharmacology program pharmacologically active concentrations of melagatran are rapidly achieved and maintained in a broad range of patients. There is also no effect of food or

alcohol and a low potential for drug interactions.

The key attributes of ximelagatran are, therefore, its oral availability, rapid onset of action, low potential for drug interactions, and use at a fixed dose without coagulation monitoring.

Now I'd like to introduce Dr. Jay Horrow, who will provide to you an evaluation of the efficacy of ximelagatran demonstrated in Phase III clinical studies.

DR. BORER: We'll just stop for one moment to make sure there are no issues that need to be clarified. The relation of renal function to melagatran exposure undoubtedly is going to be discussed to a greater extent later, but I think we should hold that until we hear from the FDA presentations, and then we can talk about that. But if there are any issues that need to be clarified regarding the pharmacology, we should do that now.

Steve?

DR. NISSEN: Two very brief questions. Is anything known about the mechanism of macrolide

interaction? Have you explored that at all?

DR. SARICH: Yes. We were slightly surprised to find that interaction since we don't interact with the P-450 system. It appears that the interaction involves transport proteins of some kind, and we've looked at a range of different compounds that we've investigated, and it at this point appears isolated to the macrolide antibiotics we've studied.

DR. NISSEN: And the second question is: You showed the coagulation effect during therapy, and I wondered if you have additional data on what happens in, let's say, the first 72 to 96 hours after terminating therapy. Is there evidence of a rebound phenomenon?

DR. SARICH: We have not observed that pharmacologically, as far as coagulation time assays.

DR. NISSEN: Okay. But that has been studied.

DR. SARICH: We've followed out to 24 hours after single-dose administration and not seen

any evidence--

DR. NISSEN: But not longer than 24 hours?

DR. SARICH: Not that I can recall.

DR. BORER: John?

DR. TEERLINK: The other question I have is: In terms of the relationship between the melagatran AUC versus the peak ALT elevations, how was the melagatran AUC derived?

DR. SARICH: Yes, these were derived using a population pharmacokinetic model. So the patients that received ximelagatran in the Phase III clinical studies had plasma samples collected. Over 80 percent of the Phase III patient population--in the long-term population had a plasma sample collected. Using a pharmacokinetic model that was developed by the team, we were able to estimate the exposure to melagatran in those patients.

DR. BORER: Ron Portman?

DR. PORTMAN: Noting differences in the chronopharmacology of drugs, were the curves you showed similar for both the morning and evening

doses?

DR. SARICH: Are you speaking about the coagulation time assay--

DR. PORTMAN: No. I was talking about the plasma concentrations.

DR. SARICH: Pharmacokinetics?

DR. PORTMAN: Right, pharmacokinetics.

DR. SARICH: Yes, they are consistent under administration during the day or overnight.

DR. BORER: Jonathan, go ahead.

DR. SACKNER-BERNSTEIN: In the analysis that you showed the stability of the concentrations of the drug over time from the SPORTIF II and SPORTIF IV population, did you perform that analysis restricting to patients who had samples at both times? Because the analysis you showed had a larger population at baseline compared to a subset later.

DR. SARICH: Right. We've done it both ways. The figure actually represents the larger number in the SPORTIF II study and a smaller number in SPORTIF IV. The intra-subject variability I

noted was only the subjects that had sampling at both time occasions.

DR. BORER: Alan?

DR. HIRSCH: In the PK and AUC curves that you've generated, were there any changes or differences noted based on ethnicity, geographic sampling of a population, or gender?

DR. SARICH: Are you asking pharmacokinetic--

DR. HIRSCH: Yes, PPK differences between subgroups.

DR. SARICH: The main factor we've observed between any subgroups has been differences in renal function, calculated creatinine clearance. We have not observed any significant effects of other demographic parameters, age, gender, race, BMI, body weight. It appears that exposure--the most influential demographic factor is calculated creatinine clearance.

DR. BORER: Susanna?

DR. CUNNINGHAM: Did you have a sufficient African American population to actually know

anything about what the African American area of the curve might be or handling of the drug?

DR. SARICH: We have performed pharmacokinetic studies in that population. I should say both--I'll show you some data here from a small study. It's not African Americans per se, but it was a study in Europe, in Paris, in fact, where we had 12 blacks, 12 Asians, and 12 Caucasians, and found no real differences between these groups.

If we looked at the entire patient population, we can see here--if we look at--you can see the Caucasian population here. There's over 6,000 patients. The blacks where we had appropriate pharmacokinetic information, were 115, as well as Asians, and the category of other, and no differences between these populations.

DR. BORER: Tom?

DR. PICKERING: Do you have any data on interaction with aspirin?

DR. SARICH: Yes, we have performed actually two studies with aspirin. There's no pharmacokinetic interaction with aspirin. We see

an additive effect on the capillary bleeding time, which is somewhat expected.

DR. BORER: Beverly?

DR. LORELL: Yes, with regard to body size, you commented on and emphasized obesity. What about the other end of the scale, very small body size? Sometimes an issue in elderly women who might be candidates for several of these indications.

DR. SARICH: We have less data in very small individuals, but what we know about that population is that it's primarily their calculated creatinine clearance that influences their exposure.

DR. BORER: Jonathan?

DR. SACKNER-BERNSTEIN: I know we're going to get back to the renal function question, but there was one set of slides you showed where you tried to give us some reassurance about the relationship between bleeding and renal function. And you showed the risk of bleeding as calculated creatinine clearance reached the low end of the

spectrum.

I wonder if you performed any sort of retrospective power calculation on your ability to detect a difference in risk, in particular in the patients who we may be likely to see treated with this drug in clinical practice, those over 70, over 75, where calculated creatinine clearances often are in the 40s. So do you have an analysis there between 30 and 50 with conditional power to actually detect a difference in bleeding risk there.

DR. SARICH: I think we could probably best address that after the presentations. We do have data there, and rather than getting into that discussion, if the Chair would agree, we could address that, bring an answer to you for that.

DR. BORER: Is that okay, Jonathan?

DR. SACKNER-BERNSTEIN: Yes.

DR. BORER: Okay. Thank you.

T1B DR. HORROW: Ladies and gentlemen, I'm Dr. Jay Horrow from AstraZeneca. We will now present Phase III data demonstrating that

ximelagatran is an effective oral anticoagulant.

In the first indication, long-term secondary prevention of venous thromboembolism, we will show ximelagatran superior to placebo. In the second indication, prevention of VTE after total knee replacement, ximelagatran was superior to well-controlled anticoagulation with warfarin. And in the chronic prevention of stroke, ximelagatran was noninferior to warfarin.

These indications represent a broad range of patient populations. We'll begin with the first one: secondary prevention of VTE.

Evidence has been accumulating that patients with acute VTE benefit from prolonged anticoagulation after acute treatment. The THRIVE III trial comparing ximelagatran to placebo contributes to this growing body of evidence. Randomized patients had an acute symptomatic VTE objectively confirmed and had completed 6 months of treatment without VTE recurrence, also objectively documented at randomization. Anticoagulation was desirable but not essential for these patients,

that is, they had idiopathic VTE or probable hypercoagulable conditions. Health status had to be compatible with survival for an additional 18 months.

In THRIVE III, 1,223 patients receives in double-blind fashion either oral ximelagatran 24 milligrams twice daily or placebo for up to 18 months. Selection of 24 milligrams for this trial came from a consideration of preclinical data and data from Phase II trials in the orthopedic surgery indication. These PK data from a Phase II European trial in patients undergoing hip or knee replacement demonstrate that administration of 8 milligrams ximelagatran twice daily, the lowest curve, achieves plasma melagatran concentrations of about 0.05 micromolar. This is the level at which anticoagulant activity with melagatran begins based on the data previously shown by Dr. Sarich.

Progressively higher doses of oral ximelagatran, 12, 18, and 24 milligrams, achieved higher melagatran concentrations, more anticoagulant activity, and more time above the 0.05

micromolar threshold for each dose.

Outcome data from that same orthopedic surgery trial suggest that 24 milligrams is the most promising dose for efficacy. The 24-milligram dose also had a reassuring bleeding profile. We chose 24 milligrams for THRIVE III with placebo comparator without establishing dose-limiting toxicity, in this case bleeding. The choice was an informed judgment taking into consideration, first, the need for efficacy demonstrated by the benefits seen here in joint replacement, an intense thrombotic stimulus; and, second, the need to avoid excess bleeding because the standard of care is no anticoagulant therapy at all.

The trial compared ximelagatran to placebo in the rate of recurrence of symptomatic, objectively confirmed VTE. VTE encompasses both deep vein thrombosis, DVT, and pulmonary embolism, PE, because PE originates from a thrombus in the systemic venous circulation, whether overt or not.

The primary endpoint compared ximelagatran to placebo using a time-to-event analysis. A

recurrence of VTE required signs or symptoms of VTE, that is, a clinical event, and subsequent objective confirmation. A blinded independent endpoint committee evaluated and adjudicated all clinical endpoints, including major bleeding events.

The ximelagatran- and placebo-treated cohorts displayed similar demographic profiles. As indicated by creatinine clearance between 30 and 80, 23 percent had some degree of renal impairment. The index VTE event was or included pulmonary embolism for more than one-third of patients. This Kaplan-Meier curve shows the cumulative incidence of the primary outcome in the ximelagatran and placebo groups, analyzed by intention to treat. Seventy-one patients in the placebo group suffered recurrent VTE, including 23 PEs, for a cumulative rate of 12.6 percent, while only 12 patients in the ximelagatran group had recurrent VTE, including only two PEs, for a cumulative rate of 2.8 percent. The 9.8-percent difference, significant at p less than 0.0001 by log rang test indicates that one VTE

recurrence is prevented by ximelagatran treatment for up to 18 months to 10 patients. The associated hazard ratio, 0.16, indicates a risk reduction of 84 percent by ximelagatran relative to placebo.

The composite endpoint of total VTE included both DVT and PE. Benefit of ximelagatran over placebo occurred for each component of this composite endpoint--clinical DVT, clinical PE, and their combination.

The superiority of ximelagatran to placebo is robust to multiple, prespecified sensitivity analyses listed here. Each comparison demonstrated a significance level less than 0.0001

Here we examine efficacy in subpopulations. Small diamonds depict point estimates of the odds ratios of ximelagatran to placebo, and horizontal bars show their 95-percent confidence intervals. Superiority of ximelagatran over placebo remains in all subgroups strata of reasonable size.

In THRIVE III, the oral thrombin inhibitor ximelagatran, 24 milligrams twice daily for up to

18 months, effectively reduced the number of recurrent VTE events following 6 months' treatment of an acute VTE. The results are robust and consistent across multiple endpoints and subgroups and demonstrate a clinically relevant benefit.

The second indication under review today is the prevention of VTE in patients undergoing knee replacement surgery. Major joint replacement surgery challenges any anticoagulant to prevent VTE without counteracting surgical hemostasis. VTE prevention contributes heavily to the benefit/risk balance for joint replacement surgery.

The current options to reduce the occurrence of VTE after total knee replacement include the injectable agents low-molecular-weight heparin and fondaparinux and oral warfarin. One FDA comment regards the choice of warfarin as the comparator for these trials.

We chose warfarin for several reasons:

First, it is the agent most commonly used for this purpose in North America, and we administered warfarin, as orthopedic surgeons do,

beginning the night of surgery.

Second, warfarin, like low-molecular-weight heparin, is a Grade 1A recommended therapy for this purpose, according to current American College of Chest Physicians Consensus Conference Guidelines.

And, third, warfarin is associated with less bleeding than the injectable anticoagulants and so is a more daunting comparator for ximelagatran in terms of surgical hemostasis.

Two independent double-blind Phase III trials--EXULT A and EXULT B--enrolled patients undergoing primary elective total knee replacement. EXULT A studied 24 and 36 milligrams ximelagatran and warfarin. We had studied 24 milligrams in this context previously and found protection similar to but not better than warfarin at p equal 0.07. We found that result surprising. Unsure whether or not it was a Type II error, we designed EXULT A with two ximelagatran arms: one using 24 milligrams and the other using 36 milligrams.

Warfarin and its paired placebo began, as

typically practiced in the U.S., the evening of the day of surgery while ximelagatran and its placebo began early on the morning after the day of surgery. Treatment continued for 7 to 12 days, after which all patients underwent bilateral venography.

Based on the results of EXULT A, EXULT B studied only 36 milligrams ximelagatran and warfarin. Warfarin was aggressively and successfully dosed to drive the INR rapidly to its target of 2.5, with an accepted range of 1.8 to 3.0. The primary outcome formed the composite of distal and proximal DVT by venogram performed between days 7 and 12, objectively confirmed symptomatic DVT or pulmonary embolism up to 2 days after venography, and all-cause mortality up to 2 days after venography. Both trials utilized the same blinded independent committee for event adjudication.

The treatment groups in the EXULT trials were balanced and represented well the population of patients in the United States undergoing total

knee replacement. More than a third of the cohort displayed some degree of renal impairment.

Here are the primary results for EXULT A and EXULT B. In EXULT A, ximelagatran 36 milligrams, in yellow, showed superiority to well-controlled anticoagulation with warfarin, in gray, at p equals 0.003. EXULT B confirmed those results, with p less than 10^{-5}. These results yield relative risk reductions of 26 and 29 percent and numbers needed to treat of 14 and 11, respectively.

In EXULT A, ximelagatran 24 milligrams, in orange, and warfarin, in gray, did not differ, with event rates of 24.9 and 27.6 percent, respectively. That p value is 0.28.

The delay in anticoagulation with warfarin administration suggests that it may act like a placebo in EXULT. In fact, warfarin rates, in gray, are the lowest ever obtained in knee replacement clinical trials with warfarin, perhaps because of the rapid achievement in EXULT of therapeutic INRs. Placebo rates are historically over 60 percent, and the mean INR in EXULT was 2.4

on post-op day 3. The warfarin group provided a formidable comparator for ximelagatran in the EXULT studies.

Here we see results for the components of the composite primary endpoint. As expected, the majority of events occurred in the distal leg. Rates for proximal DVT, for PE, and for death were low in all treatment groups. Another point raised by FDA is how clinically relevant distal DVT is as a component of that endpoint. It's important to note that 10 to 20 percent of distal thrombi extend to become proximal thrombi, and either one can cause pulmonary embolism, making all three phenomena clinically relevant components of a composite endpoint. In fact, proximal and distal deep vein thrombosis detected by venography, whether symptomatic or not, is a primary endpoint historically accepted by the agency for VTE prophylaxis registration trials.

This display of the primary outcome by subgroup strata shows differences in event incidences between the pooled 36-milligram

ximelagatran and pooled warfarin groups. These results, with small numbers in just a few subgroups, reveal no discrepancies in efficacy in any particular subpopulation.

Oral ximelagatran, 36 milligrams, provided superior protection against VTE and all-cause mortality compared with well-controlled anticoagulation with adjusted-dose warfarin, a clinically relevant comparator. This superior protection was consistent across multiple subgroups. These data support the efficacy of ximelagatran for the indication requested.

The third indication considered today is the protection of patients from stroke and other thromboembolic complications of atrial fibrillation. We have demonstrated that ximelagatran provides this protection, as well as does warfarin, across a broadly based patient population.

Two independent pivotal trials--SPORTIF III, dosed, open-label in 23 countries in Europe and Asia, and SPORTIF V, conducted double-blind in

North America--enrolled patients eligible for warfarin therapy according to existing treatment guidelines, that is, those with nonvalvular atrial fibrillation with at least one additional risk factor for stroke. Each SPORTIF trial by itself studied more patients than all previous trials of stroke prevention in atrial fibrillation combined. Each trial compared 36 milligrams twice daily ximelagatran to dose-adjusted warfarin in preventing all strokes and systemic embolism, hard clinical endpoints in an intention-to-treat fashion.

The choice of 36 milligrams came from several considerations. There is no surrogate marker for stroke and systemic embolism, and both events are devastating. Thus, we performed a dose-ranging study for safety and tolerability of ximelagatran 20, 40, and 60 milligrams in SPORTIF II, a 3-month Phase II atrial fibrillation study. While the numbers were small in that study, bleeding was most frequent with 60 milligrams and also the warfarin comparator, and less frequent

with 20 or 40 milligrams ximelagatran. We knew that 24 milligrams was effective in the Phase II European orthopedic surgery program and reasoned that any downside impact of potential additional strokes with 24 milligrams would be far worse than the bleeding seen with 36 milligrams in this nonsurgical context. Using this educated judgment, we chose 36 milligrams in the Phase III atrial fibrillation program.

Let's take a moment to consider the open-label nature of the SPORTIF III trial. The majority of prior stroke prevention trials in atrial fibrillation also utilized an open-label format based on the difficulty of managing anticoagulation in blinded fashion. SPORTIF III featured open-label dosing at sites, but also centrally randomized allocation and two additional levels of blinding: blinded local assessment of primary endpoints by study-affiliated neurologists, and blinded independent central committee adjudication of all study endpoints. SPORTIF V featured double-blind, double-dummy medication, and

for patients receiving ximelagatran and placebo warfarin, sham INR values that mimicked those obtained during warfarin therapy.

The established efficacy of warfarin precluded a placebo comparison. Because warfarin is so efficacious, it is reasonable to establish ximelagatran efficacy in comparison to warfarin, and we did so using a noninferiority design. In consultation with an executive steering committee and data safety monitoring board compose of leaders of prior stroke prevention trials and a statistician expert in noninferiority trials, we prespecified a 2-percent per year absolute noninferiority margin. The choice of this margin has been questioned. The choice of 2 percent arose partly from an expected 3.1 percent warfarin rate, but more importantly, from consideration of the clinically tolerable absolute difference in stroke rates considering warfarin's overall clinical profile. A similar consideration drove designers of the SPAF III trial to power that trial to detect a 2-percent per year event rate with upper

confidence bounds of 3 for a population at lower risk of stroke. Even so, we prespecified a more conservative 2-percent upper confidence limit. The point estimate of the difference in event rates needs to be much smaller than 2 percent for the worst case, that is, the upper confidence limit, to be less than 2.

The strength of the 2-percent per year absolute margin resides in its clinical relevance, its prespecification, and that it is conservative.

At screening, those patients already taking oral anticoagulants interrupted that therapy to decrease INR to 2 or less by the time of randomization, at which time patients received either warfarin or ximelagatran. Each trial achieved a degree of warfarin control rarely found in routine clinical practice. The warfarin-treated groups constituted formidable comparators for ximelagatran, particularly in SPORTIF V. Samsa and colleagues found that most patients taking warfarin spend more than half the time on treatment outside the therapeutic range. In SPORTIF V, only 15

percent of patients did so.

The ximelagatran- and warfarin-treated cohorts displayed nearly identical demographic profiles in each independent Phase III trial, seen here as pooled data. Patients reflected well the elderly population of nonvalvular atrial fibrillation patients requiring anticoagulation for stroke prophylaxis, and the majority had impaired renal function.

In SPORTIF III, warfarin, shown in gray, displayed an event rate of 2.3 percent per year compared to 1.6 percent per year with ximelagatran, shown in yellow.

In SPORTIF V, the rates were 1.2 for warfarin, in gray, and 1.6 for ximelagatran, in yellow.

Primary event rates with ximelagatran are nearly identical in SPORTIF III and SPORTIF V. For warfarin, the rates fall within the range of event rates in previous trials, 0.6 to 4.1 percent per year.

For comparison, the pooled rate in prior

stroke trials for patients in this risk category taking placebo or aspirin was over 8 percent per year. The difference in event rates in SPORTIF III, 0.66, favoring ximelagatran, had an upper confidence limit of 0.13, less than the prespecified 2-percent margin. In SPORTIF V, the difference of 0.5 favoring warfarin had an upper bound of 1.03, also less than the prespecified 2-percent per year margin. Thus, each trial independently succeeded by satisfying the prespecified noninferiority criterion for the primary outcome.

As expected, most of the events in this composite outcome were ischemic strokes. Hemorrhagic stroke and systemic embolism occurred more rarely and did not influence the primary endpoint substantially.

Several sensitivity analyses confirmed the results of the primary analysis. One such analysis, depicted here, included all-cause mortality in the primary endpoint at the suggestion of the agency. SPORTIF III returned event rates of

4.2 and 5.1 for a difference of 0.87 favoring ximelagatran, while SPORTIF V rates were nearly identical at 4.7 and 4.8.

Adding all-cause mortality shifted each study's event rate difference point estimate to the left in favor of ximelagatran.

Another sensitivity analysis, depicted here, used an on-treatment approach using the same endpoints and the same population, but not counting events that occurred after stopping study treatment for 30 continuous or 60 total days. The upper bound of negative 0.18 indicates superiority in SPORTIF III. The value of 1.2 in SPORTIF V indicates noninferiority to well-controlled warfarin.

For each trial, we also performed a paper comparison of ximelagatran to placebo by factoring in the results of the six prior stroke prevention trials. We obtained original data from those trials to utilize the same endpoint events as in SPORTIF. Demographics of patients in these trials were similar to those of SPORTIF patients.

In these calculations, SPORTIF III and SPORTIF V separately demonstrated statistically significant risk reductions for ximelagatran relative to putative placebo, as did the pooled SPORTIF data. Ximelagatran works as an anticoagulant in this population.

As before, here we see differences in primary event rates according to demographic subgroups. These pooled results reveal no discrepancies in any particular subpopulation, including the elderly, women, the obese, and those with poor renal function.

In conclusion, for atrial fibrillation each of two trials independently met its objective, demonstrating that 36 milligrams of ximelagatran taken twice daily prevented stroke and systemic embolism to an extent similar to that of well-controlled anticoagulation with warfarin.

For long-term secondary VTE prevention, the THRIVE III trial demonstrated that 24 milligrams ximelagatran twice daily prevented VTE recurrence compared to placebo.

And in total knee replacement surgery, the two independent EXULT trials showed that 36 milligrams twice daily prevented VTE and all-cause mortality better than dose-adjusted warfarin.

Based on five pivotal trial, each the largest in its field, involving more than 12,000 patients, these data establish the effectiveness of ximelagatran as an oral anticoagulant in a variety of patient populations at high risk for thromboembolism.

Dr. Sunita Sheth will next address particular safety aspects of administration of ximelagatran for these indications.

DR. BORER: Thank you very much, Jay.

Again, we'll take a minute to see if anyone has any issues that require clarification. Clearly, we are going to talk about or probably we're going to be talking about the selection of the delta for the noninferiority trial, but I don't want to get into that discussion now. We have some extraordinary statistical fire power here between Tom on the committee and Lloyd Fisher and Jerry

Faich sitting over there and the FDA statisticians. I think we'll wait on that until after all the presentations, including the FDA presentations, have been made. But if we have any issues of fact that need to be clarified now, let's do it.

Jonathan?

DR. SACKNER-BERNSTEIN: In the FDA briefing document, it points out that there were patients who were withdrawn from the study for whom there is not information about whether they underwent or suffered any events. If that's correct, please clarify, because it looks as though from the study flow that that means in SPORTIF V as many as 15 percent of the patients we basically would not have any clinical outcomes data available from the point in time when they withdrew. Is that correct?

DR. HORROW: We followed up on all of our patients in the SPORTIF III and V trials to the greatest extent possible, and, in fact, after we were done with our follow-up, at the time of final closure, locking the database, we were left, out of

7,922 patients, with only 63 patients about whom we were unsure of their final status.

DR. SACKNER-BERNSTEIN: So that would mean that the FDA briefing document is incorrect, because the FDA briefing document states that--and I'm looking at page 36 of the clinical review from Cardio/Renal Division. It says in the first paragraph that patients that were discontinued from study medication and withdrew from study were not followed for primary efficacy endpoints or death. And then as you turn to page 45 with the patient disposition in SPORTIF V, it looks as though there's 300 study withdrawals from the ximelagatran group and 286 from the warfarin group. So that means that about 15 percent would have incomplete clinical outcomes data, but you're saying there's only 63.

So could you explain for us where the disparity should be settled?

DR. HORROW: It is conceivable that there is a misinterpretation of the term "study drug discontinuation" and "withdrawal from study." More

likely, the misunderstanding may accrue from the follow-up efforts that we made to ascertain the vital status of every patient in the SPORTIF trials.

We followed up on every patient, aside from the 63 that I just mentioned, and are confident in their vital status, knowing whether they were alive or dead, whether they had a stroke or not, in our database.

DR. FLEMING: Could I just clarify? So I assume what you then did is you defined a date of data lock or closure where on that calendar date you wanted to follow all patients relative to their survival status and stroke status. Are you saying then for all but 63 patients you knew their survival status and stroke status as of that calendar date for data lock?

DR. HORROW: Exactly, and that would be the data lock date for each respective trial--SPORTIF III and SPORTIF V. That is correct.

DR. BORER: Steve?

DR. NISSEN: I want to make sure I

understand how you maintained the blind, particularly in SPORTIF III. Obviously with warfarin, you may require frequent dose adjustments and so on. So in the open-label, particularly SPORTIF III, how did you maintain--in both trials, I'd like to understand the procedures that were undertaken. I guess in the open-label trial there was no blinding, right? The physicians and patients knew what they were receiving; is that correct?

DR. HORROW: In the open-label trial?

DR. NISSEN: Yes.

DR. HORROW: It was open-label dosing, and so you are correct that the physicians and the patients knew the drug, and the evaluators, the neurologists locally, and the central adjudication committee were blinded and didn't know.

DR. NISSEN: Okay, I understand. And SPORTIF V, then, how did you adjust warfarin and maintain the blind? Explain to me how that was done.

DR. HORROW: It was quite tricky and

involved quite a bit of work on the basis of the investigators and quite a burden for the patients. In SPORTIF V, all of the INR values were obtained in almost all cases by only two laboratories--that's an incredible degree of standardization for thromboplastin--either the centralized laboratory or a point-of-care machine that had standardized cards.

In each case--well, for the point-of-care machine, a coded number was produced by the machine. That was called in to a central randomization area, and that service then faxed to the site either the true INR value if the patient was really in the warfarin group or a shammed INR value if the patient was truly taking ximelagatran. So the site was unaware when it received the fax what group the patient was in.

If the test was done at the centralized laboratory, then the centralized laboratory likewise sent the results to the IBRS site, the specialized service, which then, again, faxed either the shammed or the true INR value to the

site.

DR. NISSEN: And then dose adjustments, how were those then made? I mean, obviously some of the patients needed a dose adjustment, so what happened then?

DR. HORROW: Well, as you know, for ximelagatran or its placebo there were no dose adjustments. But for warfarin or its placebo, each investigator adjusted the dose based on their usual practice considering the patient and the INR value or shammed value--they didn't know which it was--they'd received by fax.

DR. NISSEN: So there was no--it was all done per local physician practice. There was no standard applied to how dose adjustments were made. Is that right?

DR. HORROW: That's correct. We did not require all the investigators to adjust their patients' warfarin doses against some standard. This was to be a very real-world--as much as we could--type of adjustment in terms of warfarin or shammed dosing.

DR. NISSEN: And I assume the reason you didn't do that in SPORTIF III was that you just felt it was too difficult.

DR. HORROW: In SPORTIF III, the investigators were very uncomfortable with blinded anticoagulation testing and were unwilling to move forward in that regard.

In SPORTIF V, our North American investigators embraced the randomization somewhat more willingly.

DR. NISSEN: So you tried to do SPORTIF III blinded but they wouldn't go along with it? I don't understand exactly what happened.

DR. HORROW: It was not possible to get the investigators in SPORTIF III to move forward with the blinded testing and anticoagulation.

DR. NISSEN: You attempted it, and then they weren't able to comply. Is that what happened?

DR. HORROW: At an investigators meeting, there was--

DR. NISSEN: A rebellion.

DR. HORROW: There was no support.

DR. BORER: Okay. Bill? And then we have Tom and Alan and John.

DR. HIATT: A comment and a question. In the knee replacement studies, you commented that you achieved a rapid increase in INR and that it was 2.4 at day 3. And I just want to comment that, you know, there's an association between antithrombotic and anticoagulant effects of warfarin. It takes 4 to 6 days for Factor II to be depleted, so that's a false sense of security around the measurement of the INR. They're still not antithrombotic.

So my question is: If you take the three-quarters of patients at the end of that study who were, quote, therapeutic versus the one-quarter that were not, did you look at a subgroup analysis around difference in VTE rates at the end of that time? Were the patients who were, in fact, therapeutic by that number equivalent in terms of VTE rates compared with the patients who were sub-therapeutic?

DR. HORROW: My understanding of the question is did we perform a subgroup analysis near the end of the treatment interval regarding patients--or based on the actual INRs of the patients. We do not have that analysis.

DR. HIATT: I think the speculation would be that the differences would be erased in those who were therapeutic, and a major difference between treatments would have been in those who were sub-therapeutic. That was my question.

DR. HORROW: This is quite possible, and it's important to understand that the EXULT trials mimicked warfarin administration in the orthopedic surgery realm as it is currently practiced today in the United States. And so it was a very relevant way to look at the effects.

DR. BORER: Tom?

DR. PICKERING: Can you tell us how the INR control rates in the SPORTIF trials compared with the same rates in the six warfarin-versus-placebo trials?

DR. HORROW: The INR rates in the six

index trials had somewhat of a spread, as would be expected, and it's actually possible to see that as the INR rates are better in some of those trials, so are the results in terms of the decrease in the warfarin event rate. And our results for INR control were really quite in the middle, 2.5, 2.4--could we have the previous slide, please? I can show you some data on them.

This would be for SPORTIF V, summary statistics. Please note in the middle column labeled ximelagatran, we are looking at shammed values, and you will note that we have 2.5 at 3 months for ximelagatran and 2.4 for warfarin, at 12 months similarly, at 24 months similarly--right in the middle of the desired interval. And, of course, the other thing that you might note here is that there is a threshold of 4.0 for the shammed values to ensure that no shammed value ended up putting a patient unnecessarily in the hospital because of an elevated shammed INR.

Nevertheless, as you can see by the ranges here, it's quite clear that the investigators would

be unable to determine whether a patient were in one group or the other.

DR. PICKERING: That really wasn't my question. I was asking if there are comparable data for the six warfarin placebo trials.

DR. HORROW: I don't have those data available to show you at this time.

DR. BORER: I think they're in one of our two books, Tom.

DR. HORROW: I believe they may be in the briefing document.

DR. BORER: If I remember correctly, they do show a fairly wide range, as you might expect, but we can get those data.

Okay. Alan?

DR. HIRSCH: I have two questions. One is to follow up Steve's question regarding the SPORTIF III blinding. I just always believe it's terribly important to have blinding as a component of major pivotal trials, acknowledging that lack of blind can really alter outcomes in unexpected ways. So I want to just run this through one more time.

Pitying the investigators that would not go along with your request, the patients knew their study assignment, correct?

DR. HORROW: In SPORTIF III.

DR. HIRSCH: In SPORTIF III.

DR. HORROW: That's correct.

DR. HIRSCH: The physicians--

DR. HORROW: The patients knew their assignment, as did the principal investigators.

DR. HIRSCH: And coordinators.

DR. HORROW: That's correct.

DR. HIRSCH: So how would we have any confidence that the adjudicating neurologist would have any blind maintained at all?

DR. HORROW: Well--

DR. HIRSCH: I worry.

DR. HORROW: Your point is well taken that that cannot be assured with certainty. We can say that there were efforts made to make sure that the neurologist was not told on purpose the assignment of the patient, and we know also that all members of the central adjudication committee, which

evaluated all the endpoint events upon which the results are based, did so in a totally blinded fashion.

DR. HIRSCH: I guess if there was concordance between those two groups, I'm somewhat satisfied.

Let me come back with a follow-up question for EXULT, if I could. The data that we have demonstrates benefits of ximelagatran versus Coumadin preventing DVT in this population at risk after total knee replacement. And as we'll discuss later, most of that data is regarding distal DVT, which I do care about. But in the database, do we have any evidence, quality-of-life measurements, girths, anything that demonstrates a clinically relevant effect for the patient? In other words, in the absence of venographic surveillance, would the patient know there was a difference in outcome?

DR. HORROW: I'd like to ask Dr. Scott Berkowitz, who is the medical director for that particular trial, to address that issue. Dr. Berkowitz?

DR. BERKOWITZ: Hi. Scott Berkowitz, AstraZeneca. There was not any type of quality-of-life assessment in this short-term trial. The symptomatic events were collected as well, including distal, proximal, and PEs. They were low, as they are in TKR trials and did not see a difference, a statistical difference.

DR. BORER: There was a question I was going to hold until the end, but it seems to be relevant right here in view of Alan's point. You probably have a back-up slide, and Alan just suggested that he probably has the data off the top of his head. But can you tell us, among people historically from older trials where data would be available who have asymptomatic distal DVT and who aren't treated, what's the risk of subsequent thromboembolic events during some follow-up period?

DR. BERKOWITZ: Well, we don't have the greatest data on that, unfortunately, in the literature. What we know is that 10 to 20 percent, depending on what you're readings--there are only three or four studies--do propagate from distal to

proximal. We know about 5 percent propagate to PE. We don't know the actual recurrence rate of what further DVTs would be after, say, 6 months. We do also know that post-thrombotic syndrome occurs in 5 percent of patients in 2 to 7 years after total knee replacement. Those are the real data that we have. Not an area well studied.

DR. BORER: Jonathan, and then Steve.

DR. SACKNER-BERNSTEIN: I noticed that in the trials for the study flow of patients in several of your trials, including THRIVE, both EXULTs, and SPORTIF V, that there is a number of patients listed as being enrolled and then a second number of patients listed as being randomized. And there's very little information in either the FDA or the sponsor's documents about what happened to those patients. So I'm wondering if you could describe it because in each of the cases you're looking at probably in the range of 10 percent of the patients who are enrolled that don't make it to randomization.

DR. BERKOWITZ: Maybe I'll first try to

answer for the EXULT and THRIVE, and then ask Dr. Horrow for atrial fibrillation.

For the EXULT trials, patients were enrolled, meaning that they were seen as an outpatient up to a month before the procedure, and then would come into the hospital, and if they had the surgery of interest, which was primary total knee replacement, then would be randomized, assuming they went through the eligibility criteria. The most common reason patients wouldn't go from enrollment to randomization is that either the--there were two: one, that the surgery was cancelled, and then the patient wasn't rescheduled for the procedure--excuse me, for the study, but did do the procedure; the other was that with these trials rapidly enrolling, we had many people lined up but then the study--we reached our enrollment. Those were the two major causes.

For the THRIVE study, these were patients who had acute events for 6 months treated acute DVT and then went on to a 6-month--either placebo or to ximelagatran 24-milligram arm, and most of these in

terms of just taking a look here--I can just show you what we've got in terms of that. In terms of the ones that were not randomized, there were 123 of those patients, and most of this turned out to be eligibility not fulfilled or withdrawn consent. And that is a common thing that patients might think more about the study if they want to participate in such a long-term--and then I could turn it over to Dr. Horrow.

DR. HORROW: In the SPORTIF trials, the major reason why patients were enrolled but not randomized was because of the failure of an eligibility criterion; in particular, the major one was the ability to achieve two electrocardiograms demonstrating atrial fibrillation in the manner specified. And as a result, the principal investigators did not enroll a number of the patients whom they at first thought were good candidates.

DR. SACKNER-BERNSTEIN: Can I just follow up? One quick point in follow-up. In the patients enrolled in SPORTIF where many of them were coming

off the vitamin K antagonist, how many--even if it was a minority, how many of those patients had some sort of clinical event that led them not to be randomized?

DR. HORROW: I understand your interest is in seeing what happens to the patients who came off of vitamin K antagonist in the enrollment period, did they happen to have events. I believe that we have some data on that, although I can't say for sure that all of these did not enroll. They may have had an event after enrollment. If you'll just give me a moment, I'll see if we can find these data.

Yes, thank you. Here we see the number of patients with primary events who had an event within 30 days of discontinuing study drug, and this would be either the ximelagatran or the warfarin group. And this would be during the course of the trial. As you can see, there's not much difference between the two groups.

I think this may address the question that you're getting at, which is what happens when

patients discontinue their anticoagulant.

DR. SACKNER-BERNSTEIN: Well, actually, I find that reassuring, that information, but really what I was getting at was the impact of the strategy that would be proposed based on the study, which is you have a patient who's on long-term warfarin and you're going to convert them potentially to a new agent. There's a period that would be followed where there's a transition, and I'd like to know if that transition period is a period that could be associated with risk as well.

DR. HORROW: I understand better. Thank you. Here are some data from SPORTIF III looking at primary events within 7 days of randomization. There were three patients who had a primary event in the SPORTIF III trial within 7 days of randomization, and, of course, the patients taking VKA--all patients had to stop their VKA in order to begin randomization. And there were two events in the warfarin group and one in the ximelagatran group.

DR. BORER: Steve?

DR. NISSEN: I want to come back to the blinding issue again, and we've been dancing around it so let me just come to the point.

Something extraordinary happened in SPORTIF III and SPORTIF V. In SPORTIF III, I calculate a hazard ratio of 1.39, 1.40 that's in favor of ximelagatran. And in SPORTIF V, the hazard ratio is 1.35 in favor of warfarin. And so you have almost a completely opposite effect on the point estimates, which, you know, is really unusual when you consider the similarity of the trials.

So we're al trying--we're all sitting here looking at the briefing document, and we're trying to figure out what could possibly have happened here so that, you know--I mean, there's essentially a 39-percent greater risk for warfarin in SPORTIF III and a 39-percent greater risk for ximelagatran in SPORTIF V. And the only big difference in the two trials is that one was blinded and one wasn't.

And so most rational people who look at that would say, well, we're going to believe the blinded results, we're not going to believe the

unblinded results. And so this is a real credibility issue, and I think we might as well just put it on the table and get your reaction to it.

DR. HORROW: In fact, there are many differences between SPORTIF III and SPORTIF V that are confounded with the open-label and double-blind nature of those two trials. The first and foremost is geography, namely, that one study was conducted in Europe and Asia and the other in North America, and practice issues may pertain.

Secondly, although SPORTIF V patients more often had hypertension, their blood pressures were 6 mm mercury lower, on average, than patients in SPORTIF III.

And, third, there was an artificially intense control of INRs in SPORTIF V relative to SPORTIF III, because in SPORTIF III there were over 270 clinical laboratories conducting INR measurements, but there were essentially two in SPORTIF V, achieving some kind of standardization that is difficult to quantify.

Another aspect that is important to consider is that the ximelagatran rates were identical in the two trials. And in the warfarin trials--I'm sorry, in the two trials, the ximelagatran rates were identical, about 1.6. The warfarin rates appear disparate. But those rates are actually within the range of rates that are seen in prior stroke prevention trials.

What we may be looking at here is another manifestation of the variability of warfarin. This slide shows in yellow the warfarin rates from the six index trials, in orange the two rates from the SPORTIF trials, and in dark brown the meta analysis rate for the trials in yellow. And as you can see, the SPORTIF rates are within the range of the warfarin rates from the previous trials.

I hope that gives some perspective.

DR. FLEMING: Could you put that slide up again? Can I follow up?

DR. BORER: Sure. Let me just put some ground rules here, though. Steve has highlighted what will be one of the key issues for discussion

later on, and rather than get into it in great detail here and get bogged down for the next hour, perhaps we can deal only with issues of fact, and then we'll get into the evaluation of those facts a little bit later.

But with that in mind, go ahead, Tom.

DR. FLEMING: If you could put that slide up, I just think for clarification, I don't think that the point you just raised really answered Steve's question. Steve's question had more to do with the heterogeneity in the relative risk estimate across to pivotal studies. This is getting at the heterogeneity of the control arm event rates across trials. And, in fact, those are different phenomenon. This really gets at the unreliability of noninferiority comparisons because of this tremendous heterogeneity, which is a separate issue.

While I have the mike, could I ask a question that I had in mind? That is, one of the things that's always concerned me in trials with venograms is that we end up with a lot of missing

data, far more than what this committee would be used to accepting in a manner to maintain integrity of randomization. I think you had 20 and 15 percent, respectively, missing the outcome assessments in EXULT A and EXULT B.

With that in mind, and also wanting to really focus on what are not surrogates but true clinical endpoints, endpoints that reflect tangible benefit to patients, I struggle to look for what are those measures that are really tangible that are measured uniformly in patients. Could you show Slide CE-19 as we look at EXULT A and B? Two of these measures are pulmonary embolism and death that should be assessed, I'm assuming, and available in all patients. Your survival figures here reflect, if I pool here, five deaths against three. The agency on page 26 of their briefing document has ten against four, so you're missing five deaths in the Exanta arm and one in the warfarin arm. Could you clarify that discrepancy?

DR. HORROW: If I may first address the issue of the heterogeneity, then we can go on to

the issue with EXULT.

If I'm not mistaken, you're referring, in terms of the heterogeneity in SPORTIF, to what may be called a study by treatment interaction, the difference in sampling and getting one set versus the other. And I think it's important to understand that in each case, noninferiority was satisfied; that is, looking at the data just in those terms and how those numbers are sorted does not take into account the noninferiority design of the trials and that the success is determined by whether or not it meets the noninferiority criterion.

The heterogeneity result which we've looked at is not robust to sensitivity analyses like the primary results are robust. So, for example, if one looks at primary events plus all-cause mortality, which was an endpoint suggested by the agency, the heterogeneity disappears and the p value is 0.23. And if you look at other prespecified outcomes, such as major bleeding, there's no suggestion of disparity there.

The heterogeneity p value is 0.81. For total bleeding it's 0.275.

And so we view the idea of disparate results in the two trials with some suspicion and think that we need to be very careful how we interpret those primary results in terms of being disparate or the same. We view them as sampling from the same pool and getting two separate results and that the best estimate of the data comes from pooling.

I'd like now to--

DR. FLEMING: Given that you didn't answer my question and you provided a different answer, let me respond to the answer you just gave. The question that Steve asked is why was there such heterogeneity in relative risk estimates. The answer that you gave was there's a lot of heterogeneity in the control arm, in the warfarin rates across trials. Logically, I would assume that if you're saying when the warfarin rate in truth is different across trials, we should expect a different treatment effect, it really makes me

worry about doing a noninferiority trial where you have to rely on historical evidence.

Could you answer, though, the question that I'd asked here about the discrepancy between your data here and the FDA briefing document?

DR. HORROW: I'd like to ask Dr. Scott Berkowitz, who was the medical person for this particular trial, to address this issue.

DR. BERKOWITZ: Yes, Scott Berkowitz, AstraZeneca. I just wanted to say in terms of the venography rate--I have the data to show you, but in terms of venograph, these two trials had the highest adequacy of evaluability ever done in clinical trials for pivotal purposes.

DR. FLEMING: That may be, and yet the reality is we're still lacking 15 to 20 percent of our randomization cohort, and we no longer are assured of integrity of randomization. So could I get the answer to my question?

DR. BERKOWITZ: So for what you saw, those data that you saw in the briefing packet were for the overall study, so you can see it's ten and

four, but I'm going to--could I have the next slide?--show you the breakout for treatment, which is the primary endpoint--

DR. FLEMING: So, in fact, what I do want is the entire study, ten and four. So is the clarification CE-19, then--

DR. BERKOWITZ: Could we go back?

DR. FLEMING: Then the reason CE-19 is leaving out the five deaths and one death is that those occurred in the non-80, 85 percent?

DR. BERKOWITZ: The deaths--I'm sorry. Say that again? I'm sorry.

DR. FLEMING: What is the reason that your slide here leaves out five deaths and one death?

DR. BERKOWITZ: That slide showed the primary endpoint which included the treatment period of day 7 to 12 days as opposed to the overall, which showed only this study and the next one, if you want to see the breakout.

DR. FLEMING: Good. And so that is--could you show it again?

DR. BERKOWITZ: Oh, yes. Can I see the

next one? Thank you. We want to see now the breakout between the treatment--

DR. FLEMING: So that the total deaths are as here, they are as there in the FDA briefing document, ten against four in the wrong direction. And pulmonary embolism is, according to the FDA briefing document, four against five as reported by the FDA.

DR. BERKOWITZ: Yes. Well, you can see down--for the treatment period, as you can see, there was one in the ximelagatran 36 group and none in warfarin. During the follow-up period, there were four in the ximelagatran group and zero in warfarin.

DR. FLEMING: And so in an ITT analysis that does include all patients and focuses on, among the most clinically relevant endpoints, death and pulmonary embolism, it appears that there are actually numerically an excess of events in the Exanta group. By my count there are 15 events against 10 events, and that's your numbers as well. Is that correct?

DR. BERKOWITZ: Well, except that the numbers that you're seeing in follow-up are after patients are off treatment but they get seen in 4 to 6 weeks.

DR. FLEMING: I want ITT, and that's what it looks like. Is that correct? It's 15 against 10 in the wrong direction? Just is the FDA summary correct on page 26?

DR. BERKOWITZ: Yes.

DR. FLEMING: And one other quick question, if I could. Again, wanting to try to focus on an ITT of a critical endpoint, all-cause mortality, in THRIVE III could you show us the ITT summary? This is the placebo-controlled trial where we see a substantial efficacy result on the symptomatic endpoint. Could you show us the ITT of the survival curves for that trial?

DR. BERKOWITZ: I'm not certain--did you want to see the slide that we showed for the original presentation?

DR. FLEMING: I believe it's corresponding to the page 7, Figure 1 in your briefing document.

DR. BERKOWITZ: Let me bring that up. I just want to be sure it's the same one that we saw.

DR. FLEMING: The one that I am in particular looking for here, because that figure includes all the data from all the trials, is in particular THRIVE III with ITT analysis of mortality over the time frame that you followed these patients.

DR. BERKOWITZ: Yes, okay, and that's what we were--yes, I'm sorry. So here you go. This is the slide.

DR. FLEMING: Mortality.

DR. BERKOWITZ: Yes.

DR. FLEMING: All-cause, ITT.

DR. BERKOWITZ: I'm sorry. I still don't understand what you--just the mortality slide?

DR. FLEMING: Yes, as you have in Figure 1 of your briefing document.

DR. BORER: You wanted to see only for THRIVE, or you wanted to for the--

DR. FLEMING: Either way, if you--okay.

DR. BERKOWITZ: This is the slide in the

briefing document that you're speaking of with all the mortality.

DR. FLEMING: Okay. And could you--so the THRIVE is, in fact, the--

DR. BERKOWITZ: I'm sorry, yes, the THRIVE is the lowest curve there, the ximelagatran versus placebo in the lowest group.

DR. FLEMING: And so essentially, while I'm focusing on THRIVE, the evidence here would suggest, even in placebo-controlled comparisons, there's strong suggestion of no differences in survival.

DR. BERKOWITZ: Well, I mean, they're lower with the ximelagatran group, but not a strong difference.

DR. FLEMING: I'm sorry. I don't--the curves look overlapping in the THRIVE III, and in the other studies they are very overlapping as well.

DR. BORER: Steve?

DR. NISSEN: Yes, I just had one more question, still trying to probe to understand the

differences between SPORTIF III and SPORTIF V. Could you show us the INR values, that is, the degree of anticoagulation control in SPORTIF III and SPORTIF V for the warfarin arms.

DR. BERKOWITZ: I'll ask Dr. Jay Horrow to present that.

DR. HORROW: I'm sorry. I missed the last two words in--

DR. NISSEN: Yes, I just want to see in the warfarin arm of the trials, I want to see what the INRs looked like in SPORTIF III and SPORTIF V.

DR. HORROW: Okay. I believe these data will address your question. There were almost 100,000 different INR values, and this summary perhaps helps. Here we have SPORTIF III and SPORTIF V and the percentage of time in specific ranges.

DR. NISSEN: It does.

DR. HORROW: Okay. Thank you.

DR. BORER: A final question of fact, Jonathan?

DR. SACKNER-BERNSTEIN: I think the key

thing is that all of the slides that show ITT are not true ITT analyses. It's not just THRIVE. It's THRIVE and EXULT, and they list that in the briefing document. There are a lot of numbers where those are different, so we should just interpret it that way.

DR. FLEMING: It was part of the reason for my asking the question. I wanted to get a verification that we were being shown, for endpoints such as mortality, a true ITT. And I understand that they're telling us they are showing us a true ITT where you have uniform follow-up through a given calendar date at which the study data freeze would have occurred, and you would have complete follow-up on mortality for all patients. Is that what that Figure 1 showed?

DR. HORROW: Yes.

DR. BORER: Okay. Thank you, Jay.

DR. HORROW: May I introduce Dr. Sunita Sheth, who will discuss particular aspects of safety for ximelagatran.

DR. SHETH: Good morning. I'm Sunita

Sheth, Senior Director of Clinical Research at AstraZeneca.

You've just seen the efficacy data supporting the benefit of ximelagatran as an oral anticoagulant. I'll now review the clinical safety date. The analysis comes from a large data set with more than 30,000 subjects, many of the patients involved having serious underlying disease and receiving multiple drug therapy.

First, I'll discuss by indication the adverse events and bleeding profiles. Efficacy for any anticoagulant is balanced by risk of bleeding. Indeed, bleeding and the prevention of thrombosis derive from the same action of drug. That's why bleeding was a prespecified endpoint in the pivotal trials. And major bleeding was adjudicated in a blinded fashion in all Phase II and Phase III trials. Then I'll focus on two specific topics: myocardial ischemic events and the hepatic findings. Finally, I'll conclude with a review of overall mortality and summarize the key points for each indication.

It may help if I display how we've organized the large data set. It divides logically into three groups: Phase I, surgical, and nonsurgical populations. The Phase I population, composed primarily of healthy volunteers dosed for up to 8 days, didn't present any safety signals. Surgical patients, mostly from the orthopedic studies with dosing up to 12 days, have different safety issues, in particular, perioperative bleeding, and so they are reviewed as a separate group.

The nonsurgical population primarily received drug for more than 35 days and provides the core safety evaluation of long-term dosing, with exposure up to 4 years. Each population pool is large, allowing a detailed assessment of safety in each case.

I will first review the safety for the surgical indication. The North American surgical population has been termed "the warfarin comparison pool" and provides the safety data for the indication under consideration today, with

post-operative dosing of either oral ximelagatran or warfarin after total knee replacement surgery. This pool includes data from three Phase III trials: the two EXULT trials as well as an earlier study evaluating 24 milligrams versus warfarin. Overall, it includes 5,236 patients.

In all graphs, ximelagatran will be shown in a shade of orange and the comparator in gray.

Here's the summary of adverse events for the surgical pool. Both treatment groups showed a similar frequency and type of adverse events. There didn't appear to be any dose response comparing the 24- and 36-milligram doses. We can look more closely at the EXULT trials where both major and minor bleeding events underwent independent adjudication. Rates of major bleeding, shown at the bottom of each bar, were 1 percent or less in all treatment groups, with no statistically significant differences for major bleeding alone or for the combination of major and minor bleeding, for which respective p values are shown.

When you look at the data for the proposed

36-milligram dose, there wasn't a difference in surgical outcome parameters, such as wound hematoma or intra-articular bleeding. Additionally, the proportion of patients receiving transfusion and the volume of transfusion were similar in each group.

Now, let me turn to the nonsurgical patients who comprise the long-term dosing group. This group is called the long-term exposure or LTE pool, with patients from all the Phase II and Phase III studies conducted so far involving dosing beyond a month's duration. In addition to patients from the atrial fibrillation and venous thromboembolic secondary prevention indications, we've included data from two other disease areas where significant trials have been conducted, patients undergoing initial 6-month treatment for a venous thromboembolic event and patients post-acute coronary syndromes. The overall ximelagatran exposure is substantial, a total of 6,768 patient years, with a median exposure of 370 days.

Across this population, doses between 20

and 60 milligrams have been used, although the majority of patients, 75 percent of them, received 36 milligrams twice daily. The comparator group includes both placebo as well as warfarin and is termed "the comparators' group." In this group, 20 percent of patients received placebo.

I'll now comment on the different indication pools.

In the VTE extended prophylaxis pool, both ximelagatran and placebo groups demonstrate similar frequency and types of adverse events. The incidence of serious adverse events and discontinuations was actually lower in the ximelagatran group compared to placebo.

In the same group, major bleeding occurred rarely, affecting six patients in the ximelagatran group and five patients in the placebo group. Ximelagatran and placebo groups also did not differ with respect to major or minor bleeding events.

In the atrial fibrillation pool, the same frequency and types of adverse events were recorded in both the ximelagatran and warfarin groups.

Discontinuations were higher in the ximelagatran group, not because of symptoms but mainly due to a protocol-mandated discontinuation for ALT elevation. I'll discuss this in detail shortly.

In the atrial fib population, the rates of major bleeding with ximelagatran did not differ from those with warfarin. Minor bleeding events occurred quite often in these trials and for that reason did not undergo adjudication. Here we see the event rates for patients with one or more major or minor bleeding events. Total bleeding occurred significantly less often with ximelagatran than with warfarin, with a p value of less than 0.001.

Overall, with regard to adverse events and bleeding, ximelagatran compared to well-controlled warfarin following total knee replacement surgery, compared to placebo and extended secondary prophylaxis of VTE, and compared to warfarin in atrial fibrillation patients demonstrated no important differences in adverse events, bleeding profile, or the safety profile of the 24- and 36-milligram doses. In addition, a detailed

subgroup analysis for bleeding supports the proposed fixed-dose approach for all types of patients studied.

I'll now review two special safety topics, coronary artery disease and the hepatic findings. First let's address the coronary artery disease findings.

The agency has noted a possible imbalance in the frequency of myocardial infarctions. Shown here is Table 12 from the FDA briefing document. The events shown here are investigator-reported events. Note that the absolute number of myocardial infarctions observed in the EXULT trials was small, and there appears in a post-hoc analysis to be a significant difference with a p value of 0.049. However, this difference is driven by a single trial, EXULT A. Furthermore, an analysis of other coronary artery disease events failed to reveal any significant difference.

FDA Table 40 shows investigator-reported coronary adverse events from selected trials from the long-term pool. This analysis suggested an

increased frequency of total coronary adverse events in the VTE treatment population. When VTE treatment and extended prophylaxis are evaluated I a post-hoc pooling and analysis, the p value is significant for both myocardial infarctions and other coronary artery disease events. However, this finding was not observed in the much larger atrial fibrillation pool. In addition, the trial in acute post-coronary syndromes where benefit was demonstrated is not included in this analysis. In fact, when all three groups are pooled, no significant difference is observed for either myocardial infarctions or other coronary events.

In addition to the investigator-reported events, the SPORTIF trials in atrial fibrillation with an active comparator, warfarin, and the ESTEEM trial in the post-ACS setting versus placebo provided an independent and objective assessment of myocardial infarctions. In fact, adjudicated events in these trials represent over 90 percent of all MIs across the program. Here, evaluation of the SPORTIF trials demonstrated an identical

incidence while the ESTEEM trial demonstrated an actual reduction in myocardial infarctions.

It is also relevant in this context that across the whole program we have no evidence of any rebound effects producing MIs after ximelagatran treatment was stopped.

So with regard to coronary artery disease adverse events, while a concern was raised regarding a potential imbalance in events, a more comprehensive analysis focusing on both investigator-reported and objectively assessed events fails to identify an increased risk.

I now want to turn to the unexpected results, the hepatic findings, and present a detailed review.

We've taken the findings very seriously, and from the large database individual case analysis and consultation with hepatic experts, we've produced a thorough assessment. I'll first review the laboratory findings followed by the adverse event data.

Preclinical toxicology and the Phase I

studies did not demonstrate any hepatic safety issue. The surgical studies with up to 12 days of dosing didn't show any hepatic changes with ximelagatran, just the well-recognized enzyme elevation seen with heparin. In the first Phase II long-term dosing study with ximelagatran in the atrial fibrillation patients, a signal of an asymptomatic increase in ALT greater than 3 times the upper limit of normal was noted. Therefore, the standard laboratory testing that was being performed early in the development program was increased in the Phase III studies.

The liver function testing panel consisted of alanine amino transferase, or ALT; aspartate aminotransferase, or AST; alkaline phosphatase, and total bilirubin. These tests were performed monthly for the first 6 months of exposure, then every 2 months up to one year, and then quarterly. In addition, weekly testing and discontinuation criteria were defined. These criteria were strengthened after one case of biopsy-documented hepatic necrosis.

As mentioned, there was no increase in ALT greater than 3 times the upper limit of normal in ximelagatran patients undergoing total knee replacement compared to warfarin during treatment. At the 4- to 6-week follow-up, there were eight patients in the ximelagatran group and three in the warfarin group that developed an increase in ALT. In general, these increases occurred 3 weeks after discontinuation of drug. It's important to note that two patients with the transaminase elevation in follow-up in the ximelagatran group had received low-molecular-weight heparin. The ALT elevation in all patients but one in each group is documented as resolved. We believe that patients undergoing orthopedic surgery with short-term dosing of ximelagatran are not at an increased risk of ALT elevations or liver injury.

Now, let me summarize the incidence of enzyme elevations of the long-term exposure pool. The incident of ALT greater than 3 times the upper limit of normal was 7.9 percent for ximelagatran compared with 1.2 percent for comparators. It's of

interest to note that there was no difference between groups for isolated elevations of bilirubin. The vast majority of these enzyme elevations were asymptomatic.

Our experience shows that the time signature for ALT elevation follows a consistent pattern. This graph depicts the number of patients with first ALT greater than 3 times the upper limit of normal over time. The y axis represents the cumulative risk of an ALT greater than 3 times the upper limit of normal and the x axis time in months. As can be seen, the occurrence increases above background rates after 1 month and approaches background rates after 6 months. Ninety-three percent were detected during the first 6 months, and 98 percent within the first 12 months.

I now want to turn to the disposition of patients with an ALT increase. Of the 546 patients in the ximelagatran group that had an increase to greater than 3 times the upper limit normal, 46 percent of patients continued to treatment and completed the study. The other 54 percent

discontinued study drug. Overall, 96 percent of ximelagatran-treated patients returned to less than or equal to 2 times the upper limit of normal ALT, regardless of continuation or discontinuation of drug. Of the 74 patients in the comparator group, 31 percent continued treatment, and the other 69 percent discontinued treatment. Overall, 93 percent of comparator-treated patients recovered.

The algorithm allows continuation of treatment for mild and transient increases on drug. These data demonstrate the reversibility of the ALT increases.

Patients who continued drug recovered by a median of 28 days, and those who discontinued drug by a median of 40 days. Eighteen patients were rechallenged early in the program. Only two patients had a subsequent ALT rise. One pt with a peak ALT of 10 times the upper limit of normal was rechallenged after 65 days and did not have a repeat elevation until 2 months later. The second peak was at 3 times the upper limit of normal, and the drug was discontinued.

The second patient did not have a true rechallenge, but had multiple episodes above 3 times the upper limit of normal, but overall recovered with continuation of the drug. There was no evidence in these or any other patients for an immunoallergic response.

Hepatic experts that we consulted suggested that the elevation of ALT greater than 3 times the upper limit of normal and clinical jaundice, in the absence of an alternative diagnosis, can be considered a signal of severe hepatic injury. We selected a more conservative definition to standardize the levels and timing and included cases with ALT greater than 3 times the upper limit of normal and bilirubin greater than 2 times the upper limit of normal, the latter occurring within one month of the ALT rise.

A total of 37 patients, or 0.53 percent, in the ximelagatran group had this concurrent elevation of ALT and bilirubin, compared with five patients in the comparators' group, with an incidence of 0.08 percent.

Please note that one additional case has been included in this analysis at the request of the FDA. We had fully documented this case involving a fatal GI bleed in the submission and had also highlighted it as a case of interest in the safety review.

I'll now review the outcome in patients with a concurrent increase in both ALT and bilirubin. Confounding diagnoses were noted in 25 of the 37 patients on ximelagatran. Seven patients in the subset died of unrelated causes. Twelve patients did not have an alternative diagnosis for the enzyme elevation. Of these 12, two died with a GI bleeding event and will be discussed shortly. The ALT and bilirubin in all other patients recovered. Of the five cases in the comparator group, four had an alternative diagnosis, and only one had an unexplained increase. Two patients died from pancreatic cancer. The other patients recovered.

We have been investigating a possible mechanism for the hepatic changes, but so far this

has not been elucidated. Preclinical studies evaluating reactive metabolites, mitochondrial dysfunction, and protein binding have not been revealing. There is no evidence for involvement of the P450 system. The asymptomatic and nonprogressive pattern of ALT increase has been noted with other drugs, including tacrine, INH, amiodarone, among others.

We wanted to understand if there's a subgroup that's at increased risk. Because the number of patients with concomitant ALT and bilirubin is so low, this analysis was performed on the occurrence of ALT greater than 3 times the upper limit of normal. Therefore, these results should be interpreted with caution. A step-wise logistic regression was performed looking at demographic factors, statin use, and baseline disease. As expected, the most significant factor in this analysis was ximelagatran treatment with an odds ration of 6.82.

Other factors that demonstrated statistical significance all had an odds ratio of

less than 2. These includes patients post-ACS, patients being treated for an acute venous thromboembolic event, body mass index less than 25 kilograms per meter squared, and female gender. Statins and creatinine clearance were not identified as significant factors.

The variable of ALT greater than 3 times the upper limit of normal is generally asymptomatic and reversible. Therefore, this analysis does not allow a prediction for those at risk for severe liver injury. We are, therefore, recommending ALT testing for everyone who starts long-term treatment with ximelagatran.

Now let's look at the adverse event data from these patients. No difference is noted between groups for clinical hepatobiliary adverse events.

T2B I will now briefly review three selected cases in the group of patients with concomitant increase in ALT and bilirubin associated with ximelagatran. These cases were selected by the FDA as three deaths with associated

severe liver injury. The first two cases occurred on the first algorithm, and the third case on the second more conservative algorithm. The second and third case did not demonstrate compliance with the algorithm in effect at the time. The deaths in all three cases are also confounded by other factors.

In the first two cases, the ALT and bilirubin increase was unexplained, and the terminal event in both cases was a GI bleeding event.

The first patient, an 80-year-old male, had a hepatic biopsy with documented hepatic necrosis about 1 month before death. This patient had evidence of decreased hepatic function. However, the ALT was recovering when he died from a perforated duodenal ulcer. This patient had been on prednisone.

The second case presented hypertensive to the hospital with an elevated ALT of 11 times the upper limit of normal and a bilirubin of 1.4 times the upper limit of normal after missing two weekly tests for an elevated ALT. The INR was 3.4 and the

APTT was 69 seconds. His last dose of ximelagatran had been earlier that evening. The patient had a prior history of duodenal ulcer and Bilroth II anastomosis with bleeding at the site detected on this admission. During the 24 hours from the admission to death, the patient received massive transfusions. During this time his bilirubin increased from 1.4 times the upper limit of normal to 9.4 times the upper limit of normal, with 50 percent noted as indirect bilirubin. At the time of death, the bilirubin was 7.3 times the upper limit of normal and the ALT less than 2 times the upper limit of normal.

The third case was a death due to fulminant reactivation hepatitis B with an elevated ALT upon study initiation. This patient was on two immunosuppressive drugs: prednisone and azathioprine. Ximelagatran was not discontinued when the ALT reached greater than 5 times the upper limit of normal as recommended. The patient had a rapid and fulminant course attributed to the hepatitis B. However, the investigator could not

rule out that the drug did not contribute to the fulminant course.

To summarize the hepatic findings, ALT elevations greater than 3 times the upper limit of normal occurred in 7.9 percent of ximelagatran-treated patients, occurring primarily within the first 6 months. The elevations were typically asymptomatic and reversible, without any evidence of an immunoallergic reaction. An incidence of 0.5 percent of concurrent ALT greater than 3 times the upper limit of normal and bilirubin greater than 2 times the upper limit of normal was observed. Exposure response suggests that exposure is not predictive of individual risk of transaminase elevation, and no patient subset was identified to be at higher risk of developing severe hepatic injury.

Based on the data, we are proposing ALT testing in the label reflecting the more conservative testing schedule used in clinical trials. To make sure that ALT testing becomes the standard of care with ximelagatran, we also

submitted a risk minimization plan which set out our initial proposals to support ALT testing in practice. This proposal was developed after extensive external consultation and field testing, but we recognize that it may need to be developed further in the best interests of ensuring patient safety. We have a meeting arranged with FDA on this topic in the near future.

A few comments on the principles of our Risk Minimization Action Plan. The ultimate goal of the plan is to prevent any hepatic failure caused by treatment with ximelagatran. To do this, the Risk MAP will help to ensure compliance with labeled ALT testing recommendations. This proposal was developed to provide access to ximelagatran by those patients who will benefit while minimizing risk. It targets patients, physicians, and pharmacists. It has a strong educational focus and is enhanced with practice management tools and special packaging. In addition, following discussions with FDA, AstraZeneca will be proposing additional enhancements to ensure our ALT testing

recommendations are followed. Finally, we have proposed continuous evaluation of program effectiveness.

AstraZeneca understands that the full benefit of ximelagatran can only be realized if it is used in accordance with the labeled recommendations, and to that end we are committed to developing the specifics of the program in consultation with the agency.

To complete the assessment of safety, we will finish with the overall mortality in the long-term exposure pool to get an overview of risk. The patient population was primarily an elderly population with multiple comorbidities and concurrent medications. Despite an increase in ALT in the ximelagatran-treated patients, no difference in all-cause mortality was noted. Mortality was similar in the ximelagatran group compared to patients on placebo, patients on placebo plus aspirin, and patients on warfarin.

Let me finish by summarizing the benefit/risk comments for each indication.

Ximelagatran prevented venous thromboembolism and/or all-cause mortality compared with warfarin in total knee replacement surgery with a number needed to treat of 12. No difference was seen in bleeding, transfusions, or surgical outcome.

Ximelagatran demonstrated clear benefit over placebo with a number needed to treat of 10 in the long-term prevention of recurrent VTE events. This included a clinically important reduction in pulmonary embolus, a condition that can result in serious morbidity and mortality. The incidence of bleeding was comparable to placebo.

Ximelagatran was as effective as warfarin in reducing the risk of stroke and other thromboembolic events in patient with atrial fibrillation. Bleeding was lower on ximelagatran. With regards to the hepatic findings, while the risk per year for stroke or venous thromboembolism is continuous, the risk for an ALT rise and subsequent severe liver injury is limited primarily to the first 6 months of ximelagatran therapy. But the protection from a thrombotic event by

ximelagatran is continuous and consistent over time.

To aid effective management of the hepatic risk, ALT testing will be recommended in our proposed labeling, and in addition, we have submitted a Risk Minimization Action Plan which we will discuss further with the FDA.

We conclude that ximelagatran, the first new oral anticoagulant in over 50 years, does have a positive benefit/risk in each proposed indication provided that the drug is used properly. We look forward to your comments and further dialogue with the agency.

Thank you. I'll take questions.

DR. BORER: Dr. Sheth, I think we need to take a break. I've been chastised when we haven't done that. So we'll take a 10-minute break, and then we'll go on to the questions of fact about the safety data, and I think we can then go on to Jonathan Halperin's presentation, and we'll just make up the remaining FDA time after the public comments later so that you can get your whole

presentation in.

So we'll take a 10-minute break right now. Look at your watch because 10 minutes from now we're going to start again.

[Recess.]

DR. BORER: While everybody is getting back in here and sitting down--or not sitting down--let me raise an issue for you to begin to think about as people are coming back in.

Steve Nissen asked earlier about pharmacological evidence of rebound, and there didn't appear to be significant rebound, although I don't know what that means in the context of studies with limited power. But there didn't seem to be significant rebound of pharmacological effects, although the follow-up, as I recall, was relatively short. So we don't know about late pharmacological changes. But as I look at these data from each of the trials, I'm struck with a difference between the on-treatment and post-treatment frequency of major adverse cardiovascular events that I'd like to hear some

discussion about from you. Is this real or is it not? That is that if you look at the number of myocardial infarctions or other cardiac events that occurred on ximelagatran versus the comparator, the numbers were different but not all that different. It depended on the trial. It varied from trial to trial, and we can talk about that potential adverse event disparity later. But I'm concerned or I want to ask about something else.

If you look at the number of events that occurred on-treatment, the numbers were relatively close one way or the other from trial to trial to trial. If you look at the numbers that occurred post-treatment, the proportion of patients who had events on ximelagatran in the post-treatment period was greater as a percentage of the whole than was the case for any of the comparators. The post-treatment events on warfarin or on placebo were fewer as a proportion of the whole of the total number of events in those comparator groups than was the case with ximelagatran, and in some cases the post-treatment events were more frequent

than the on-treatment events with ximelagatran. That's an observation.

Have you noted that? And is that true? And do you have anything to say about it?

DR. SHETH: The numbers differ a little bit between the different patient groups. So let me start first with the long-term exposure pool and some of the specific populations within that pool.

If we can take a look again at the--and we're talking coronary events, Dr. Borer?

DR. BORER: Yes, we can limit it to coronary events, however they're defined.

DR. SHETH: What you see is that, you're right, there is a difference--I'm sorry. Let's put that up. You do see an increase--and these are both myocardial infarctions and total other coronary artery disease events other than MI compared in the VTE treatment and the VTE extended prophylaxis compared to warfarin. But these numbers are actually quite small. We're talking about a total of 16 patients here, 3, 16, 10, et cetera, versus 1, 0, 12, 3.

If we take a look at two populations where you might say that the risk is actually increased, the atrial fib group had higher incidence of both diabetes, hypertension, for example. You don't see that--those events, again, plus that in the post-acute coronary syndrome population, which is certainly a high-risk group for events. Can we take a look at the next slide? I'll come back to the after-treatment in a second.

Ninety percent of the MIs--and this was during the trials--occurred in these two settings, and you don't see a difference there, and you see a benefit on treatment with ximelagatran.

But if we take a look, let's say, at the post-acute coronary syndrome population, again, a higher-risk group, after treatment stopped, the incidence between those two groups was about 1.5 percent--I think it's about 1.5 percent in both groups.

DR. BORER: Okay. I'm sure you're right, and the data you just showed I think are very reassuring, and I think we all saw them in the book

here. But, again, I'm making a slightly different point, and maybe the data aren't available or aren't sufficient to draw a firm conclusion about them.

What I am talking about is the proportion of coronary events that occurred after stopping treatment on ximelagatran as a percentage of the total number of events compared with the portion that occurred after stopping treatment with warfarin or placebo as a percentage of the total number of events in those groups. I believe that the proportion of events that occur post-treatment is higher in the ximelagatran groups across all the trials, if you look at trial after trial, than is the case for the comparators, which raises some question about the possibility of a rebound phenomenon or something else, some other pathophysiological process that's being allowed to happen or occurring because of the use of the drug once it's stopped.

DR. SHETH: I understand what you're asking. We don't have that specific analysis, so I

won't be able to address it at this moment. You're asking for those proportions of patients after they stop treatment over the total number of events, and right now I don't have that analysis.

DR. BORER: Okay. You can pull it together later, but it's in the books. If you look at the data that are presented, if you look at the numbers, that sort of jumps out at you. So you may want to look at that, and you can talk about it after lunch or something.

DR. SHETH: Okay.

DR. BORER: Okay. Well, why don't we go on and see--Alan?

DR. HIRSCH: Well, just one comment to follow up Jeff, and if you're able to provide that after lunch, I specifically would ask you provide that not in the ACS population, because the population that will be exposed to this if this drug comes to market that really is vulnerable that I'm concerned about is that non-ACS population.

DR. SHETH: Okay.

DR. HIRSCH: I don't want that to be a

Band-aid for a potential adverse effect.

DR. BORER: Steve and then Bill.

DR. NISSEN: Just so you understand what we're concerned about--and several of us have made this observation--it is that because ximelagatran is a short-acting agent compared to Coumadin, our worry is that when you stop the drug, there's some phenomenon that goes on for a few days or a few weeks in which a patient has increased vulnerability and that that is the explanation for the excess cardiovascular events. And we want to understand whether you have some response to that that we can factor into our thinking.

DR. SHETH: Can I ask, would it help the committee to take a look at other thrombotic events in terms of incident or rebound phenomena? Because certainly patients who are usually at risk for venous events might typically get those kind of events. Would that help--

DR. NISSEN: It only helps a little bit. The problem is that the pathophysiology of arterial and venous events are different.

DR. SHETH: Right.

DR. NISSEN: And so, you know, it appears that there is this excess of arterial thrombotic events post-treatment, and we're trying to understand that in order to factor that into the thinking here of the committee.

DR. SHETH: Right, although in maybe the treatment and prevention groups--

DR. NISSEN: Yes, yes. I have another question, and forgive me for this, but I have to probe on something that I think is important. If you could put up Slide No. CE-19, please? I see these patients that are going to have knee replacement all the time in consultation. They almost all get sent for cardiac clearance because they're older and they have a lot of cardiovascular risk factors, and I'll bet the other cardiologists at this table, like Jeff probably sees plenty of these as well. And so when I see them, there are three things that I worry about. I worry about, of course, them dying. I worry about them having a pulmonary embolus. And I worry about them having a

myocardial infarction.

And so, you know, to do the simple math here, which is what all of us are kind of looking at, if you look at the serious endpoints, the feared complications, what you see is--in EXULT A and B, you see three plus six is nine events with ximelagatran, and you see eight events here, PE or death, with warfarin.

If you now put up Slide No.--

DR. FLEMING: Steve, just before you go, those nine and eight are 15 and 10 in the FDA briefing document. It's worse than this. It's 15 and 10.

DR. NISSEN: Okay. I'm trying to be--you know, not make this any more painful than it has to be.

Now let's look at Slide CS-14, so we'll take nine and eight, so CS-14, and now I look at myocardial infarction, and it's 16 to 4. And so when you put it together, you know, you see that the really serious events, the bad things that can happen to that patient I'm seeing in consultation

look a lot worse on ximelagatran than warfarin. And so one has to ask the question: Does it really look as good as it looks?

And so what are your thoughts about this? I mean, MI is as bad an outcome as PE, isn't it?

DR. SHETH: Yes, it is. In considering those numbers, I won't dispute how--the numbers that we just looked at, they are higher in the ximelagatran group compared to the warfarin group in the orthopedic surgery population. The only comment I'd make is that, unfortunately--those are really small numbers, and the question is: Is this a really--a true difference? And I would anticipate that if it was a true effect that we would really see a significant effect in the long-term group just because it's so much larger.

We also have another study that we started to do in extended prophylaxis in orthopedic surgery, so we'll be able to collect more data in that study as well. But, again, the numbers are small so it's hard to know if this is a true difference or not.

DR. NISSEN: But, of course, the difference in the long-term studies is that this is one where you get the short-term administration, then you withdraw the drug, and so it speaks more to this question of an acute rebound sort of phenomenon. I mean, I hope you can appreciate why it's something that really struck many of us on the committee as being a problem.

DR. BORER: It's also a potentially remediable problem, so it's important that you should know about it.

Bill, and then Beverly.

DR. HIATT: Yes, just to follow up on that, it does seem like the surgical population may not be the same as the long-term treatment population, and the concept of risk occurring--excess risk occurring in that population is very real.

Then the other question I have is, turning to the SPORTIF IV data, you didn't present that in any of your safety data. Is that correct?

DR. SHETH: The SPORTIF II and IV data are

actually pooled in the atrial fibrillation pool that we performed. So it included that Phase II trial, yes.

DR. HIATT: If you look at page 97 of the briefing document, there are several phases to SPORTIF IV, and I count a total of 17 deaths on treatment versus warfarin is four. So you're saying those deaths are included in the overall safety data you presented?

DR. SHETH: They are included, but I'll just point out that there are about 2 to 3 times more patients on--3 times more patients on ximelagatran than on warfarin in SPORTIF IV. So they're not balanced groups. The denominators are not balanced.

DR. HIATT: Correct.

DR. SHETH: But those deaths are included in the atrial fib pool and consequently in the long-term exposure pool.

DR. HIATT: Okay.

DR. BORER: Beverly, and then Dr. Sjogren.

DR. LORELL: To follow up on this concept

of potential rebound--

DR. SHETH: Can you speak louder?

DR. LORELL: Yes, I can. To follow up on the issues that were raised about potential rebound in the post-surgical population, can you enlighten us as to how investigators were instructed to use or no instructions on aspirin? Was aspirin deliberately not used in that surgical population? And then were there any instructions at the termination of treatment?

DR. SHETH: Let me ask Dr. Berkowitz, who was the physician for those studies, to describe the use of aspirin instructions for the surgical population.

DR. BERKOWITZ: Scott Berkowitz, AstraZeneca. I didn't get the second part. The first part was that aspirin was precluded, kept to a minimum, and patients weren't to be on it routinely.

DR. LORELL: So I think the second part, was there a strategy in that trial when the study drug was stopped about reinstatement of aspirin in

patients who had risk factors? You know, the point that Dr. Borer made, this is a group with rich risk factors.

DR. BERKOWITZ: I'm sorry. I think I got all your question. The studies were designed to leave to the discretion of the investigators to put the patients back on the medicine, so we did not prespecify how to do that.

DR. LORELL: Okay. And related to that, have you done any studies after withdrawal of the drug to look at what happens to platelet function?

DR. BERKOWITZ: In our clinical trials for VTE and orthopedic surgery and I believe in the atrial fibrillation trials, we did not do any platelet studies.

DR. SHETH: I can mention we actually looked and did an analysis of patients both on ximelagatran, on aspirin and off aspirin, for events in the atrial fibrillation pool. If you're interested, we can show that if that would be helpful. And this is not exactly the same as the patients who discontinued after orthopedic surgery.

But if you're concerned about any increased beneficial effect--let's see. Actually, what you see is that there is an incremental benefit in patients who are on aspirin, but you see that same benefit on warfarin, and you don't see a difference of the effect between the two anticoagulants when aspirin is added.

DR. BORER: The question that Beverly is asking, though, is what about after you've stopped the ximelagatran and the warfarin. In that period, were people still on aspirin or were they not? And did the fact that they were or weren't have any impact on the post-treatment events?

DR. SHETH: We didn't make specific recommendations after the trial. They were to go on their regular medications per their physician.

DR. BORER: Okay. Dr. Sjogren, then Alan, then Ron.

DR. SJOGREN: My question pertains to the potential hepatic toxicity, and I have a couple of questions. One is you are proposing to follow up patients with ALTs, and then if they go over 2

times the upper limit of normal, to follow up a little more closely and eventually discontinue the drug. I'd like to know what kind of information do you have in the patients that you followed up that developed the ALT abnormality to back up that kind of recommendation. That's one question.

The second question is: Do you have any information on patients with chronic liver disease that are treated with this medication? What happens to them?

And one request. Do you have slides of the liver biopsy that was done that we can look at?

DR. BORER: Before you begin to answer, let me just state a rule here. We're not asking you to tell us your algorithm for following patients. Dr. Sjogren is just asking about the data that might be used to inform the development of such an algorithm and then the issue of the chronic use and the slides.

DR. SHETH: Okay. Let me answer the latter two questions first, and I'm going to have to ask for a clarification on that first one.

We do not have a slide of the hepatic biopsy right now. The chronic disease, because we identified early in the Phase II trial, SPORTIF II, that there was this asymptomatic transaminase increase, we actually excluded patients who had known hepatic disease from the trials, as well as patients who had an ALT above 2 times the upper limit of normal. So that to the best of our knowledge, patients who--with the exception of the reactivation hepatitis B, should not have, in fact, been enrolled in the trial, and we would, in fact, propose a contraindication for those patients. So we don't have data to understand the safety in that group.

In terms of follow-up, are you asking me--you want to know what did we do to follow up all patients who had an elevation or what their outcome was?

DR. SJOGREN: No. What I'm asking is, you're proposing how to follow these patients, and you obviously during the studies have shown us that some patients continue on therapy despite ALT

elevation. I want to know what happened to those patients, how high those ALTs go, and when did they come back to normal. Did they relapse? What happened to those patients long term to give me an idea that indeed, you know, your risk management assessment is correct?

DR. SHETH: Okay. If I can take a look at the scatter graphs, please? And I believe in your briefing document you have the same figures, and these are actually the individual patient data for both patients who continued and patients who discontinued study drug. And I think that individual data would be the best look, and if I can take you to the far--I guess my right, is that right? Okay. Continued study drug here, not real large. So this is the continuation of study drug, and what you see is that patients who continued study drug on average returned back down to less than 2 times the upper limit of normal with a median, I believe I said, of 40 days and a little bit shorter if they discontinued study drug.

I want to point out that these scales are

not identical, and I apologize for that. But if you take a look in your briefing document, you can take a closer look at this.

So this is pretty much what happened. There was an early occurrence and a reversibility. I just want to make the point that those patients who were allowed to continue once we had identified and put into place some criteria were not necessarily the patients with the highest elevations or persistent, with the exception of a couple of peaks that got--that you saw up there.

DR. SJOGREN: In the earlier slide, you showed us that 96 percent recover. So should I understand that 4 percent didn't? What happened to that 4 percent?

DR. SHETH: We can take a look at that 4 percent. Of that 4 percent--if we can take a look at the actual outcomes of the 4 percent of patients. It was actually a total of 22 patients. Some of those patients didn't recover because they died of other causes, and I will show you what those were. And then there are about 11 patients

who didn't recover for varying reasons, and I'll actually go through them. So that 4 percent is--okay. It should be--I think it's actually supposed to be 22. So 22 and 5 comparator patients, and if we look at the ximelagatran patients, we had 11 fatal cases, which I'll review shortly, and four nonfatal cases. Three patients, the investigator suggested, had alcohol-related problems, not just routine alcohol use, and one patient with hepatitis C. Five patients, which we are calling here lost to follow-up in the sense that in our database we did not have a last value that was less than 2, but we did get follow-up from the investigator, with one patient, quote-unquote, doing well, according to the investigator. Our goal was to find out were they alive, did they have hepatic disease; one who was sent on active military duty, so assume that person is probably well; one with normalized AST; the ALT was not done. But we found that in our studies the AST tracked with the ALT and typically did not rise as high. And then only two that we really truly had

no further information.

If we could take a look at the 11 fatal cases? Thank you. These are what the causes of death were. We had at least three patients here who had malignancy, malignancy here, metastatic cancer, and pancreatic neoplasia, and then assorted other cases, stroke, ischemic, cardiomyopathy, heart failure, renal failure, sudden death, and heart attack.

I want to just point out that these two GI bleeding events and this reactivation hepatitis I did present earlier in detail during the core presentation. So this is the outcome of those patients who did not recover.

DR. BORER: Alan, and then Ron.

DR. HIRSCH: Well, actually, Dr. Sjogren's comments were very similar to my questions, but maybe I'll add some speculation for the sake of discussion at this moment. What makes this meeting so incredibly interesting is the fact that we're talking about changing thrombin as a major regulatory molecule, and I don't think we've ever

had long-term data to understand how that major impact could affect human health.

So just interpreting these data, my concerns are, if I can go to Slide CS-23, the recovery time after an ALT increase one more time. This confused me, and maybe you've clarified this. It appears from this that it took a mean of 40 days to recover if I stopped the drug if I were the treating doctor but less if I continued the drug?

DR. SHETH: Correct.

DR. HIRSCH: And that seems discordant with the scatter graph you just showed me.

DR. SHETH: The scatter graph had two different scales. We couldn't quite get those scales right. The reason this is, it's probably likely due to the recommendations we made to investigators about how to actually manage ALT. The patients who had persistent increases or particularly high increases were told to discontinue, and that might indicate a different level maybe of severity. Those patients who had either lower or mild increases--and I believe you

have the algorithm in the briefing document. We can review it if it's helpful. But those patients with lower increases or not persistent were allowed to continue. So they're almost pre-selected to have different rates of recovery.

DR. HIRSCH: Okay. That's satisfying. So maybe we'll take a mean of 30 days here or 35 days for both groups. Can I just make one comment then? There's obviously for a drug with a short half-life a longer-term tissue effect, which is something that Bev mentioned vis-a-vis platelet function, I'm mentioning for what happens to the liver or the gut. And so any monitoring plan would have to take into account a relatively long period of vulnerability whereby changing drug discontinuation may not actually affect the natural history of recovery. Does that make sense?

DR. SHETH: I'd actually like to ask Dr. Lewis to address that question. Dr. Lewis is our hepatologist from Georgetown University. He might be better able to address that.

DR. LEWIS: Thank you. James Lewis. I'm

the Director of Hepatology at Georgetown.

What you saw in the other slide in terms of recovery, one of the other explanations is that for those who discontinued drug, they had--in some of those cases, the enzymes were higher, somebody was more nervous, and it may have just taken a little bit extra time for those values to normalize. And that's not atypical of what we see with many other drugs. The ones who were able to continue drug, they were at less elevated numbers, and they came down.

The whole question of whether there's any delayed toxicity, we have not seen that. There are no cases of chronic injury. This is a short-term drug. While you're on it, you've seen the percentage of patients whose enzymes can rise from mechanisms that are not defined. We don't know what those are yet. It would be nice if we did. We think that with the monitoring that was put in place--which was fairly conservative. If your enzymes started out normal and went to twice normal the ALT, you had to have your enzymes monitored

much more frequently. And if they continued to rise, the drug was discontinued, which is what we do with several other agents.

So if you're asking is there going to be a long-term effect, I don't think so. I know that the FDA raised the issue in the short-term treatment, and there the numbers were normal at the beginning, they were normal at the end of therapy, and then three weeks later, as Dr. Sheth told you, something made those enzymes go up again, but in a very small group of post-op patients, lots of other things can happen.

DR. HIRSCH: That's reassuring. There's no longer-term toxicity. There's still a period of clinical vulnerability. That's different.

DR. BORER: Before you sit down, Dr. Lewis, just one more word to complete the answer to that question. You said there was no evidence of long-term problems in the people who were treated short term. But my recollection from the data is that the follow-up was 4 to 6 weeks. Do we have any information of vital status or anything else

from 6 months later or a year later so we can be reassured that there really isn't anything that happened to them later?

DR. SHETH: I'll take that, actually. No, we don't have information out to 6 months.

DR. BORER: Okay. Tom--I'm sorry, Ron, Tom, and Beverly.

DR. PORTMAN: As the renal part of the cardio/renal group, I have a couple of questions.

First, in looking back at the myocardial infarction issue, it's noted in our briefing book that the major cardiovascular risks between the treatment and comparator group were not different, but not listed there is the prevalence of chronic kidney disease between the groups. Did you look at that?

DR. SHETH: We did not specifically look at that. What we have is a breakdown of demographics by mild, moderate, and severe renal impairment. But I don't think that's what you're asking.

DR. PORTMAN: Right. For the patients who

had the myocardial infarction, was their renal function worse than the group that didn't have it?

DR. SHETH: Okay. I don't have that right at this moment, but we can take a look into that.

DR. PORTMAN: We know that it's a very powerful risk factor for cardiovascular disease, and it would be interesting to know if there was a difference between those groups.

DR. SHETH: And you're looking specifically for the patients who had an event as opposed to those who did not?

DR. PORTMAN: Well, I think it needs to be looked at overall, but in particular for those who had an event, yes. If you could provide that information at a later point, that would be very interesting.

Another issue relates to the fact that I think the company already admitted that they have a lot of work to do in determining how to dose this drug in patients who have chronic kidney disease. And, in fact, taking a fixed dose of a drug in a patient, a drug that's cleared by glomerular

filtration is a little bit of a foreign concept in nephrology. And it's been demonstrated that there are higher levels as the GFR decreases and that there is a trend toward increased bleeding as GFR decreases as well.

Is there a relationship or could you review the data for me, is there a relationship between the hepatic toxicity and the decrease in GFR?

DR. SHETH: Yes, we can take a look at that. Let's take a look at creatinine clearance and how about ALT greater than 3 times the upper limit of normal, we can take a look at that. And what you see--let me wait until we get the slide and we'll look at the data. Here we go.

This is in the long-term exposure pool, and just to orient everybody, creatinine clearance, these patients with normal creatinine clearance, mild renal impairment, moderate, and severe. This was an exclusion within the trial, but a few people did sneak in. So we need to present that data here.

We actually looked at it for both ALT greater than 3 times the upper limit of normal, greater than 10 times the upper limit of normal, and ALT greater than 3, and bilirubin greater than 2 times the upper limit of normal.

For the ALT greater than 3 times the upper limit of normal group, you do see a slight increase from 7 percent, to 8 percent, to 10 percent in terms of patients who develop a transaminase elevation. If we come to those patients with severe hepatic injury, we don't see a difference, but the numbers are very small. Again, the denominator is also very small. So it may be difficult to see.

We do see a slight increase, ALT greater than 10, going from 1.8--not really much difference between normal and mild renal impairment, but to the moderate group up to 2.6 percent.

DR. PORTMAN: Well, that certainly speaks to the need for drug dosing by GFR.

DR. BORER: Tom, and then Beverly.

DR. PICKERING: Yes, I wanted to ask you

about the predictors of hetaptotoxicity. In your slide--I think it was CS-27--you don't list statins as a predictor, but in the FDA analysis they did. And since statins also affect liver enzymes, I wonder if you could comment on that.

DR. SHETH: Yes, in the original analysis, we had good treatment as a factor, and when we put in ximelagatran treatment as a factor, statins actually was not significant. So we did not demonstrate a significant odds ratio for statin use and the risk of developing an ALT greater than 3 times the upper limit of normal.

DR. BORER: Beverly?

DR. LORELL: Thank you. That was a good segue to my first question. If a patient did get an elevation of LFT in the studies, were statins simultaneously stopped?

DR. SHETH: No.

DR. LORELL: They were not?

DR. SHETH: No.

DR. LORELL: All right. That's helpful to understand.

The other thing I'd love to hear a comment on, thinking about how to use this drug in the real world, and perhaps Dr. Lewis could comment on this as well, first, did you at baseline, in your baseline laboratory testing for chronic use, measure serology for hepatitis B and C? And, secondly, there is a little wisp of a signal here that could be a nothing or could be a something, that if you have chronic infection with hepatitis B or C, there could be an interaction or synergy. So what do we know about that, and how do we think about that in the real world going forward where both are fairly common?

DR. SHETH: Before I bring Dr. Lewis up to answer the latter part of that question, I just want to say that at baseline, viral testing for hepatitis A, B, or C was not performed. But once we identified that we did have this signal, we actually made an effort in every patient who had an elevation above a certain level to request the investigator to do not only hepatitis A, B, and C, but also CMV, EBB, do an ultrasound, and assorted

tests for collagen vascular disorder. And part of that was to understand also were there other things at play.

In some of those cases, some of those patients did have a diagnosis of hepatitis B, not necessarily active. But I'd like to ask Dr. Lewis to discuss the implications of that.

T3A DR. LEWIS: The use of any drug in somebody with chronic liver disease, where you're dealing with a potentially hepatotoxic agent, is something we wrestle with all the time. There are not enough patients in this database to know if it's a true risk factor. There are examples, real use among patients with HIV and tuberculosis who are being treated with those drugs who have underlying hepatitis B or C, where we know there's a higher risk of hepatic injury in those settings. Those are about the only examples that I know where there may be a virus interaction with certain medications.

Whether or not we've identified such a thing here, the database doesn't permit that. The

one patient who had the reactivation of hepatitis B was being treated with immunosuppressives, had active hepatitis B before he even got into the trial. And as you heard, such patients would not normally be prescribed the drug, and the labeling would contraindicate that until we do learn more.

For patients who have cirrhosis but not decompensated disease, the pharmacokinetic pattern of the drug shows that there is a slight rise in the melagatran levels. But it's acceptable and it doesn't seem to make a huge difference. But, again, those are patients who we wouldn't enter into the trials to begin with.

So there's a little bit of information on chronic liver disease, but not a lot.

DR. LORELL: So to press you just a little bit on this--and you may not know the answer to this and are still thinking about this with the FDA. Would you recommend that common hepatitis serologies be done before starting this drug, even if the ALT was normal?

DR. LEWIS: No, I wouldn't.

DR. LORELL: You would not.

DR. LEWIS: And even though we know that patients with hepatitis C, for example, can have normal liver enzymes and have mild liver disease, the algorithm that will be put in place is pretty rigorous. And if your enzymes start to rise or if you develop any symptoms, a full investigation would be done at that time.

So I don't think it would be cost-effective to do that when you already have normal baseline values. I don't think we need to know, unless there's extenuating circumstances, if you're pregnant or something like that.

DR. LORELL: Thank you.

DR. BORER: Steve?

DR. NISSEN: What rate of acute liver failure is the company's point of view that we should assume in our deliberations about risk/benefit? Obviously, when it comes down--and I need to know what your thoughts are about this. The agency's documents suggest were based upon Hy's rule that we should assume a rate of 1 per 2,000

for acute liver failure. The observed rate is about 1 per 2,000. What is the company's position on the likely rate of acute liver failure if this drug is used in a large population?

DR. SHETH: Okay, two points on that one. I think the first important point is that the number of patients which severe liver injury associated with death are actually quite small. So 1 in 2,000 might represent the highest frequency, but, in fact, we don't know what the true frequency is based on the very low number. Our goal is actually to prevent any hepatic injury. In other words, we do not want to market this drug with the possibility that patients are going to be at high risk for hepatic injury. And based on that, we actually proactively submitted a risk minimization plan, which will be modified to assure that patients are protected from that risk.

So it would be difficult to hypothesize what that would be, but our goal would be really to prevent it.

DR. NISSEN: I understand what your goal

is, and we all have the same goal here. We really want the same thing. You know, we want to get--if a drug is effective and safe, we want to get it out there. But we've got to decide.

So I have an agency document that says that I should assume a rate is 1 in 2,000. Do you disagree with that? Do you think that the rate is not--could not possibly be that high?

DR. SHETH: Yeah, I guess there's a little bit of difficulty around some of the confounding factors that resulted in death, and not all three cases had evidence of acute hepatic failure, although I'll leave that part of the discussion to Dr. Lewis, if we wanted to go there.

DR. LEWIS: The true incidence of hepatic failure in this data set, it's hard to determine, and there are definitions that we have to agree to. What's acute liver failure as opposed to an ALT going up and having an associated bilirubin elevation? And Hy Zimmerman's rule, and all of us who deal with liver disease in this room are students of Hy Zimmerman University, and we all

know what his descriptions were based on retrospective studies in older drugs, that if you had clinical jaundice and severe hepatocellular injury, that determined--there was an associated 10-percent mortality. In an era where we didn't monitor patients, this was the natural history of drug-induced liver disease.

We're now trying to wrestle with what the true signal should be based on these kinds of enzymes. In almost all these patients, they're asymptomatic. There was one individual where the algorithm was changed for this individual because when his values went up above twice normal, he wasn't brought back, and they continued to rise, and the action--I didn't take care of this individual, and so we may never know. But if you look at what happened to him, he was on--he was recovering, but because he had asymptomatic very high elevations--they actually did a liver biopsy. They saw subhepatic necrosis. They put him on steroids, which may have contributed to a large ulcer that eventually killed him because it

perforated and he had a massive bleed. But all the indications were he did not have encephalopathy. His coagulation parameters off of any anticoagulants were improving.

I acknowledge he was drug-related, but would he have recovered? We may never know. This is the actual data on this individual. Things were getting better, but then he died suddenly at home of the bleeding.

The hepatitis B patient who reactivated, again, may have had an increase go up and--but for other reasons, I think he died of fulminant hepatitis B. Again, he shouldn't have been in the trial perhaps.

And the third patient we know even less about because he was massively transfused. He had about 60 units of blood products. His bilirubin rose, and his bilirubin when he was admitted was just over 1, and then it jumped dramatically within 24 hours, which I think being mostly indirect bilirubin was related to hemolysis that was going on. His haptoglobin was zero. And the indirect

bilirubin--and that puts him in the category of an ALT that's elevated with a high bilirubin. Bilirubins were only total in this study, so we're overestimating the number of people who could have had indirect causes, like Gilbert syndrome.

So if we take the worst case, we've got 1 in 2,300 from the data set, and these were pretty much outside of the algorithm that's now being proposed, and I hope that we will be able to reduce that down to zero. As you said, that's everybody hope, and it's how hopefully we can work with everyone here to ensure that this drug is used safely.

DR. NISSEN: But you understand the dilemma that we're in here. We're going to be asked some questions later about risk/benefit, and I really need to come up with in my own mind what I think the actual likely rate of acute liver failure is for this drug. And I'd like to ask you a related question.

In clinical use, as opposed to in clinical trial use, do you think that the following of the

algorithm is likely to be as good in clinical practice as it is in the trial, better than or worse than?

DR. LEWIS: I hope it will be better than.

DR. NISSEN: I understand what you hope, but I'm not asking about what you hope. I mean, I've got to be--I've got to pin you down on this because I'm going to have to vote on this later.

DR. LEWIS: It will be better, and the cases that are highly confounded that we're dealing with--and if you asked me my rate of liver failure, it would say it's one case, the one with the biopsy, because we know they had hepatic necrosis, and whether he died of that or not, different story. But I'm going to let Sunita give you some more insight into the monitor.

DR. BORER: Let me call a halt to that, if I may, and forestall that discussion. I think that we don't know and, in fact, we're not going to determine here what kind of risk management plan you're going to develop. The issue will be if you could develop one, is there something here that is

worth giving to patients. But that's going to come up in the questions.

Let me limit this part of the discussion to one more question because John Teerlink has been waiting for a while, and, Dr. Sjogren, we'll hold yours until after Jon Halperin's presentation because we're going to run out of time and we do have other question time after the formal presentations. And we're limited by a schedule determination that says between 1:00 and 2:00 we must have the open public hearing.

So let's go on to John Teerlink now.

DR. TEERLINK: This question is actually a point of clarification in regards to Slide CS-27, our old friend. I noticed that--is this slide including all of the patients and then for all the risk factors, and do you have an similar analysis for just looking at the ximelagatran patients? Do you have predictors of ALT greater than 3 times upper limit of normal for solely the ximelagatran-treated patients, a multivariate analysis of that?

DR. SHETH: No, we do not.

DR. TEERLINK: That might be helpful for us in deciding what are the predictors of that increase in ALT.

DR. BORER: Okay. Dr. Teerlink, I've learned that this is "ximelagatran."

[Laughter.]

DR. SHETH: Can I now introduce Dr. Jonathan Halperin, professor of medicine at Mount Sinai Medical Center in New York City, and also the Chair of the Executive Steering Committee for SPF, to give his views on the benefit/risk of ximelagatran.

DR. HALPERIN: Thank you very much, Dr. Sheth.

Mr. Chairman, members of the committee, ladies and gentlemen, I'm Jonathan Halperin from the Mount Sinai Medical Center in New York City. I direct a large anticoagulation clinic and have a longstanding research interest in thromboembolism, specifically in stroke prevention for patients with atrial fibrillation. I have served as a consultant

to AstraZeneca, as co-chairman of the executive committee governing the SPORTIF clinical trials.

Now, Drs. Horrow and Sheth have presented the efficacy and safety data upon which the sponsor bases its application to use ximelagatran as an oral anticoagulant. My task is to put these data into the perspective of clinical practice and to offer an assessment of the balance of benefits and risks associated with use of ximelagatran for each of these indications.

Let me begin by addressing the hepatic risk associated with ximelagatran. In these trials, elevations in liver enzymes, specifically serum ALT above 3 times the upper limit of normal, typically occurred within the first 6 months of treatment and were usually asymptomatic and reversible, even when the drug was continued. In my experience, these reactions are manageable because they arise early when surveillance for medication side effects is familiar to most physicians. Since the course was not invariably benign, however, clinicians and the manufacturer

must be vigilant to prevent more severe liver reactions, the frequency of which, like many safety issues, cannot be fully appreciated before the drug is brought to market and used more widely.

A cautious algorithm and a risk minimization program are necessary, and I believe they can be clinically achievable. With proper use, the benefits of ximelagatran can considerably outweigh the risks.

The benefit/risk ratio is not a fixed property of any molecule. It varies depending upon the patients in whom it's used, their underlying need for the therapy, and their propensity for the development of adverse events.

In the THRIVE III trial, for example, ximelagatran demonstrated convincing antithrombotic efficacy, achieving greater than 80 percent relative risk reduction for the primary endpoint of symptomatic venous thromboembolism, with bleeding indistinguishable from placebo. In this indication, as shown here, ximelagatran demonstrates a positive net clinical benefit.

From this and other recent studies, the advantage of extending anticoagulation beyond 3 to 6 months to reduce recurrent thromboembolism seems clear. My practice includes vascular medicine, and I generally recommend continuation of anticoagulant therapy for patients with persistent thrombotic risk factors and for those with idiopathic thrombosis in whom no correctable cause can be identified and eliminated.

In chronic indications such as this, patients and physicians may find hepatic surveillance with diminishing risk over time preferable to the coagulation monitoring, the dose adjustments, the dietary constraints that are a never-ending part of life with warfarin.

To complete the picture, I await the results of studies focused on the early phase of treatment of acute venous thrombosis with ximelagatran.

Now, in the absence of anticoagulant prophylaxis, deep vein thrombosis develops within the first 10 days following knee replacement

surgery in up to 70 percent of patients. In the United States, warfarin is the medication most frequently prescribed in this situation, even though its delayed onset leaves anticoagulation intensity deficient immediately after the operation.

In the EXULT trials, the efficacy of ximelagatran was superior to adjusted-dose warfarin in patients undergoing orthopedic surgery of this type, and bleeding was comparable with the two strategies. Here, with 7 to 12 days of treatment, the liver enzyme problem is not seen. In this indication as well, then, a net clinical benefit makes ximelagatran an appealing alternative to warfarin.

In the third indication, prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, previous trials have demonstrated that the high-risk patients of the sort enrolled in the SPORTIF trials would face an annual rate of stroke and systemic embolism around 8 percent without anticoagulation and about

3 percent on warfarin. The SPORTIF results seem convincing. Ximelagatran performed at least as well as carefully modulated warfarin, offering consistent efficacy with a 1.6-percent annual rate of stroke and systemic embolism in both trials. There was no increase and perhaps even a slight decrease in bleeding complications.

Anticoagulation in the warfarin arms was about the best ever reported in a large population of patients with atrial fibrillation. When interpreting the results of the SPORTIF trials, therefore, it's important to bear in mind that the comparator was warfarin on its best behavior. Rates of intracerebral hemorrhage were unusually low compared with other anticoagulation trials.

From the perspective of a treating physician, an anticoagulant that reduces the stroke rate in high-risk cardiac patients at or below 2 percent per year, with a low rate of major bleeding, while avoiding the complexities of warfarin, has until now been unavailable. And when tallying the risks and benefits of ximelagatran,

remember as well that the outcomes we seek most to prevent--strokes and systemic embolic events--are devastating, often fatal.

Taking these together with major bleeding and mortality from any cause, including hepatic disease, there is to my mind a clear advantage to therapy with a direct thrombin inhibitor. This net benefit will weigh heavily with clinicians caring for patients with atrial fibrillation as they consider the trade-offs against warfarin.

One in four people over age 40 will develop atrial fibrillation and face a risk of ischemic stroke about 5 times greater than individuals without this condition. Over half the strokes occur in patients over 75 years old, making atrial fibrillation the most common cause of stroke in elderly women. As the population ages, the number of patients with atrial fibrillation at risk of stroke is projected to double over just two generations.

Of the more than 2 million Americans who have atrial fibrillation today, about half need

anticoagulation but fewer than a quarter are treated with warfarin. In primary care practice, less than a quarter of patients on warfarin have an INR in the therapeutic range at any given time. Even in specialized anticoagulation centers where care is provided by carefully trained nurses following strict protocols and when patients are fully adherent, anticoagulation intensity is seldom maintained within the desired therapeutic range more than about half the time. No other drug has generated such a burden just to support its normal use.

Based on all the available evidence, I see ximelagatran as a true therapeutic advance, the first oral direct thrombin inhibitor to have been extensively evaluated in clinical trials using fixed doses without coagulation monitoring. In these trials, ximelagatran proved an effective alternative to warfarin with a favorable benefit/risk ratio even when the hepatic findings are taken into account. As more and more patients need treatment, the quest for an alternative to

warfarin has become urgent. On average, untreated patients with atrial fibrillation face a 35-percent lifetime risk of stroke, yet thousands are inadequately treated and hundreds of strokes and thromboembolic events occur across the nation every day that could be prevented with an anticoagulant safer and easier to administer than warfarin.

The convenience of stable dosing and predictable anticoagulation with ximelagatran will appeal to patients and physicians alike, potentially enabling more to sustain anticoagulation over time.

We stand now at the threshold of a new era in antithrombotic therapy. While other orally effective alternatives to warfarin can be expected in the years ahead, none is even close to coming into hand for clinical use. There's a pressing need for a better oral anticoagulant, and ximelagatran has attracted the eager interest of all who share the goal of bringing effective therapy to many more patients to prevent thousands of thromboembolic events.

Thank you very much.

DR. BORER: Thank you very much, Jon.

You know, it may be, both in the interest of time and the interest of efficiency, useful for us to hear the first FDA presentation right now when Jonathan Halperin's summary is fresh in everyone's mind, because the first FDA presentation by Dr. Ruyi He is specifically about risk/benefit assessment. Can we go ahead and do that then? And we'll hold questions until we've heard both.

DR. HE: Good morning--or I should say good afternoon. I'm Dr. Ruyi He, medical team leader in the Division of GI and Coagulation Drug Products, and I'll take the next 15 minutes to go over my assessment of efficacy and safety for Exanta. I will divide my presentation into two parts: short-term use and long-term use. For each part, I will discuss both efficacy and safety concerns.

Efficacy: short-term use in patients undergoing total knee replacement surgery. Exanta was significantly better than warfarin for primary

endpoint: the incidence of total VTE and/or all-cause mortality. However, this efficacy result was driven by decrease in asymptomatic distal DVT which is not clinically meaningful. There was no differences between groups for symptomatic DVT, proximal DVT, PE, or death.

This table was directly copied from the sponsor's submission. It shows no difference between groups for death, PE, or symptomatic DVT. The main difference between groups was the incidence of symptomatic distal DVT, 19.2 percent versus 26.7 percent in one study and 21 percent versus 31 percent in the second study.

Now let's move to safety assessment for short-term use: bleeding events. A higher incidence of bleeding events occurred in the Exanta group than in the warfarin group. This includes both major bleeding and minor bleeding. There were two fatal bleeding evens, and both occurred in the Exanta 36-milligram group.

This table summarizes the number of patients with ALT elevation more than 3 times upper

limit of normal either during the 7 to 12 days of therapy or 4 to 6 weeks follow-up period. There was no difference between groups during the treatment period; however, there was a seven-fold higher event rate in the Exanta group than in the warfarin group during the follow-up period. There was no long-term follow-up. The drug effect on liver toxicity beyond 4 to 6 weeks is unknown.

This table summarizes acute MI/CAD events that occurred in the two short-term pivotal studies. Because the sponsor has shown this table in her presentation, I will not go into detail for this table. The only thing I want to mention is that the treatment group was well balanced for baseline condition, such as diabetes, hypertension, or coronary artery disease.

My safety concerns for short-term use of Exanta are: twofold higher incidence of major bleeding events in the Exanta group; two, higher incidence of ALT more than 3 times upper limit of normal during the follow-up period, and no long-term follow-up data available; three,

potential for duration of treatment to be more than 12 days in clinical practice; and, four, almost threefold higher incidence of acute MI event in the Exanta group.

Now let's move to long-term use, efficacy in patients with atrial fibrillation. The sponsor conducted two noninferiority clinical studies; one was open label and the other was double-blind. For those two studies, the sponsor prespecified 2-percent noninferiority margin was too liberal, and not formally agreed to by the agency. The two studies produced divergent results. Based on the double-blind study, it could not be ruled out that the risk of stroke was twofold greater on Exanta compared to warfarin.

Long-term use, liver toxicity. The studies excluded patients who might have potential live impairment, such as patient who had a liver disease, ALT more than 2 to 3 times upper limit of normal, treatment with NSAID, or alcohol abuse. Before November 2001, liver function test was as follows: monthly for 6 months, if ALT more than 3

times, then weekly; if more than 7 times, Exanta was stopped. After November 2001, because one patient died from liver failure, monitoring of liver function test was enhanced to monthly for 6 months; if ALT more than 2 times, then weekly; if more than 5 times or more than 3 times for 4 to 8 weeks, Exanta was stopped. About 14 percent of the patients being followed by later monitoring.

This table summarizes the number of patients with ALT more than 3 times upper limit of normal alone or with both ALT more than 3 times and a total bilirubin more than 2 times upper limit of normal. This group of patients represent severe liver injury. You can see that there was more than a seven-fold higher incidence in the Exanta group than in the comparator group for ALT elevation more than 3 times, 7.8 percent versus 1.1 percent; same as severe liver injury cases, 37 cases versus 5 cases only. Nine out of 37 patients died, and three of them may have been related to Exanta. Let me go over these three cases with you.

The first case was an 80-year-old man on

Exanta 36 milligrams twice daily for atrial fibrillation. At baseline, his liver function test was normal; ALT was normal. Liver function test was done monthly per protocol. The first month his ALT was normal. The second month it was elevated to 2 times upper limit of normal. However, the third month his ALT was very high, up to 20 times upper limit of normal. At this time Exanta was stopped. However, his condition did not better. ALT continued to increase, total bilirubin increased, INR increased, and albumin decreased. This patient died from GI bleeding with coagulopathy 2 months after Exanta was stopped. Autopsy showed a small, friable liver with extensive necrosis. This is the same as liver biopsy report that was done a month before his death. The most likely diagnosis for this case is Exanta-induced hepatitis.

The second case was a 77-year-old man on Exanta 36 milligrams BID for atrial fibrillation. At baseline, his ALT and albumin was normal. Albumin was 3.6. Liver function test was monitored

monthly per protocol. The first month his ALT was normal; however, the second month ALT was elevated to 4.6 times upper limit of normal. Then per protocol, liver function test monitoring was changed to weekly. Repeated result is unknown. Two weeks later, the patient developed bloody stools. At the emergency room, his blood pressure was 76/45, and hemoglobin was 7. At this time PT, PTT, and INR was all elevated. INR was 3.4. The plasma melagatran level was 0.25 micromolar, which is in the therapeutic range. This level of melagatran should not cause PT, PTT, and INR elevations. At the ER, his ALT was high, 569, and the albumin was low, only 2.0, decreased from baseline 3.6 to 2.0. All of this indicates that this patient had severe liver impairment at this moment. The patient received transfusions. After transfusion at emergency, a gastroscopy was done which showed active bleeding site. The patient received more transfusions; however, the severe coagulopathy had developed. This patient died a few hours later. No autopsy was done, and in this

case was not included in the sponsor's background package.

The third case was a 73-year-old man on Exanta 36 milligrams for DVT. His baseline ALT was elevated, but less than 2 times upper limit of normal. After a few days on Exanta, he fell sick and the liver function test was done early. At day 12, ALT was up to 4.5 times, and at day 18 up to 7.8 times. Hepatitis B was diagnosed on day 18, and Exanta was stopped on day 24. After Exanta was stopped, the patient's condition continued to worsen. He developed hepatic encephalopathy and died from liver failure 20 days later.

According to the literature, mortality of acute hepatitis B is between 0.1 percent and 1 percent.

This table summarizes discontinuation of study drug due to an adverse event. A significantly higher number of patients from the Exanta group stopped Exanta due to an adverse event; 4.6 percent in the Exanta group compared to 0.3 percent in comparator group stopped study medication

secondary to abnormal liver function test.

Also, more patients in the Exanta group discontinued study treatment due to acute MI and bleeding event; 2.8 percent versus 1.9 percent for acute MI; 1.2 percent versus 0.7 percent for bleeding event.

This table summarizes acute MI/CAD events that occurred in the two proposed long-term use population, that is, patients with atrial fibrillation or patients with VTE. The sponsor also showed this table; however, I want to make a few comments on this table also.

First, I modified this table and included the population for post-acute coronary syndrome. Let's move to post-acute coronary syndrome population first.

The total CAD events in this population was 27 percent in the Exanta 36 milligram BID plus aspirin group. This is combination therapy. It's a combination aspirin plus 36 milligrams Exanta. Compared to placebo plus aspirin, that is 30 percent in the placebo group. Two groups, no

significant difference. But this is combination therapy.

And the second point I want to make is the baseline event rate for CAD was very high for the post-ACS population. The baseline condition, baseline event rate was 27 to 30 percent, and for the atrial fibrillation population, also baseline event rates are high, that is, above 7 percent. Because of this high baseline event, it is difficult to assess small proportion of difference.

The third comment I want to make is VTE prevention study is a placebo-controlled study. You can see ten cases in the ximelagatran group versus only three cases in placebo group for acute MI event.

And, lastly, I want to point out these two populations is proposed in this three indication, two of long-term indication. This is the two populations for the long-term use population. In the VTE population, it is significantly higher for both acute MI and CAD event.

Lastly, the treatment group also was well

balanced for baseline condition that included diabetes, hypertension, and coronary artery disease.

My safety concerns for long-term use of Exanta are significant higher number of patients with severe liver injury after exposed to Exanta, include three deaths despite protocol-specified liver function test monitoring; higher incidence of withdrawal due to adverse event, including acute MI and bleeding events after exposed to Exanta; and higher incidence of acute MI in VTE population, including in placebo control study.

This concludes my presentation. I want to thank all the members of the Exanta review team, including especially those listed on this slide.

DR. BORER: Okay. Thank you very much.

It's 20 after 12:00, and we must begin at 1 o'clock the open public hearing. So what I'm going to do, unfortunately, is take a break now for lunch. We'll have adequate time for questions afterwards, and I'm sure there will be many. And we can complete the FDA presentation after that,

and we'll go on to our open discussion.

So be back here by 1 o'clock at the latest because that's when we begin.

[Luncheon recess at 12:20 p.m.]

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

[1:00 p.m.]

DR. BORER: We will reopen the meeting with public comment, and before we begin I want to remind you that both the Food and Drug Administration, that is, the FDA, and the public believe in a transparent process for information gathering and decisionmaking. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement

to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

With all that having been said--and it's quite a mouthful--why don't we begin with the first speaker.

DR. MESSMORE: Mr. Chairman and members of the Advisory Committee, as you can perceive, my voice is not good today, but I will at least introduce my talk and I will be assisted in this endeavor by Dr. Wahi, who is a member of our research group at Loyola University Medical Center. I am Dr. Harry Messmore, M.D., FACP, and I am sponsored by the Thrombosis Hemostasis Unit of Loyola University Stritch School of Medicine. This unit has been in research for more than 30 years in drugs of this nature and has been funded with various grants by low-molecular-weight heparin groups, pentasaccharide, and direct thrombin inhibitors. I am being paid for my expenses as

well as an honorarium since I am a consultant to that group, a senior member who is not employed by them at this time, but I am a volunteer who is paid a consultant fee periodically for special studies of this type.

I am a clinical hematologist who has had long experience in clinical and laboratory investigations of the low-molecular-weight heparins and antithrombin drugs, and I would like to, therefore, make a statement that we have several--a number of reservations regarding approval of this drug. My formal statement then will be read by Dr. Wahi, who will be able to, I think, get the message over more clearly than I can with my voice today.

Thank you.

DR. WAHI: Mr. Chairman and members of the committee, I am likewise sponsored by the University of Loyola's thrombosis research group. We feel that there are some reservations which we need to bring to your attention. We feel that for the following reason the FDA should take a good look at this drug:

Number one, in patients who are high risk for orthopedic surgery for prophylaxis of venous thromboembolism in patients undergoing total hip replacement and total knee replacement, ximelagatran in our opinion requires further study before it's approved for the following reasons:

Number one, for both total hip replacement and total knee replacement, ximelagatran should be compared to low-molecular-weight heparins for at least 28 days for total hip replacement and 17 days for total knee replacement. The low-molecular-weight heparins are FDA-approved for these indications and are in current use. They have been shown to be most effective when used for 28 to 35 days in the case of total hip replacement and 17 days in the case of total knee replacement.

Warfarin we do not think is a good comparator drug because it is inferior to low-molecular-weight heparins in its efficacy.

For secondary prevention of venous thromboembolism in patients after standard treatment of an episode of acute venous

thromboembolism, as studied in the THRIVE III trial, we feel that further studies are required to show that the abnormal liver function tests, by which we mean greater than 3 times normal levels of APLTs in 6.4 percent of the patient populations, are not--further studies are required to show that this elevation of enzymes are not associated with long-term sequelae.

T3B For preventing stroke and other thromboembolic complications associate with atrial fibrillation, as studied in SPORTIF III and V trials, we feel further studies are needed before approval is considered. We base this opinion on the fact that ximelagatran caused abnormal liver function in 6 percent of the patients in the reported study. The long-term consequences of this should be studied before the drug is approved in this indication. Although it was judged to be noninferior, these potentially harmful side effects will offset its noninferior status.

Furthermore, we feel that the possibility of hemorrhage due to increases in blood levels over

time in a population whose renal function is deteriorating due to increased age or other factors would require periodic monitoring of its anticoagulant effects, as well as the monitoring of renal function.

We also believe that evaluation of drug interactions with drugs such as cholestyramine and related drugs that could bind the drug and prevent absorption from the intestinal tract are also needed.

Furthermore, many of these patients with atrial fibrillation have associated congestive heart failure on the basis of coronary artery disease, which itself impairs hepatic function and may enhance the liver toxicity. We feel that studies of the drug in this subset of patients and other patients who are at increased risk for liver disease, such as chronic hepatitis, et cetera, should be asked for.

In summary, we believe that lack of comparator studies with low-molecular-weight heparins for the high-risk period of 28 to 35 days

post-operatively in the total hip replacement patients and 17 days in the total knee replacement patients leaves the public uncertain as to whether ximelagatran is an effective and safe prophylaxis of venous thromboembolic disease in high-risk orthopedic surgery patients.

Furthermore, the second point is that we feel that the drug has not been adequately studied for long-term safety in atrial fibrillation patients, and its effectiveness as compared with warfarin is not sufficient to warrant its use in the presence of potential hazard in terms of liver damage.

Monitoring of liver function as well as the blood levels of the drug in the very elderly, over the age of 80, should be done before it is approved for this age group of Tunisia.

The last point I would like to make is that for the secondary prophylaxis of venous thromboembolic patients, in patients previously treated for an acute episode of venous thromboembolic disease such as the THRIVE III

trial, the issue of liver damage requires consideration of whether there's clearly sufficient advantage over warfarin to warrant taking the risk of hepatic injury. A peer-reviewed publication of the efficacy and safety of this drug, given for the first 6 months following an acute venous thromboembolic episode is not yet available to permit me to comment on approving it for this indication.

It is also a concern that physicians will be using this drug off-label even if it is approved only for the patients already treated for 6 months with warfarin.

Thank you very much for your attention.

DR. BORER: Thank you very much, Dr. Wahi and Dr. Messmore.

Before we go to the next speaker, I have one announcement. For recording purposes, please speak into the microphone. Anyone who speaks, get the microphone close to you, if you need to. And please silence the cell phones, if anybody has one in here. It's heard on the recording and makes it

hard for the transcriptionist to transcribe the meeting.

Okay. Can we have the next, speaker number two, please?

MR. BARANSKI: Good afternoon, Chairman and committee members. My name is Jim Baranski. I am the CEO and executive director of the National Stroke Association. I would like to point out that I am here, as they say, on my own nickel. However, the National Stroke Association, like most not-for-profit associations, derives its funding from community-based projects from the government, as well as from industry, of which AstraZeneca is one of our many industry sponsors.

For those of you who may not be familiar with the National Stroke Association, we began our mission in 1984, and that mission was to reduce the incidence and impact of stroke. Over the years, we have developed, with the help of many of the leading thought leaders of stroke, programs to better educate the professional community as well as the public.

In 1999, we were the first ever to produce primary prevention guidelines. Those guidelines were published in JAMA. At the end of this month, we will be publishing secondary recurrent guidelines. Those will be published in the Journal of Stroke and Cerebrovascular Disease.

I guess, you know, after hearing a number of the comments earlier, please understand, I am not here to debate the data, the difference between 1.6 or 1.4 percent. Really, I am here to express the concern that the patient constituents, as well as the professionals that we represent, have a tremendous concern over the current problems of warfarin. As we all know, the issues of monitoring INR, I can tell you that when I speak to patients, the cattle rancher in the middle of Montana, monitoring INR for him is a great challenge. And you know what? I'm not so certain that his professional is that confident about their ability to monitor INR. It seems to me that the most valuable aspect of an opportunity here today is this whole ability to try to close the gap that

currently exists. That gaps that exists is really 50 percent of AF patients are being treated currently on anticoagulants. Only 50 percent, out of the total population of AF that I don't think we've mentioned today, there's 2.2 million Americans currently that struggle with this problem.

So to our way of thinking, if we have this 50-percent gap that exists, and if one of the reasons--one of the reasons that we're hearing from our constituency is because of the whole problem of monitoring, of INR monitoring, and the fear that has developed over the past 60 years, then we embrace this as an opportunity or any other therapeutic opportunity to try to bridge that gap, to remove the fear, to try to help create better patient treatment for a population that, by and large, is aging quickly and it's very difficult for these people to maintain the patient medications that are currently available.

Thank you.

DR. BORER: Thank you very much, Mr.

Baranski.

Let's go on to the third speaker.

DR. ANSELL: Mr. Chairman and members of the committee, good afternoon. My name is Jack Ansell, and I am a practicing hematologist and a professor of medicine at Boston University School of Medicine, where I also direct the anticoagulation service at Boston University Medical Center.

I've spent the last 25 years or so treating patients with thromboembolic disease and managing patients on oral anticoagulants. I'm also the founder and Chair of a professional group, the Anticoagulation Forum, which is a network of over 3,000 health care providers who manage oral anticoagulation in anticoagulation clinics and interface with somewhere between 400,000 and 500,000 patients on oral anticoagulants.

In the spirit of full disclosure, let me first say that I consult for AstraZeneca and have research support from AstraZeneca, the company whose product is being discussed today. But I also consult and receive research support from a number

of other competing pharmaceutical companies in this field. For me it is not the company but the products that are being developed that is important.

I'll also say that I am here on my own account to testify and to make this statement today, with no honorarium or expense coverage from AstraZeneca.

I am not here today to comment simply on the attributes of a new anticoagulant. I also want to emphasize just how problematic existing therapy is with oral anticoagulants. And, finally, I want to comment on how important today's review will be in the context of a number of new anticoagulants that will come before this group sometime in the next 5 to 10 years.

One not need be in the medical profession to know something about Coumadin, the oldest and the only oral anticoagulant available. There is probably no more than one degree of separation between anyone on this planet and someone who receives Coumadin therapy or a similar agent. And

for those more intimately familiar with this drug, they know the vicissitudes involved in taking Coumadin. It is not an easy drug to take and certainly not an easy drug to manage. Warfarin, the generic name for Coumadin, is a drug that under the most ideal conditions would probably never come close to approval if it were under review today.

What, then, is wrong with warfarin as a therapeutic modality? Let me summarize. Warfarin has many drawbacks. You've heard a number of them today. It has an unpredictable response in therapeutic levels that requires the need for frequent venipunctures, frequent INR monitoring and dose changes, frequent visits or contacts to a health care provider to manage that therapy. Warfarin interacts with multiple drugs and foods that increase the risk of bleeding or thrombosis and affects the quality of life.

Warfarin has a narrow therapeutic range such that the bleeding risk increases significantly with too high an INR, and the risk of thrombosis increases when the INR is too low.

Warfarin is associated with a very high incidence of major bleeding or thrombosis that is not reflected by the clinical trials that many of us are familiar with. In the real world of warfarin management, rates of major bleeding and thrombosis combined are as high as 15 percent per year of treatment. Imagine going to your physician with new onset atrial fibrillation and having your doctor say, "Here, take this pill to prevent a stroke. But, by the way, there may be something like an 8- to 15-percent chance of you having a major complication or life-threatening complication with this drug."

Warfarin therapy is associated with an impaired quality of life for both the patient and the doctor as well, and it's one of the most common causes of malpractice litigation.

In order to optimize anticoagulation management and to prevent complications, an entire industry has sprung up around oral anticoagulation. This is the industry of anticoagulation clinics, and it is my organization that exists to serve

those providers who work in these clinics.

What do we need to improve anticoagulation therapy? Well, we need new drugs that work in different ways. We need drugs where the therapeutic response is predictable and monitoring is not required. We need new drugs that have few, if any, interactions with other drugs or with foods. We need new anticoagulants that have a relatively wide therapeutic window so that the risk of bleeding or thrombosis is minimized. And, most importantly, we need new agents that are available in oral formulation so that we can reduce hospitalizations and the need for daily injections, whether in the hospital or out of the hospital.

So I am not here to simply speak for the drug under review today. Ximelagatran has performed exceedingly well in extensive clinical trials, and as a physician, I have full faith in using Exanta for the indications being discussed. But ximelagatran is simply the first of a number of new oral anticoagulants that will come before the FDA in the next several years, and these drugs must

be viewed in the context of what they are intended to replace.

One must balance the needs for a better therapy, even if that therapy is not perfect, against the very imperfect and often dangerous therapy we currently use, and in some cases don't use because of fear of complications.

For me, it's an exciting time to be working in this discipline. We are on the cusp of a revolution in anticoagulant therapy. Ximelagatran represents the first new oral anticoagulant since the discovery of dicumarol in 1940. Exanta is poised to have a major beneficial impact on the outcomes of patients currently taking Coumadin, on their quality of life, and on the overall cost of health care.

Thank you very much.

DR. BORER: Thank you very much, Dr. Ansell.

Can we have the fourth speaker, please?

DR. LURIE: Good afternoon. I'm Peter Lurie. I'm a physician with Public Citizens Health

Research Group. We take no money from industry, from government, or from any professional organizations.

Our remarks this morning will take the form of a brief summary of the safety and efficacy data that exist for each of the three indications, and then afterwards, I'll talk briefly about the risk management program that has been proposed by the sponsor.

In summary, our position is that for the first and third of these indications, there are, in fact, no convincing evidence--no convincing data showing the effectiveness of the drug for those two indications, and we're unconvinced that for the second, the long-term prevention of venous thromboembolus after standard treatment, that the risk management program so far proposed is going to be adequate to reduce the risks particularly to the liver associated with that indication.

Let's go through the first one, by which I mean the knee replacement indication. The sponsor's data indicate that the drug failed to

reduce the incidence of symptomatic proximal or distal deep venous thrombosis compared to warfarin. There is an impressive-appearing reduction in the incidence of asymptomatic DVTs, but closer inspection reveals that essentially all of that reduction occurred in asymptomatic distal DVTs that were diagnosed only by venography. As the medical officer concludes, this "is not clinically meaningful."

In addition, although there are two drugs that are approved for this indication, the sponsor chose instead to compare ximelagatran to warfarin, which is not approved in this country for this indication. This seems like an unfair comparison. Warfarin takes 3 to 5 days to even reach therapeutic levels compared to merely hours for ximelagatran. And, indeed, the medical officer said this comparison is unfair, particularly because the study only lasts 7 to 12 days, and so many of the warfarin patients were not adequately anticoagulated.

Moreover, any convenience advantage over

approved medications conferred by ximelagatran being an oral medication is really diminished in this short-term, substantially inpatient setting.

But even in the short-term studies, there were some safety concerns. Major bleeding was increased in the ximelagatran-treated group, although not statistically significantly so. But there was a statistically significant increase in coronary artery disease events which were described by the medical officer as "unexpected and worrisome." In addition, the rate of ALT was increased both at the end of treatment and, more ominously, 4 to 6 weeks after the treatment had been completed.

In sum, ximelagatran's efficacy appears to be limited to asymptomatic distal DVTs, and even then, only after comparison to a drug unapproved for this condition. It's a classic technique if you're going to do an active controlled trial to pick the comparator that is likely to benefit your active drug, and I think that's what was done here.

Given concerns about the propensity of the

drug to induce bleeding, cardiovascular events, and ALT abnormalities, and the existence of other approved medications for this condition, we do not believe that ximelagatran should be approved for this condition.

As to the second indication, long-term secondary prevention of VTE after standard treatment, there's only a single 18-month placebo-controlled trial, THRIVE III, which has a decidedly modest 73-percent follow-up rate. However, although it has no impact upon mortality, ximelagatran did show an impressive reduction in both symptomatic VTEs as well as pulmonary embolus. And so we do think that it appears to be superior to placebo for this condition.

However, one then needs to think about the safety issues, and I'm going to discuss the safety issues for this and the third indication together.

For all the patients receiving ximelagatran on a long-term basis, 7.6 percent developed ALTs greater than 3 times the upper limit of normal, 7 times higher than the case in the

comparators group. It is noteworthy that in trials--let's step back and say let's compare this to the situation with troglitazone or Rezulin. Those were typically 6-month studies, which is in a way analogous to the situation here because the great majority of hepatotoxicity does occur within the first 6 months of treatment.

Troglitazone caused an increase above 3 times the upper limit of normal in only 1.9 percent of patients compared to 0.6 percent on placebo. Compare here to 7.6 percent with 1.1 percent on the comparators. That drug, of course, eventually got banned, but only after there had been 94 cases of liver failure, most of them fatal.

More serious hepatotoxicity, defined as 3 times the upper limit of normal or twice the upper limit of normal for bilirubin, were observed in 37 patients, which works out to a relative risk of 6.6-fold over the comparators. And as you know, nine patients died and three were judged by the medical officer to be related to ximelagatran, which works out to about 1 in 2,000 patients. This

rate will likely be higher in clinical practice as patients excluded from the clinical trials come to be treated with ximelagatran. And not so far emphasized in this hearing but available in the medical officer's summary is additional information about how high those elevations of ALT can be: 4.3 percent had ALTs greater than 5 times the upper limit of normal, 0.4 for comparators, and 1.6 percent had ALTs greater than 10 times the upper limit of normal, 0.1 percent for comparators. And as we have seen, there is no subgroup that adequately can be predictive of where the toxicity will occur.

For the second indication, there is a non-statistically significant increase in coronary artery disease for both long-term indications. So, in sum, for the second indication, while the drug appears to be effective, although not reducing mortality, the risks are significant and I'll talk about the risk management policy in a moment.

Finally, the third indication related to atrial fibrillation. Two studies have been

submitted, and in our estimation both are seriously flawed. A noninferiority trial is in conceptual terms, I think, the right way to go for this indication, because I don't think it would be ethical to randomize people to placebo. But if you do it, you have to do it right. And in this case, the company has prespecified a noninferiority margin of 2 percent. The medical officer says that this 2-percent margin was "not agreed to by the agency," and, moreover, "the margin chosen was too liberal," rather different than what the company told us this morning.

The two studies, despite being similarly designed, had divergent results, as was pointed out this morning, and the relative risks, which I calculated to be the same as you, were 0.71, i.e., that ximelagatran looked better in the less important open-label study, and 1.39, i.e., ximelagatran looked worse in the more important double-blinded study. The statistical reviewer correctly states, "In general, the results from the double-blind studies are more reliable for many

reasons." And then he goes on to say, "Unless the clinical judgment is that a loss of 2 percent"--the noninferiority margin--"of the effect of warfarin is clinically acceptable"--and I would just add, 2 percent in the context of very varying rates with respect to warfarin alone shown on one of those slides. "unless the clinical judgment is that a loss of 2 percent of the effect of warfarin is clinically acceptable, in my opinion ximelagatran has not been demonstrated to be noninferior to warfarin." I think that's absolutely right.

So, in view of the significant problems with trial design and the toxicity which I've already described with respect to long-term use, we don't think it should be approved for this either.

The sponsor has proposed an ALT monitoring program that is similar to that adopted in the clinical trials, but despite that, cases of severe liver injury, including fatal ones, occurred even with levels of compliance that are likely to have been much higher in the clinical trials than they will be in actual practice. And if we look again

at the situation with Rezulin, which had a liver function test requirement, but the third month of therapy fewer than 5 percent of patients were getting the required LFT monitoring. So that's of great concern as well.

FDA's Office of Drug Safety concludes, "We do not agree that the sponsor's proposed Risk MAP program is adequate. Currently, the proposed monitoring plan provides no guarantee of safeguarding the patient from developing a rapid onset and life-threatening reaction."

It's also true that the risk management program does not even begin to address the problem of delayed hepatotoxicity in the prophylactic use after surgery indication. And, furthermore, it makes no attempt to reduce the risk for bleeding or coronary artery disease.

There are a number of approaches that go beyond the Risk MAP or LFT monitoring approach that have been put forth for consideration by FDA, and if the drug is approved--which, as I've said, for two out of three indications, at least, it should

not--these should be implemented, and mention has been made of a black box warning, mandatory patient registries for long-term users that would be linked to performance, physician-patient agreements, and restrictions on promotion, distribution, and packaging.

Thank you very much.

DR. BORER: Thank you, Dr. Lurie.

Can we go on to the fifth speaker, please?

MR. LODWICK: I'm Al Lodwick. I'm a pharmacist, certified anticoagulation care provider in Pueblo, Colorado. I have been a consultant for AstraZeneca, but currently have no contract with them, nor any other financial interest in this product. You might argue that I have some financial interest in that I spend my full-time monitoring warfarin, but that's beyond the scope of this.

I also own a website, warfarinfo.com, that puts me in contact with people around the world with anticoagulation and its related problems.

A replacement for warfarin has long been

awaited. Exanta has generated a great deal of anticipatory excitement. The fact that it will not have to be monitored had been repeated so often that it has become almost a mantra.

In the published premarketing studies, approximately 6 percent of the participants experienced some, at least transient elevations of liver function tests. Please notice I said "published premarketing studies." The Wall Street Journal of September 8, 2004, published an article about Forest Laboratories settling a lawsuit brought by the New York Attorney General over suppressed data concerning several of their drugs. The same article mentions GlaxoSmithKline settling a lawsuit brought by the same party for concealment of data about Paxil. Meanwhile, Eli Lilly and Merck & Company have announced plans for a clinical trial databases. This raises the issue of whether or not there are unpublished studies about Exanta that could be pertinent to this Advisory Committee's decision, and I suggest that the committee ask that question rather than wait for an

Attorney General to ask it.

While I have no insight as to what this body will recommend or what the final decision on Exanta will be, I'm assuming that it will eventually be approved for marketing in the United States with some requirement for monitoring liver function tests. History provides us with some rather troubling incidents where recommendations of the FDA have been widely ignored by clinicians. In view of this, in the near religious fervor that this drug will not require monitoring, I request that the Cardiovascular and Renal Drugs Advisory Committee recommend that any liver function monitoring requirement be stated in the strongest possible terms in the labeling of Exanta. In addition, all advertising material should boldly state this requirement.

Consideration should also be given to a warning label for patients stated, "You should have had a liver function test before you start taking this medication, and this should be repeated every month for the next x months. Failure to do so

could result in potential liver problems being overlooked."

Thank you for your time and consideration.

DR. BORER: Thank you, Dr. Lodwick.

We'll go on to the sixth and final speaker?

DR. COLGAN: Mr. Chairman, committee members, and members of the FDA, my name is Kevin Colgan, and testifying with me is Victor Tapson, who is sitting back in the front row. Dr. Tapson is professor of medicine at Duke University School of Medicine and practices in the Division of Pulmonary and Critical Care Medicine at Duke University Medical Center. I am Vice President for Outcomes Research at EPI-Q, Incorporated. I am a pharmacist with other 20 years of practice experience in hospitals and health systems. And I am a member of the board of directors of the American Society of Health-System Pharmacists.

However, we are here today representing our fellow researchers from the National Anticoagulation Benchmark and Outcomes Report

Steering Committee, also known as the NABOR Steering Committee. They include Richard Becker, who is a cardiologist also from Duke University Medical Center; Dr. Albert Waldo, who is an electrophysiologist from Case Western Reserve University and the University Hospitals of Cleveland; Dr. Joseph Caprini, who is a vascular surgeon from Evanston Northwestern Hospital and the Feinberg School of Medicine; Dr. Thomas Hyers, who is an internist from St. Louis University School of Medicine and CARE Clinical Research; Dr. Richard Friedman, who is an orthopedic surgeon from the Charleston Orthopedic Associates and the Medical University of South Carolina; and Dr. Ann Wittkowsky from the University of Washington School of Pharmacy and Medical Center, director of the anticoagulation clinic; Dr. Agnes Lee, who is a hematologist from McMaster University; and Dr. David Ballard and Dr. Roger Khetan. Dr. Ballard is head of quality improvement at Baylor Health Care System, and Dr. Khetan is a hospitalist.

Over the past 18 months, the NABOR

Steering Committee has performed an anticoagulation benchmarking study in U.S. hospitals. We have studied atrial fibrillation, acute myocardial infarction, deep vein thrombosis/pulmonary embolism, and venous thromboembolism prophylaxis for total knee replacement, total hip replacement, and hip fracture repair surgery. Our study was funded with an educational grant provided by AstraZeneca. They had no role in the design or the conduct of the study, collection, management, analyses, or interpretation of the data. In addition, we have funded the cost of attending this open hearing ourselves--we are here on our own nickel--because we are genuinely overwhelmed by the degree of inadequate treatment we observed in our study. Therefore, we sincerely appreciate the opportunity to comment at the Advisory Committee Open Hearing for ximelagatran.

The NABOR Steering Committee brings two perspectives to the issues being addressed today. First, we bring the perspective of researchers. We have each been involved in anticoagulation and/or

process improvement research and espouse the practice of evidence-based antithrombotic therapy through the implementation of professional guidelines published by the American Heart Association, the American College of Cardiology, the American College of Chest Physicians, the American Society of Health-System Pharmacists, the European Society of Cardiology, and many other professional groups.

Second, we are clinicians who daily care for patients requiring anticoagulation therapy. We realize the necessity of anticoagulation therapy and experience the real world benefits and the shortcomings of warfarin, which has been our primary oral weapon against thromboembolic disease for decades.

We understand that the Advisory Committee's principal concerns are efficacy and safety. However, there is a third dimension that we would like to discuss today, and that is the dimension of both the non-treatment and sub-optimal treatment of patients at risk of stroke and venous

thromboembolism. And to show you the magnitude of this problem, presently there are 4.7 million stroke survivors living in the United States with 15 to 30 percent of those being permanently disabled. Stroke costs the United States $31 billion in direct costs and $20.2 billion in indirect costs annually. Fatality from thrombosis is about four times as prevalent as fatality from malignancy.

Our NABOR study was performed at 38 U.S. hospitals from 28 different states and included 3,778 randomly selected record for patients primarily treated during the calendar year 2002. It was a retrospective, benchmarking study that included 21 teaching hospitals, 13 community hospitals, and four veteran administration hospitals.

Of the 945 patients with a primary or secondary diagnosis of atrial fibrillation, 86 percent were stratified as having a high risk of stroke using the American College of Chest Physicians risk stratification scheme. Of those

stratified to high risk, only 55 percent received warfarin, which has been shown to reduce stroke by approximately 65 percent in unselected patients with atrial fibrillation. Interestingly, this result confirms other studies dating as far back as 1980 and is practically the same at that published by Jencks, the Centers for Medicare and Medicaid Services in 2003 for results compiled from 1998 to 2001. Furthermore, neither warfarin nor aspirin were prescribed in 21 percent of high-risk patients, including 18 percent of those with previous stroke, transient ischemic attack, or systemic embolic event, despite 43 percent having no identifiable bleeding risk. We felt it logical to expect that atrial fibrillation patients with previous stroke, TIA, or systemic embolic event, and thus the highest annual stroke rate, would be much more likely to be treated with warfarin. However, only 61.2 percent received warfarin. This was disturbing, considering that the number needed to treat to prevent just one stroke in this population ranges from just 7 to 10.

Of the 939 patients with deep vein thrombosis and/or pulmonary embolism, we found inadequate treatment overlap of a heparin compound and warfarin, which included only one in four patients who had at least 5 days of concomitant therapy. We found a tendency to delay discharge in isolated DVT patients rather than providing ambulatory bridge therapy which resulted in a 3.8-day lower length of hospitalizations in those who received it. And we found inadequate or lack of treatment at discharge. Ten percent of DVT patients were discharged without a prescription for an oral or an injectable anticoagulant after receiving a mean duration of only 10.6 days of treatment during hospitalization, many of whom were diagnosed with idiopathic disease or who had previous DVT or malignancy. In many of these patients, we would expect an extended duration of anticoagulation therapy for at least 6 months or longer.

Of the 928 patients who had undergone orthopedic surgery, 38 percent underwent total knee

replacement, 30.6 percent underwent total hip replacement, and 31.4 percent underwent hip fracture repair. Surprisingly, 14.4 percent received inadequate prophylaxis with aspirin or no prophylaxis at all; 6.1 percent received nothing. Total knee replacement patients received a mean of 3.2 days of post procedure anticoagulation in the hospital; however, 17 percent did not receive a discharge prescription for anticoagulation. Likewise, 17 percent of total hip replacement and 47 percent of hip fracture repair patients did not receive a discharge prescription for anticoagulation after a mean of only 3.4 and 4.7 days of post procedure anticoagulation, respectively.

Now, I've given you a lot of data, but let me interject that the NABOR Steering Committee members are very concerned about the magnitude of under-treatment we observed in our study. And if it is representative of treatment in the United States, it represents a substantial public health problem. Despite its enormous preventive potential

oral anticoagulation is prescribed for a little more than half of high-risk atrial fibrillation patients. At least one in ten DVT and pulmonary embolism patients and one in five orthopedic surgery patients do not receive adequate anticoagulation and/or duration of therapy. This level of non-treatment and sub-optimal treatment in part shows the real-world limitation of anticoagulation with warfarin. After decades of research on the benefits of warfarin to prevent stroke in atrial fibrillation and to treat and prevent venous thromboembolism, clinicians still don't use the drug at all or use it incorrectly. We feel that having an alternative oral anticoagulant could increase the number of eligible patients who are treated and hopefully reduce the death and disability caused by cardioembolic stroke and venous thromboembolic events.

Lastly, anticoagulation always has involved a balance of risk and benefit. The SPORTIF, THRIVE, and EXULT randomized controlled clinical trials have demonstrated the efficacy of

ximelagatran for preventing blood clotting. Ximelagatran does not have to be constantly adjusted, may have less risk of bleeding and a lower potential for drug interactions than warfarin; however, it requires monitoring of liver function. We believe the balancing of risk and benefit would be enhanced if another effective oral anticoagulant with a tolerable risk profile was available for prescription in the United States. Having two oral agents, namely, warfarin and ximelagatran, would provide practitioners greater flexibility in best matching an oral anticoagulant with the unique needs of every patient.

On behalf of our steering committee, we thank you for the opportunity to comment on our concerns for primary and secondary prevention of thromboembolic disease and how our research findings weigh in the consideration of the New Drug Application for ximelagatran.

Thank you all very much.

DR. BORER: Thank you very much, Dr. Colgan.

Is there anyone else who hasn't registered who has a statement during this open portion?

[No response.]

DR. BORER: Okay. If not, we'll move back to our agenda. We're going to follow this plan: First, I short-circuited a question by Dr. Sjogren earlier, and if you want to raise that question now, we'll start with that. Then we'll go on to allow Dr. Sheth to answer the questions that we raised earlier that I think she has answers to now. Then we can have questions regarding the risk/benefit analysis from the entire committee for Dr. Halperin and for Dr. He, and then we'll complete the FDA presentation with any questions that we have that follow, then the charge to the committee, and then we'll close the meeting to non-committee speakers and go through our analysis based on the questions we've been given, which should bring us right up to about one minute to 5:00.

Dr. Sjogren, do you want to go ahead?

DR. SJOGREN: My comments have to do with

the liver test, particularly ALT, and the FDA description of the three patients that died I think answers my question in a better way than earlier, because that's exactly what I was asking: What happened to the ALTs over time? And I calculated that some patients that started with normal ALTs promptly went into major abnormalities in 12 days, in 30 days, in a very short time. And so the proposed monitoring for these patients would not touch--would not have caught these patients because, you know, they expect to be an ALT that is twice the normal and then go on with monitoring.

So I'm still very concerned about that, and I would think that as a liver doctor, if I saw any abnormality, I would discontinue the drug immediately based on what the FDA has shown us. And I would prefer that patients have an ALT to begin with before they start the drug, and if it is abnormal, then I would not feel safe to give the drug. I think there are some patients that just the toxicity progresses very fast and we're unable to tell who those are.

DR. BORER: I should point out we don't actually know what the algorithm is that the company ultimately will come up with. Their Risk MAP is something that they'd have to talk to the FDA about. But all these points that you've made I think we have to keep in mind.

Okay. Dr. Sheth, as you get prepared to respond to the several questions, I found in my briefing document the areas that had caused me to raise the question about rebound, and perhaps so that everybody can look at these data, they're on page 47, Table 18 of the FDA briefing document. The FDA briefing document. Oh, I'm sorry. You're quite right, there are. This is called "Clinical Review DGICDP." And the next is "Clinical Review DCRDP" and that is Table 45 on page 75 of that tab. And the only reason I note these is that it was from these tables that I made the calculations that led to the question. You may want to look at the primary data that generated the question.

Okay. Dr. Sheth?

DR. SHETH: It's not a very good

reproduction. Is this the table that you're talking about?

DR. BORER: Yes, indeed.

DR. SHETH: Okay. All right. Let me do this. The data that we prepared looks at the number of myocardial infarctions that occurred after treatment over those that occurred during and after treatment. I think that was one of the questions prior to the break. And if I could start first with the long-term exposure pool, and then I'm going to move actually to the warfarin comparison pool, which is, I think, the real question of interest, so that would be O-49, please. Okay.

Just focus on this bottom line, total MIs, and this should be the number of myocardial infarctions that occurred after study treatment stopping over the total number in the program, and that would be--for the long-term pool, it's 28 percent versus 23.

Can I have O-48, and let's do the surgical population, please?

T4A Here, on this bottom line, the patients with an MI after stopping treatment, it's broken up into 36 and 24 milligrams, over the total during the program, and it's four out of ten for 36 milligrams, one out of seven for 24 milligrams, and two out of four for warfarin, and one out of two. The percentages are listed here, but I just caution that the numbers are very small in this analysis.

I'd also like to ask Dr. Peter Kowey to come and discuss this a little further, if I may.

DR. FLEMING: While he's doing that, can you leave the previous slide up?

DR. SHETH: O-47? I think the one just before, is that correct?

DR. KOWEY: This problem with myocardial infarction and coronary events that occurred in the orthopedic surgery population was a particular concern to us when we learned that there was a concern by the agency. Obviously, those data weren't quite known to the sponsor and to the consultants. And the reason why it was a surprise to us is because, under ordinary circumstances,

when we're confronted with a question having to do with something like an acute ischemic syndrome, acute ischemic events, and you ask us the question could this drug somehow have been causing an issue, the reaction is go study the highest-risk patient population and show us the data in a population of individuals who are at maximum risk. That's an acute coronary syndrome population.

And so we thought and I still think that the data from ESTEEM really provides the most information that we have about the question of whether this drug under some circumstances could be causing an acute coronary syndrome. Keeping in mind the fact that ESTEEM finished with a 14-day wash-out period during which patients were still counted in the trial and events were still counted in the trial. And even with that, there was no signal that there was an excess risk of having acute coronary events, and obviously there was an advantage to ximelagatran.

So the answer to the question of what does it mean when you see a short orthopedic experience

study where you see this excess event rate. Clearly, we agree with you that that's a different setting, and the patients are freshly post-operative, and there may be something uniquely susceptible about those individuals. But with those kinds of numbers and the very small numbers of events that were seen in those trials, in the setting of having a very definitive clinical trial--and, again, that's the reaction that I would have, is go do a study in the maximum at-risk population. You have those data. It seems to me--in addition, in that study you have withdrawal data. It seems to me that that probably answers the question.

Therefore, I think that what you're seeing in the orthopedic surgery experience is not real and that it represents a play of chance.

DR. BORER: Okay. I'll do something that I shouldn't do, which is to tell you my bias, which is that I agree with you about the importance of ESTEEM. But the question was specifically not about total MI risk. It was about the potential

for rebound that might have to be remediated with some adjunctive therapy if this drug were approved and used.

DR. KOWEY: Yes, I agree with you, and I think there are two pieces of information that gave me reassurance on that because, Jeff, honest, we thought the same thing. One piece of information is that in SPORTIF there were patients who went on and off the drug on a regular basis. As you know, this drug is not indicated for cardioversion, for example, so there were patients that were going on and off the drug constantly in SPORTIFs. And in SPORTIF, as you say, in an adjudicated--that's the other thing, by the way. I was a little bit surprised that we weren't giving a whole lot more weight to adjudicated events than we were to investigator-reported events, which we traditionally don't really do. I pay a lot more attention to what an adjudication panel blinded would do with this.

The other piece of information, as I said earlier, is that also in the ESTEEM experience,

there was a withdrawal phase so that we do know that we have an opportunity to really observe the maximum risk population coming off the drug without an excess event rate.

Those two pieces of information for me were very reassuring and, again, that's why we were a little bit taken aback by the challenge from the orthopedic surgery population.

DR. BORER: Okay. Thank you, Peter.

Dr. Sheth, there was another issue, I think--

DR. FLEMING: Jeff, before we go on, could we--

DR. BORER: Oh, I'm sorry, Tom.

DR. FLEMING: The slide came off again. It was O-49.

DR. SHETH: Thank you. Can we put that back up?

DR. FLEMING: Just to make sure I'm understanding--the denominator, actually, is keenly of interest to me here as well, the 186 and 138. Jeff referred to Table 18, and that was certainly

one that had drawn my attention as well. The total MIs there when you look at on and off, it's 144 against 113. This adds another 42 and 25 through, I assume, a more comprehensive sweep than got reported here as AEs. So these are the numerators, the 186 and 138, that correspond to the long-term follow-up denominators of 6,900 and 6,200. Is that correct?

DR. SHETH: That's correct.

There were a couple other questions I'd like to get back to that were brought up this morning, and I think I just want to say that, in fact, not only in the clinical trial program did we require an ALT prior to starting; we would require that prior to starting drug as well to address that concern, and to also address the concern of how to--that we're going to assure appropriate testing compliance in practice. I'd actually like to ask Dr. Cameron to answer that. I think that's in response to a concern brought up earlier by Dr. Nissen.

DR. CAMERON: Thank you. Hamish Cameron,

AstraZeneca. Really to try and help Dr. Nissen, who posed this dilemma in terms of risk assessment, it's a dilemma I think we all share given the database we have, but recognizing it is a very large database based on development in five different indications where many of the patients are elderly and nearly half the patients have renal impairment. So it's a pretty sort of stress test environment.

We would like to get a better handle on this risk. We believe that--we want to know what the risk of liver failure might be. We believe that many of the cases that we're looking at today are quite confounded, and it makes it rather difficult to reach a crisp judgment. We do not believe the risk is as high as the 1 in 2,000 figure, but we do want to commit to undertake work to explore this.

Now, I think we've probably reached the limits of what major information we'll get out of clinical trial settings, and in a sort of postmarketing program we are developing programs to

exclude risks in the level of about 1 in 10,000. We believe that would be the right sort of gold path to be going, and we've already developed programs for discussion with regulatory authorities both here and in Europe, and we'll be discussing that with FDA at the upcoming meeting.

Probably just an additional sort of add-on to that--and I know that, Chairman, you have not wanted to get into algorithms in detail and risk management and so on, but I think it is an important part of what plays on your judgment, I would imagine. We proposed a program based on education, compliance enhancement, and unrestricted distribution. And we've read the FDA comments, and we're obviously very eager to hear your comments today. And we understand the need we have to augment that program in order to reach alignment with FDA and get something in the best interests of patients. And we're prepared to add more control of mandatory elements to this program such like physician attestation or a patient registry approach, liver function testing, this type of

thing, remembering that I think we have to try and achieve the balance, which is one of our big considerations with the first program, potential unintended consequences. Given the story of warfarin, given the under-treatment, we wanted to make sure it was a balance between doing what's right for individual patient safety management, but also thinking about the population perspective.

We have proposals for that, and in the upcoming meeting with FDA, we'll be putting that forward as well. So I hope that gives you some reassurance we're addressing the issue of estimating risk to help that judgment. We'll also do it in a way that we get an answer quickly as possible through postmarketing approaches.

DR. NISSEN: Here is what I'm trying to weigh here a little bit. Do you know what percent of patients in the clinical trials didn't show up and get their ALT done? In other words, what was the compliance rate with getting blood drawn for ALT? And I want to weigh that against what I think we know something about what compliance may be.

You understand what I'm getting at, trying to understand the risks.

So what percent of patients in the trials--do you guys know that?

DR. CAMERON: I'll let Dr. Sheth take that.

DR. SHETH: Let's put this up. This is overall compliance. It's a bit of a busy slide, but it's broken up into several components: compliance to laboratory testing, and we looked at in terms of just overall monthly, weekly, as well as discontinuation, meaning did they meet the criteria and then did they discontinue on time. And the overall compliance was about 69 percent for ximelagatran and comparators. The monthly compliance was around 70, so there's not that much difference. And the weekly compliance overall was 68 to 53 percent on comparators. This might reflect a little bit the SPORTIF III trial. In terms of discontinuing on time, about 71 percent in the ximelagatran group.

DR. NISSEN: Now, the question, of course,

is: What's that likely to look like if the drug is brought to market? And, you know, I wonder if the agency actually has any feedback for me. This would help me a lot to know. In the other drugs where you've mandated, you know, liver function monitoring, do you have any sense for what the compliance is like in the real world?

DR. AVIGAN: Dr. Kate Gelperin has a presentation which will deal with that issue, I think in some comprehensive way.

DR. NISSEN: Okay, good. That will be helpful. But that was great because now I can compare it to what we hear from the FDA.

DR. SHETH: I think the final question I recall from this morning was did we have some test, a laboratory testing that might look at the issue when patients came off drug that might indicate any rebound effect, and I'd like to ask quickly Dr. Troy Sarich to address that.

DR. SARICH: Yes, Troy Sarich, AstraZeneca. I can just comment in regard to the issue of whether there's some unknown rebound

effect of this agent that you want to know about. Everything we know about this drug is that when it's present in the body, it's active; when it leaves the body, there's no residual effect. And in our clinical pharmacology program, we had over 1,100 healthy volunteers that either took single doses or repeated doses for up to 8 days. All of those volunteers had laboratory testing, coagulation assays done at the time of discharge from our units, and they were also brought back 2 to 5 days after discharge. And there was really nothing to suggest that these patients had any altered coagulation status after a single dose or a repeated dosing period. This is really sort of, to us, a non-issue with the drug. We believe once it's gone from the body, it's not having any measurable effect that we've been able to detect.

DR. NISSEN: I hear you, but, of course, normal volunteers are not the people who get the drug. And, you know, these older people that undergo surgery, you know, surgery induces a lot of very profound changes, including changes in the

coagulation system. And the problem--and I think Tom Fleming has been trying to get to this as well--is, you know, there's really a very strong signal in the data, one that actually achieves statistical significance, and you see it in both of the short-term trials, not in just one of them, and you see it in the pooled data and you see it everywhere.

So we're trying to understand it, but it sure looks like a signal to anybody who would look at this data objectively. And, you know, I know that normal volunteer data has been done, but there may be effects that we don't know about, and we're trying to understand those.

DR. BORER: Alan, and then Bill.

DR. HIRSCH: Well, I just was going to echo the same comment. To say that you're satisfied is one thing, but I was looking for the same kind of data Bev was asking for, which is something very specific in a relevant population, thrombin gene expression rates, platelet Factor IV, beta thromboglobulin, d-dimers, some real evidence

there was a real effort to look at upregulation of the pathway, and I haven't seen that yet.

DR. HIATT: Yes, just to follow up on that, I'm reminded of the oral 2B3A antagonist experience, and the issue was that these drugs has short receptor occupancy time and that platelets became prothrombotic when the drug came off the receptor, a similar kind of PK sort of behavior as you have, and that the concept was when patients fell below inhibition of platelet aggregation of maybe 80 percent, they became prothrombotic.

Now, if you look clinically, if the all-cause mortality rates are the same amongst groups, but you're preventing major thrombotic events, there must be some offsetting competing mortality weighing against that. And so I think this question keeps coming up about is there a rebound, is there prothrombotic events, and I don't think you really know the answer to that question.

DR. SHETH: If I can ask Dr. Troy Sarich to respond again, thanks.

DR. SARICH: If we could just look at CP-6

one more time. This was from my core presentation, and I'll just take a little more time to go over it this time.

We have looked at things like beta thrombo-globulin, which is a measure of platelet function, and in this analysis what we did is we looked at a range of concentrations of melagatran, and plotted here is the reduction in beta thromboglobulin levels as concentrations increase, and this is actually a conglomeration of data collected at different time points after drug administration, including data at 10 hours after drug administration, which in healthy volunteers constitutes quite low levels of melagatran.

You can see that as concentrations go up, the effect increases. When concentrations start to go back toward baseline levels, the effect on beta thromboglobulin goes back to baseline.

We also see that here with thrombin generation using thrombin/antithrombin complexes. So, really, we don't see any type of hysteresis, any unrelated pharmacologic effects once the drug

is eliminated from the body. And I take the points, of course, we cannot exclude anything. There are unknowns possibly. But from all the data we know, we have not seen any delayed pharmacological activity beyond when the drug is gone from the body.

DR. HIRSCH: But I did see that slide, and I'm satisfied that it shows that effect in a healthy volunteer in a non-post-operative state where there aren't acute phase reactants, there aren't external stresses. That's not really what I'm asking.

DR. BORER: Jonathan?

DR. SACKNER-BERNSTEIN: As a follow-up to that, even if you're measuring these tests within 10 hours of dosing, you're still at a point where the drug concentration is above 0.05 micromolar, which means you're still at a level where you have a therapeutic effect. And all of the questions, I think, are focusing on what happens to the patients once the drug concentration is below a therapeutic level, but within that period of time right after

it's been used.

I'd also like to propose just another way of trying to interpret this risk of myocardial infarctions and acute coronary events and coronary disease AEs. We're using the ESTEEM trial to say that we're looking at a high-risk population, and that would be the place where it would be the most easy for us to detect a signal, if there were one there, of an adverse effect of the drug. Although I can't tell with certainty from the documents because you don't have all of the concomitant medications listed for all the trials, from the information in this I would bet that the ESTEEM trial patients were actually treated extremely well for coronary risks. So they were treated with statins, with beta blockers, with ACE inhibitors and anti-platelet agents, et cetera, all of which may actually be protective against some effect of ximel--I can't say it either. You know, if indeed there were a pharmacologic effect, perhaps those drugs are protective. It could also explain why the signal for myocardial infarction appears to be

weaker in the SPORTIF trials where almost half the patients were on statins, over half were on ACE inhibitors or ARBs. A large proportion of the patients were on beta blockers compared to the THRIVE and the EXULT patients, where I would doubt, given their age and their list of comorbidities, that they're on many cardio-protective meds.

So I'm not quite convinced that ESTEEM means that we don't have to worry about this signal of coronary events.

DR. BORER: Okay. Do you have anything else that you wanted to say, Dr. Sheth, or are we--

DR. SHETH: I think we've addressed all the questions. I just want to clarify just one piece of information on discontinuations due to bleeding being higher on ximelagatran than warfarin that was presented or on comparators that was presented earlier. That was primarily--actually, only driven by the SPORTIF III trial where in the open-label, physicians had the alternative to put their patients on warfarin if they came off ximelagatran. But if they were on warfarin, they

did not have an alternative if the patient bled.

In the other trials, you do not see the same increase for discontinuation for bleeding, so I just wanted to clarify that piece of information.

DR. BORER: Okay. Thank you very much.

Now, let's go back to questions, and, again, I'm going to--I know this is difficult to do, but let's try to limit it to questions of clarification, if we can, for Dr. He and for Jonathan Halperin regarding the risk-to-benefit relation. Anyone on the committee who has questions, now's the time. I have a few if you don't.

It's primarily regarding the FDA presentation. Starting with Slide 3, Point 2 of the FDA's Slide 3 is that efficacy result in Exanta is driven by decrease in asymptomatic distal DVT, which is not clinically meaningful. I think this is an important point, and I asked you some questions about that earlier. But I would like to hear something else. In Jonathan Halperin's presentation, he pointed out that 70 percent of

people untreated would have distal DVT, and there is some concern about propagation, although it seems that the data are not as well defined as they might be.

If indeed asymptomatic distal DVT is not clinically meaningful, that would be very important. I'm not sure on what basis we say that. So I'd like to hear that, and I really want to hear from Bill and from Alan as well about that.

DR. HIATT: I don't think we have a real lot of certainty about that, but the risk is certainly there. And it was also mentioned in the sponsor presentation about post- (?)-itic syndrome, which is a very disabling manifestation that does occur 2 to 4 years after an acute venous event, and not also well characterized. So I think that risk has to be considered as well as the risk of an embolus. So I would not discount these asymptomatic distal clots.

DR. BORER: Dr. He, on what basis do you say it's not clinically meaningful?

DR. HE: In the clinical practice, all of

this data was detected by the venogram. In the clinical practice, usually we don't use a venogram to detect asymptomatic patients. If patients do not have a symptom, you don't want to use a venogram to detect a patient who has a DVT or not.

Secondly, if you have asymptomatic distal DVT, majority of physicians do not treat it, and this patient--it is basically the one you detect by the venogram, and in that case the basis I say if you found asymptomatic distal DVT by venogram, that is clinically meaningful, it is really--I really don't think it is very clinically important.

DR. BORER: You know, I'm sorry we don't have an orthopedic surgeon here on the panel or somewhere standing close by. But, you know, just to nail down the point, because I do think it's important, and I want to hear from Alan and from Beverly about this, of course. You know, many orthopedic surgeons would not--as you say, they wouldn't treat somebody because the person had a distal DVT. They would have treated him beforehand. They would have given an anticoagulant

of some sort as early as possible after an operation because of the concern about DVT. So going and doing a venogram would be irrelevant. Presumably, you've already taken the preventive steps. I'm still a little unsure about this. Maybe we can go to Alan, then Beverly, then Ron.

DR. HIRSCH: Well, I think it's a large statement to say it's not clinically relevant, so I would disagree with that statement. But, on the other hand, our database is incomplete and we have to acknowledge that. My instinct personally is that it is clinically relevant, but let's define what that means.

First of all, we don't have long-term, prospective, randomized trials of treatment of distal, meaning infrapopliteal DVT to know its real impact on human health in this country, which is crazy. But in the absence of that, most of us would believe that there are three clinically possible impacts. Just to state them, I guess not measured in this study, you know, one would be propagation so it becomes clinically relevant at a

small rate. The second is the quality of life post-thrombotic impact. Nobody likes a swollen leg, estimated to occur in probably between 5 and 30 percent of the population, and local discomfort. And, more important, again, if we took a 5- or 10-year time frame long-term recurrence of deep vein thrombosis distal to that fact, it's probably pathophysiologically relevant; we just don't know the rates.

So I'd just be careful with not making too strong a statement.

DR. BORER: Beverly, and then Tom. I said Ron, but I meant Tom.

DR. LORELL: Thank you. And, Dr. Hirsch, I appreciate your comments on this.

I think my comments are very similar to Dr. Hirsch in that the setting of this as a clinical trial looking at the question of whether a new molecule is effective in reducing thrombosis, as a clinician I would look at this as a continuum as opposed to being separate buckets of thromboembolic events. So I think with Dr. Hirsch,

I would share the concern that there is clinical meaning to having distal venogram detected thrombus.

DR. BORER: We run very close to the always difficult issue of surrogates versus clinically relevant endpoints here. But, you know, I too feel very concerned about saying it's not important.

DR. HIRSCH: In a sense, Jeff, this is a surrogate for the purpose of this study, with the possible long-term benefit if there were longer-term data.

DR. PICKERING: The American College of Chest Physicians, actually a consensus, did comment on that, and they suggest--in terms of endpoints, we suggest a middle ground based on large trials that use a clinically important VTE outcome consisting of a composite of fatal PE, symptomatic, proven DVT or PE and asymptomatic proximal DVT.

DR. BORER: John?

DR. TEERLINK: So taking into account that the distal DVT has some clinical meaning, I'm just

trying to put it into a context of the clinical trial. I would guess that the at least short-term symptomatic, the painful thrombosis would have been picked up as symptomatic thrombosis in this trial. So that actually is accounted for in the symptomatic group. I would expect that the progression of this thrombus, this distal thrombus would have been also detected as a proximal thrombosis. So that part of the endpoint, at least acutely, recognizing that it can propagate later, but at least within the scope of this trial is being accounted for in the endpoint. So I think actually we can acknowledge that the distal thrombosis is important clinically, but much of its clinical import is being picked up by the progression of disease in the proximal DVT measurements or in the symptomatic measurements, neither of which were different in the study.

DR. BORER: Tom, and then Steve.

DR. FLEMING: We've got a hierarchy, as we often do in clinical trials, of what I would call clinically relevant events moving on down to what

would be surrogate events. And in this trial, in this setting, you've got death, you've got stroke, you've got MI. Those are all very profound. You've got PE. Then you've got symptomatic DVT. And then in the asymptomatics, you're down to proximal, and Tom's list left off distal asymptomatic, left off completely. I've heard nothing to argue that asymptomatic DVT, in particular distal, is anything but, at best, a surrogate endpoint. It is not a clinical efficacy endpoint. A clinical efficacy endpoint by definition is one that unequivocally reflects tangible benefit to patients, prolongation of survival, symptomatic disease.

If you're doing a venogram and you identify a distal asymptomatic, it might mean something. But listening to Alan, we don't know. That's an unvalidated surrogate at best. I don't see that we've said anything that could put it into any definitional category other than an unvalidated surrogate. And what's problematic now is when that component contributes the vast majority of the

events and almost the entirety of the signal.

DR. HE: I have one thing I want to point out. This is a short-term treatment, average patient only using 8 days' treatment. That means if you detect a distal asymptomatic DVT, you only treat for 8 days. That means you are not waiting for this distal DVT to progress to a proximal DVT because you already stop treatment after 8 days. And, you know, this short-term treatment doesn't help that DVT at all.

DR. NISSEN: Yes, I think I understand the spirit of your "not clinically meaningful" statement, and let me see if I can characterize it. I think what he's really saying, which is really very much what John said as well, is that if you didn't do the venogram, you'd never know. And so it's an event that you only detect because you're doing a procedure that would never--would not be done clinically in an asymptomatic patient. And so you're adding a bunch of events to the mix that would be undetected.

In other words, if you took 1,000 patients

and compared these therapies, you wouldn't see any difference unless you went ahead and venogram'd them all, which is not something we do clinically.

Now, there is one issue, though, that I would take issue with, and that is that because we're talking about a short-term trial, we haven't factored in the possibility that those distal asymptomatic events, you know, DVTs, would 6 months from now or a year from now result in a clinically important recurrence. We don't know that. And I think we have to acknowledge that we don't know that, but it may suggest a potential study, you know, to the sponsor that would be, I think, a tremendous addition to the field, which is to detect these, and then, you know, since we don't know what their natural history is, to randomize those patients to be treated or not be treated and find out whether any agent long term can prevent the conversion of asymptomatic distal DVTs into symptomatic pulmonary emboli or proximal DVTs that are worrisome.

DR. BORER: Alan, then Tom, and then I

want to give the sponsor an opportunity to respond. Maybe Jonathan would like to say something. Tom, did you have something? No.

DR. HALPERIN: Thank you very much, Mr. Chairman. I agree with the perspective that Alan Hirsch has stated, and I think these are clinically important events because of our understanding of the pathogenesis of the clinical syndromes. And I would just add one other thought, and that is this notion that these patients are asymptomatic, lacking an orthopedic surgeon to testify for you here today, the next best thing, perhaps quite a distance, is a clinical cardiologist who takes care of these patients. All of these patients are symptomatic. They all have painful, swollen legs in the first 10 days after orthopedic surgery of this type.

And so the problem here is not an ambient population walking around out there in whom we're doing a bunch of tests and finding clinically trivial events. We're taking a bunch of patients all of whom have the symptoms of deep venous

thrombosis, looking to be sure that those symptoms are or are not related to surgery versus surgery thrombosis, and considering significant the condition that leads to proximal venous thrombosis and pulmonary embolism in almost every case in which those two more severe syndromes arise.

Thank you.

DR. FLEMING: Jeff, maybe I do want to comment.

DR. BORER: Tom?

DR. FLEMING: It's a clinical event because we understand the pathogenesis. Wow. That would mean that the vast majority of surrogate markers are then clinical events. The distinction here between a clinical event and a surrogate endpoint is a clinical event unequivocally reflects tangible benefit. It is direct evidence of an effect on symptoms, duration of survival, et cetera.

A surrogate endpoint, and in this case an unvalidated one, is one that provides a potential clue that you might be having clinical effects in

the manner that Steve was talking about. Maybe we do here, but we're not talking not about establishing plausibility to do a trial. We're standing here to decide whether the evidence is in hand to approve an agent. And in the absence of a signal in the non-symptomatic distal categories, in the absence of a signal there, we're left with a hypothesis that could, in fact, be validated in a future trial with sufficient numbers in follow-up to show that this is an effect that translates into clinical benefit. But at this point, if we only know there's an effect on asymptomatic distal, that's hypothesis generating.

DR. HALPERIN: I would agree with all of that except for the word "asymptomatic." It means, as you say, the surrogate, and I accept that distinction that you made. But none of the patients are asymptomatic. They all have, I presume, all of the symptoms of deep vein thrombosis. The problem is that the symptom doesn't correlate entirely with the disease in this case.

DR. HIRSCH: And one more series of bridging words. This is not a clinical clue. This is actually a hard endpoint. The sponsor should be congratulated, actually, for taking patients through a clearly defined venographic endpoint at no essential risk, demonstrating clot--you know, abolition or amelioration of clot formation. However, though we have a hard event, the question is is it a hard clinical event for which you'd seek drug approval, and in that sense this is sort of like looking with surveillance echos for LVH, carda duplex for IMT change, renal dipsticks for, you know, proteinuria and saying because we've changed that, the patient will feel better. Mrs. Smith taken care of by Dr. Halperin here would not necessarily know the difference.

DR. BORER: Steve, with your permission, maybe we'll hold your comment about this until we get to the more complete--

DR. NISSEN: I have an unrelated--

DR. BORER: Oh, you have a question. Okay, go ahead.

DR. NISSEN: Because I didn't get a chance to ask it earlier, is the SPORTIF V data going to be published? And if not, why not?

DR. HALPERIN: We anticipate publication, yes. We're still in the final stages of negotiation with the New England Journal of Medicine, and if they were faster, we'd have a more assured answer for you.

DR. BORER: Okay. I have another issue to raise based on the FDA presentation, and it's really a question for the sponsor about the point that the FDA raised. Do we have data--you know, we've been concerned in the short-term trials that patients were only followed for 4 to 6 weeks, and we don't really know what might have happened to them afterwards. But you exposed, you know, about 15,000 people, 17,000 people to the drug. Somewhere along the way there may be some subgroup that was treated short term and you actually found out whether they were dead or alive 6 months later. So I want to ask whether you have anywhere in your database something that could be reassuring about

the potential for late manifestations of toxicity from short-term treatment.

DR. SHETH: So you're asking do we have something like 6-month vitality data on our orthopedic surgery population across both the European and North American pools?

DR. BORER: Right, anywhere.

DR. SHETH: I don't believe we have 6-month. I think 4 to 6 weeks was the greatest follow-up we have. The only thing I'll tell you, though, is that in the EXULT A trial, which time-wise was conducted before--right before EXULT B, EXULT B followed it. A lot of those sites were the same sites, and a lot of the investigators were the same investigators. And the conduct of that second trial was then over the next year. And if those investigators were seeing their patients come back either with DVT or dying, I doubt that they would have been participating in the second trial, and I'm sure we would have heard about it. So that we had contact with all of those investigators during that second trial, so it's not a formal

follow-up, but I would anticipate we would have heard something if they thought that their patients were having adverse events delayed.

DR. BORER: Okay. A simple question here. On Case 2 that was presented to us by the FDA showing that a major problem occurred when a 0.25 micromolar concentration of melagatran was present in the blood, was the drug stopped when the ALT was found to be 4.5 times normal? Was it stopped ever? I mean, there's no notation here of stopping the drug.

DR. SHETH: That particular patient, which was the 77-year-old male who had an elevation of his ALT to 4.5 times the upper limit of normal and then missed two subsequent tests, at that time the discontinuation criteria--actually, this is the first algorithm that he should get weekly testing after 3 times the upper limit of normal, and then if it reached 7 times, he'd stop, or if it was persistent. So, no, he didn't stop his anticoagulation. His last dose then would have been the day--essentially before he got admitted,

because he came in around 3:00 in the morning and the blood work was drawn then. So we don't know what time the night before he might have taken his last dose, but it would have been within clearly a 12-hour period, but we don't know.

DR. BORER: Okay. I mean, that uncertainty may be important in interpreting this blood level data, but hearing that this horrible situation had developed with a blood level that is putatively therapeutic and probably not toxic is a concern, and it suggests the potential utility of something that probably hasn't been done because I'm not entirely sure how you do it but Alan mentioned it, which is looking for genotypic evidence of abnormal handling or abnormal response. But, you know, I wouldn't have expected you to do it because I don't know what you'd be looking for yet.

Slide No. 15.

DR. SHETH: In terms of the genotypic, we are actually conducting a pharmacogenomic study looking retrospectively, actually trying to

understand people at risk for severe liver injury, and we'll also carry forward from that study--for any future studies our goal is actually to implement similar testing more extensively in all future trials. So we've already initiated that effort.

DR. BORER: Well, I congratulate you. I think that's the most appropriate thing to do.

My next question is with regard to FDA's Slide 15. This is long-term exposure, but there were several long-term exposure populations, and I want to know which populations were and were not involved here, included here. Does this--I guess it does with the numbers you show, but does this include ESTEEM and SPORTIF?

DR. HE: This is long-term exposed sick population include all of the patients exposed to Exanta more than 35 days.

DR. BORER: So this is everyone who--

DR. HE: Long-term exposed sick population.

DR. BORER: Let me just look at that for

one minute.

DR. HE: This one is long-term exposed safety population. That includes all of the patients exposed to Exanta more than 35 days. And this table was summarized from the sponsor's table in Module 2, Table 53.

DR. BORER: Okay. Thank you.

And I think I had a similar question on 16. As I look through the cardiovascular events that were being tabulated, they included myocardial infarction and a lot of other things. There was angina, which I assume means any anginal event or perhaps it's a chest pain event. I mean, what's angina?

DR. SHETH: The data shown on the previous table and this table reflect investigator-reported adverse event, so that these were not prespecified. And so the physician may have just said patient had chest pain and that might have coded to the adverse event term of angina or angina aggravated, terms that you're seeing in those listings. So it's just simply investigator-reported adverse events as per

their terms.

DR. BORER: The reason I'm asking this, I'm trying to get a handle on the reality of this apparent cardiovascular risk associated with the use of this drug that we inferred from the short-term study and the long-term prevention trials, because when I look at ESTEEM, page 6 of the ESTEEM tab in the sponsor's book, and when I look at the FDA--this is the Cardio/Renal review, page 76, these were the SPORTIF patients, I look at these two trials and the results look different from what we're inferring and what was admittedly unexpected in the short-term trial and in the prevention, the VTE prevention trial.

On page 76, as I look through this, it looks to me as if there are--if you aggregate these events, it looks as if there are fewer cardiovascular events in the patients in the SPORTIF trials who were on ximelagatran than on warfarin. Maybe I'm reading this wrong, but--

DR. HE: In the patients in the atrial fibrillation population, they do show numerically

higher CAD and MI events in the ximelagatran group compared to in the warfarin group. That is 7 percent compared to 6.7 percent. As I mentioned before, because this is high baseline event rate, it's very difficult to assess the small portion of difference in this population, yes, but they still show the trend in the ximelagatran group higher than comparator group.

DR. BORER: Okay. Now, you just highlighted the question I actually had, which I had forgotten, so thank you. You said that this was a high baseline risk or a high baseline frequency of events. And, again, I'm not sure--just for purposes of clarification, I'm not sure on what basis we say that. This was a long-term trial. The absolute frequency of myocardial infarction was relatively low, not terribly unexpected given the population that was studied. And angina is angina. It wouldn't be terribly uncommon to see angina in this population.

So I'm not sure why we would say that it's a particularly high event rate. Compared to what?

T4B DR. HE: Compared to the population for short-term surgical population and VTE population.

DR. BORER: Okay.

DR. HE: Because the difference between groups are small, less than 1 percent. If you assess ACS population, the baseline event rate is 27 percent. If you assess 1-percent difference between the group at this high baseline rate, it is difficult to make any conclusions. That is why I focused on surgical population. All of the surgery, the patient went through total knee replacement surgery, before they go to surgery they go to you, go to the cardiologist to eliminate any high possibility to have an MI. So that is why that population had event rate low. In this population, so I can see the difference, you know, even smaller difference, I can see it. Same thing for the VTE population. Baseline event, very low, 0.16. And for the treatment, VTE treatment, only 0.1 percent. In this low event rate population, I can see the difference. If any difference, I can

make an assessment maybe this difference between the treatment, you know, this gave me a signal as a medical officer, when I see this kind of event rate, you know, that gave me a signal, gave me attention--to pay attention to this kind of thing. So high event rate, what I mean is between the difference populations.

DR. TEERLINK: But, Jeff, that doesn't make any sense. I mean, you have to have a lot of events. The confidence interval around these small event rates has got to be huge. The confidence interval around the big events rates has got to be small. I totally disagree. It's the opposite of what you're saying.

[Pause.]

DR. HE: No.

[Laughter.]

DR. HE: Okay, let me say it this way: Because the baseline event rate like we're looking for atrial fibrillation, the difference right now is 7 compared to 6.7 percent. Do we know this difference, 0.3 difference, does that come from--

DR. TEERLINK: What's the confidence interval around the difference? That's the point I'm trying to make. The smaller the event rate, the bigger the confidence interval around that difference. The higher the event rate, usually the lower the confidence interval.

DR. HE: Yes, that is why when you go to--okay. Let me put it this way. If ximelagatran causes MI, they will cause in a very small proportion of the patients. It's not like liver toxicity. You can see it so clearly. It's 8 percent compared to 1 percent. This difference, if any, very small. This is a small proportion of difference. If you assess this population who have a baseline event rate at 7, it's difficult.

DR. TEERLINK: I agree with that because one of the questions will be, if you want to prove safety around cardiovascular events in this knee replacement population, it's extremely difficult because you going to need a huge population studied for a long time and a lot of events to know if there's anything going on. The absence of events

makes it very difficult to know if there's anything going on or not.

So to try to answer safety around a cardiovascular problem that this drug might cause in this population I think is very difficult.

DR. HE: That's true. I agree with you. It's difficult to assess in the atrial fibrillation population because those patients have so many other underlying diseases--hypertension, diabetes, you know, so many other things. Those patients may cause MI--may have MI secondary to other risk factors, not secondary to ximelagatran. That is why in this mixed population it's difficult to address a single factor that comes from ximelagatran. That is what I tried to say.

In here, in surgical population, surgical population has already been evaluated by the cardiologist before the surgery. So those populations--

DR. TEERLINK: You'd like to think so. That may not be true.

DR. HE: I hope so, yes, because I get a

lot of this kind of consultation working in the hospital. You know, they just ask me clear up this patient because this patient wants to go to surgery.

Anyway, that is what I mean, because in here there are so many risk factors to cause MI for the patient, diabetes, hypertension, coronary artery disease, so many other things. But in here, their baseline rate is so low so you--probably the risk from ximelagatran is higher than others.

DR. FLEMING: Can I comment, maybe--

DR. HE: You can see the difference between the groups.

DR. FLEMING: I think what Dr. He may be saying here is that if you have an intervention that, let's say, increases or induces a 1 in 200 risk of MI--that's a half a percent. If that is occurring in the backdrop of very few MIs, you're going to be able--i.e., a natural history of that population in the absence of this intervention has a very low MI rate, you can pick up that effect, about 1 in 200 in small numbers. If it's occurring

in the context of a 5-percent background rate or a big background rate, this added half percent is going to be diluted. You're not going to be able to see it.

So you're right in the sense that if you're arguing you're going to detect a relative risk increase, like a doubling, then the more events you have, the more power you have to pick up a doubling. But if you're talking about an absolute increase of a half a percent, 1 in 200 patients, then the higher the background rate, the more diluted that's going to be, and the less likely or less sensitive you're going to have to pick that up.

DR. HE: Thank you so much. You make my point very clear.

[Laughter.]

DR. BORER: Can I say, I think we'll have to let it go at that, and we can do the evaluation internally, and then answer the questions with that evaluation when we get to it, because we have some more to do.

Tom, did you have a point you wanted to make?

DR. PICKERING: I have a question on a different topic, and that is, in the FDA analysis there are statements that in the SPORTIF trials the results show that ximelagatran may not be more than 50 percent as effective as warfarin, which would mean that it would lower the rate by, I guess, about 31 percent, which is only slightly better than aspirin, which according to meta analysis is about 22 percent. So I'd like to hear what Dr. Halperin and others have to say about this.

DR. HALPERIN: There are a number of difficulties in interpreting the SPORTIF results, partly related to the selection of a noninferiority margin, which was really driven by a clinical judgment--a clinical judgment about how much is the disutility of warfarin worth in terms of event savings. And the Executive Steering Committee, in consultation with others and with reference to previous trials, and specifically with consideration to the risk profiles of the patients

enrolled, made a judgment that that's 2 percent.

Now, I'm not prepared to discuss a putative placebo analysis. I'll leave that to the statisticians, because to me the historical nature of that analysis makes it difficult for me to interpret clinically.

As a clinician, I'm interested in seeing that my high-risk patients have low event rates on treatment. If I can sustain that treatment better with one agent, that makes that agent more appealing to me.

This isn't a conventional clinical trials horse race where you're going to do a photo finish and decide which wins. This is an issue of recognizing that the big picture is how many patients can be kept in the saddle at the end of the race, and from a public health perspective, how many horseless riders are there, because that's the problem. And in the trials, I'm not even sure, to tell you the truth, which of the two SPORTIF trials brings us closer to that truth.

Of course, we respect the value of blinded

trials. I'm certainly a champion of that. But for the last 15 years in stroke prevention studies, we have debated whether they are really closer or further from the truth. The real world of anticoagulation therapy may be better reflected in the open-label SPORTIF III trial. I don't think we'll ever see in clinical care warfarin delivered as it was delivered in SPORTIF V with a common thromboplastin for most of the variables. There was much less within patient variability and much better patient time in therapeutic range in SPORTIF V than even in SPORTIF III, and SPORTIF III was better than almost any other trial ever reported.

So it's difficult and it's a judgment that the committee will have to make, and that's why in the design of these trials--and I, as you know, did co-chair the Steering Committee for this--we said the best thing to do is to present both. We've delivered the first controlled study of blinding anticoagulation trials for stroke prevention.

DR. BORER: Thank you very much, Jon.

Tom will give his opinion in the context

of the questions, but before we get to that, we have two statisticians here representing the sponsor. Perhaps one or both of you want to make a statement about the design of this noninferiority trial.

DR. FISHER: I'm Lloyd Fisher, professor emeritus at the University of Washington. I'm a biostatistician.

I'm going to briefly present three slides, and I'll address two issues just because I prepared myself and here it is, my 15 minutes--or 15 seconds of fame. But these address both the percent preserved and also the interaction within the SPORTIF trials.

I first heard about that in a meeting with Dave DeMent, who was the statistician on the DSMV for the trials, and Dave said that he was not very impressed that there even was an interaction. I have to say I have to agree with him, although by our usual standards there is. But it is 0.02--0.02 with a 3 or 6. It's not very overwhelming in the context of a big clinical program where you look at

so many different events. So there are multiple comparison issues.

Secondly, of course, we're talking about ximelagatran and placebo, but this is all on top of actually what I think has quite convinced me a very large warfarin benefit with respect to these endpoints, even though the FDA reviewer said warfarin may not be any better than placebo. I personally just don't really believe that in the clinical context of all we know.

Let me talk about relative risk. There's a number of ways of looking at relative risk. Statisticians like a log scale, and I like plots on a log scale, and logs of relative risk mathematically are a lot better. Things become normal more rapidly and so on and so forth. But if you're talking about measurement of effect, I prefer one minus the relative risk, and the reason is that one minus a relative risk is the proportion of events that are avoided by a treatment if the relative risk is less than one, so it actually refers more directly to numbers of patients and

something on a logarithmic scale. And the number of individuals benefit, the fraction preserve then would be the ratio of one minus the new treatment to placebo, which, of course, we haven't measured because it's an active control trial, divided by the presumed one minus the active control to placebo. That would be the proportion preserved.

In this analysis, using the relative risk, I make the assumption, which is true in most of these things, and there's no way to avoid it, it does have the pitfalls of historical controls, and from a scientific point of view, it would be nice, or if it were ethical to treat say AF patients with placebo, but it clearly is not.

Having said that, here is a slide--ignore the 95-percent confidence intervals for reasons that I will talk about in a moment. In SPORTIF III, the estimated effect to preserve using this method is 71.3--pardon me. The estimated percent preserved in SPORTIF III is 116 percent. In SPORTIF V, it's only 78.3 percent because, as has been pointed out, numerically the warfarin did

better. And if you pool the studies together, as you know from the slides you've seen, it's about a wash. So the estimated effect is about 101 percent. And I computed some confidence intervals using something called the delta method, but I did some simulation and what are called the coverage probabilities. Does the 95-percent confidence interval actually cover the true value under certain assumptions? Ninety-five percent of the time it didn't work out very well, so I did one other method of evaluating things, and it also related to how you weight SPORTIF III and V.

For this purpose, I took a paper by Rothman, Lee, Chen, Chi, Temple, and Hsu, not because they're all at the FDA, although that might make it more acceptable, but because actually it's really a very nice paper and it has a lot of very good ideas and examines things in more depth than any other paper I know of. But using logarithmic scale, the mathematical properties are very nice. So I took weighted averages of SPORTIF III and SPORTIF V, and the first question I asked

myself--personally, I do attach quite a bit of weight to SPORTIF III. But I think SPORTIF V for two reasons has more weight. It is double-blinded, but perhaps as importantly, it's here in North America, so that although the AF is an area where I think the concomitant medication and procedures do not vary as much as in an acute coronary setting, nevertheless, there could be differences. And then I tried to make that quantitative. Well, if I'm going to give some weight, what does that mean? And what I did was I assigned a variety of weights, and I said, well, what weight do I need to put on SPORTIF III to reject the hypothesis that the percent preserved--that F is the fraction preserved. I didn't mention it on the last slide. What weight do I need on SPORTIF III to reject the hypothesis that the percent preserved is at least 50 percent of the warfarin effect? And if I weight things roughly 3 to 1, I place 3 times as much weight on SPORTIF V as on SPORTIF III with 95-percent confidence you have preserved 50 percent, which is not a magical number but it is a

number that the Cardio/Renal Committee has used in the past and there is some historical precedent.

And then I went down and I tried some--I said, well, what would the mixture be to get a p value of 0.01, of 0.002, which isn't quite pooling because it's this mixture, but basically is the pooled data. And in addition, I did the following: The pooled data, the lower limit of the 95-percent confidence interval using a method that I do have a lot of faith in is 71 percent.

So if you take all of the SPORTIF data, you're 95 percent confident that at least 71 percent of the warfarin effect has been preserved.

And with that, I'll concluded.

DR. BORER: Thank you very much, Lloyd.

Does anyone want to ask any questions of Lloyd? Tom, as I said, will give his analysis later, but, Jonathan?

DR. SACKNER-BERNSTEIN: If I understand this correctly, does that mean that you're saying that this kind of statistical analysis that you just concluded with is one that you can use to say

with a degree of confidence that you've preserved at least 50 percent of the effect?

DR. FISHER: Correct. But there are the assumptions about the historical controls, and we only do this in a situation where we can't ethically use placebo. But (?) those assumptions, that's correct.

DR. SACKNER-BERNSTEIN: Thank you.

DR. BORER: Okay. Let's go on to the remainder of the FDA presentation, and I think we've pretty much talked the rest of the issues to death, so then we'll be able to get our charge and go on to our questions. The next presentation is by Dr. Gelperin.

DR. GELPERIN: Good afternoon. My name is Kate Gelperin. I'm a medical officer in the FDA Division of Drug Risk Evaluation. Today I will present a review of ximelagatran-associated liver injury and the sponsor's proposed risk management plan.

I will discuss our assessment of the risk of severe or fatal liver injury with ximelagatran;

our evaluation of the sponsor's proposed risk management plan; and present a brief history of risk management with hepatotoxic drugs.

To be effective, a risk management plan must address specific risks and have clear goals. In the case of ximelagatran, the nature of the risk may be different for short- or long-term exposure, and thus may require different approaches to risk management.

Proposed indications for this drug include short-term use after total knee replacement surgery with intended duration of therapy last 7 to 12 days. In contrast, intended duration of therapy for patients with atrial fibrillation or secondary prevention of venous thromboembolism would be months to years.

For the purposes of this analysis and consistent with FDA practice, severe liver injury was defined as concurrent elevation of total bilirubin greater than 2 times the upper limit of normal within 30 days of an increase in ALT greater than 3 times the upper limit of normal.

In short-term trials with ximelagatran, a mild liver injury pattern was seen at the follow-up visit with unknown potential for a delayed injury. No clear signal for severe liver injury was observed; however, potential for a delayed injury pattern or for risks associated with extended duration of therapy in patients who require longer post-operative antithrombotic prophylaxis based on current practice guidelines were not explored. The potential for extension of use beyond 12 days in some surgical patients with higher risk of thromboembolic complications remains a concern.

In the long-term experience population, abbreviated here as LTE, mean treatment exposure to ximelagatran was 357 days, or roughly one year. Substantial risk was noted for severe liver injury which occurred in 1 of every 200 ximelagatran-treated patients, or one half of 1 percent. It is also notable that there were three liver injury-related deaths for which study site investigators as well as FDA considered that ximelagatran caused or contributed to fatal liver

injury.

In the long-term clinical trials, 37 cases of severe liver injury were observed among patients randomized to ximelagatran versus 5 in comparator groups. The observed relative risk of severe liver injury with ximelagatran was 6.6 and was statistically significant compared to warfarin or placebo.

The lab value cut-off used to define severe liver injury in this severe liver injury is somewhat arbitrary. Additional data cuts were analyzed for concurrent ALT and total bilirubin increases, such as ALT greater than 3 times the upper limit of normal and total bilirubin greater than 1.5 times the upper limit of normal. Each of these more conservative data cuts also showed a highly significant relative risk for liver injury with ximelagatran versus comparator.

There were a total of 66, or roughly 1 percent, of ximelagatran-treated patients in the long-term pool who developed concurrent increases in total bilirubin greater than 1.5 times the upper

limit of normal and ALT greater than 3 times the upper limit of normal. Of these, 45 cases were judged by the sponsor to be possibly related to ximelagatran treatment. There were only five comparator cases which were considered drug-related by the sponsor, yielding a relative risk of 8.1, which was also statistically significant.

You have seen this graphic representation of cumulative risk of ALT elevation over time previously.

In 37 ximelagatran-treated patients who developed severe liver injury, initial signs of liver injury as evidenced by ALT greater than 3 times the upper limit of normal were noted as early as the first week in one patient, within two weeks in another patient, and within 30 days for a total of six patients. Of these six patients with signs of early injury, alternative causes of liver injury were ruled out in four cases, which the sponsor agreed were related to ximelagatran treatment.

The sponsor judged that severe liver injury was causally related to study drug in 19

ximelagatran-treated patients versus two patients in the comparator group who met the definition of severe liver injury used in this analysis. The estimated relative risk of drug-induced severe liver injury equal to 8.5 was also statistically significant.

According to the sponsor's analysis submitted to FDA, 14, or 39 percent, of the 36 patients with severe liver injury failed to discontinue study drug at the correct time based on the monitoring algorithms. In a number of cases of severe liver injury, there was a rapid rise in serum ALT from levels that were normal or close to normal to high levels in less than a 30-day interval, often with a delayed rise in bilirubin noted despite stopping the drug.

This slide shows the sponsor's graphic representation of serum ALT and total bilirubin levels in a patient with ximelagatran-induced fatal liver injury that was previously discussed by Dr. He. This is the patient who had biopsy demonstrated hepatic necrosis. The Y axis on the

left represents multiples of the upper limit of normal for ALT. The Y axis on the right depicts the multiples of upper limit of normal for total bilirubin, and the X axis depicts days on study.

Serum ALT values are graphed in red, and total bilirubin is graphed in blue. Horizontal red and blue lines show the cut-off for 1 times the upper limit of normal and 2 times the upper limit of normal for total bilirubin and ALT, respectively.

The purpose of this slide is to illustrate progression from an ALT value on day 56 that was around 2 times the upper limit of normal to ALT greater than 20 times the upper limit of normal on day 85, a period of only 29 days. Although ximelagatran was appropriately stopped 3 days later on day 88, ALT and bilirubin levels continued to rise, and the patient expired on day 143 with a GI bleed and coagulopathy.

Dr. Hyman Zimmerman observed in his textbook on drug-induced liver disease that instances, even very few of them, of transaminase

elevation accompanied by elevated bilirubin, even if obvious jaundice was not present, have been associated with, and have often predicted, postmarketing serious liver injuries, fatal or requiring transplant). In these cases no biliary obstruction was present. Dr. Zimmerman's observation is termed "Hy's Law" and has been borne out by a number of drugs.

Dr. Zimmerman noted in his textbook that drug-induced hepatocellular jaundice is a serious lesion with mortality ranging from 10 to 50 percent. More recent mortality estimates continue to regard the combination of pure hepatocellular injury and jaundice as ominous, with about 10 to 15 percent of patients who show such findings as a result of drug-induced injury going to die or require transplant. The explanation for this outcome is that significant hepatocellular injury great enough to interfere with bilirubin excretion must involve a large fraction of the liver cell mass.

In the ximelagatran clinical development

program, cases of severe and sometimes fatal liver injury occurred despite a transaminase monitoring program. We anticipate that the frequency of severe liver injury with ximelagatran to be expected after marketing for long-term use would be equal to or greater than that observed in the clinical trials. The frequency of severe liver injury in the long-term trials was 1 in 200, or 0.5 percent.

Based on a hypothetical scenario of 100,000 patients in the general population exposed to ximelagatran for a similar treatment duration and managed by health care providers as seen in long-term trials, one would expect some 500 individuals to develop severe drug-induced liver injury. Of these, 50 patients--that's 10 percent of the 500--with severe liver injury would like progress to fulminant liver failure, liver transplant, or death, according to Hy's Law.

Using the lower boundary of estimated mortality risk, the projected rate of liver failure, transplant, or liver-associated death with

ximelagatran is 10 percent of 1 in 200, or 1 in 2,000. Consistent with this prediction, three deaths associated with severe liver injury occurred in the ximelagatran long-term clinical development program for a proportion of one fatal liver injury in 2,300 patients exposed to ximelagatran.

Beyond standard labeling, there are three major categories of tools as described in FDA's draft guidance on Risk Minimization Action Plans, or RiskMAPs, that can be considered in developing risk management plans: targeted education and outreach, which includes providing educational materials to health care professionals and patients; reminder systems, which may include informed consent or dispensing of limited drug supply; and the most stringent category, performance-linked access systems, which may include restricted access or restricted distribution of drug. At this time the sponsor has proposed a risk management plan that consists of labeling and targeted education and outreach.

Although the sponsor has proposed

transaminase monitoring to manage the risk of long-term use, a specific risk management plan for short-term use has not been submitted, the assumption being that the intended treatment duration would not exceed 12 days.

With regard to long-term use, the sponsor proposes to put into labeling a recommendation for baseline and monthly serum transaminase monitoring, using the second and more stringent of the two algorithms implemented in long-term trials. This is the currently proposed monitoring algorithm, although I understand it may be up for discussion.

The success of the sponsor's proposed risk management plan is based on an assumption that progression to severe liver injury can be adequately minimized through monitoring serum ALT at specified intervals. However, as discussed previously, the tempo of ALT rise from normal to high observed in some cases of ximelagatran-induced severe liver injury was rapid, making a 30-day monitoring interval for ALT less than 2 times the upper limit of normal potentially problematic for

this drug.

In addition, the sponsor's analyses showed that compliance with appropriate study drug discontinuation triggered by monitoring in the clinical program was variable, and we heard some estimates presented this morning around 70 percent or so.

Finally, reversibility of injury after drug is stopped must be considered. As I showed earlier, in at least one well-documented case of fatal liver injury with ximelagatran, stopping the drug at the time of liver injury recognition did not prevent progression to a fatal outcome.

The observed compliance with ALT monitoring in clinical trials reflects a best-case performance. In practice, one would expect lower compliance. For this reason, we anticipate that the rate of severe liver injury observed postmarketing would be similar to or higher than that seen in long-term trials with ximelagatran.

FDA experience with drugs that can cause idiosyncratic liver injury has shown that, to date,

there are no risk management tools that have been proven to prevent the risk for drugs with a rapid rate of progression to severe idiosyncratic liver injury. One caveat may be noted: Limiting the usage of the drug on a population basis has been associated with a marked decrease in spontaneous reports of liver failure postmarketing in the case of drugs such trovafloxacin and pemoline.

Troglitazone, or Rezulin, an oral hypoglycemic agent, is an example of a drug with so-called Hy's Law cases observed during clinical trials portended a significant postmarketing issue with severe liver injury and fatal liver failure. In response to reports of liver failure received by FDA after troglitazone approval in 1997, a series of "Dear Health Care Professional" letters were sent to practicing physicians warning about severe liver injury and recommending monthly transaminase monitoring.

A study of compliance over a 3-month period showed that only about 5 percent of patients received the recommended monthly monitoring for 3

consecutive months in the study. Troglitazone was withdrawn from the U.S. market in March 2000 after 94 cases of drug-induced liver failure had been reported.

An analysis of 94 cases of liver failure which had been reported to the FDA showed that the progression from normal hepatic function to irreversible liver injury occurred within less than a 1-month interval in 19 patients, who were indistinguishable clinically from the 70 patients who had an unknown time course to irreversibility. Progression from jaundice to hepatic encephalopathy, liver transplantation, or death was rapid, averaging 24 days. The authors concluded that progression to irreversible liver injury probably occurred within a 1-mont period in most patients, casting doubt on the value of monthly monitoring of serum transaminase levels as a means of preventing severe drug-induced liver injury. A key issue in effective intervention to prevent fatal liver injury is recoverability at time of sign or symptom onset.

In the clinical trials which led to troglitazone's approval, there were no cases of liver failure. In the NDA database, n equaled 2,510; 1.9 percent of troglitazone-treated patients had ALT greater than 3 times the upper limit of normal, and five patients had ALT greater than 30 times the upper limit of normal, two of whom had jaundice. Although the size and extent of exposure to study drug was very different in the troglitazone and ximelagatran clinical programs, with many more patients studied long term on ximelagatran, some comparisons may be made.

Unlike ximelagatran, there were no cases of acute liver failure or fatal liver injury observed prior to troglitazone approval. Also, a more than four-fold difference is seen in the percent of patients with ALT greater than 3 times the upper limit of normal, with roughly 8 percent on ximelagatran and 2 percent on troglitazone. Consideration of the markets experience with troglitazone may be relevant to risk assessment of ximelagatran.

Bromfenac, DURACT, which was approved by FDA in 1997 for use as a short-term analgesic for periods of 10 days or less, is an example of a drug which could have been used safely for short periods, but, unfortunately, during marketed experience the drug was used in excess of the recommended duration. No cases of liver failure or fatal liver injury were seen in clinical trials. In short-term trials, the product showed a low rate of 0.4 percent of patients with ALT elevations greater than 3 times the upper limit of normal. A much higher rate of transaminase elevation was observed in patients with osteoarthritis or rheumatoid arthritis who were treated in longer-term trials. For this reason, bromfenac was approved with a warning that the short-term management of pain should be less than 10 days' duration, but liver enzymes should be monitored if used for more than 4 weeks.

Post-approval, reports of hepatic failure, including four deaths and eight cases requiring liver transplant, were received. All but one of

these cases involved the use of bromfenac for more than 10 days, the maximum recommended duration of treatment. In response to the reports, FDA and the company strengthened the warnings in the U.S. package insert with a black box, and the company issued a "Dear Health Care Professional" letter. Despite these efforts, the FDA and the company continued to receive reports of severe injuries and death with long-term use of bromfenac. Given the availability of other therapies, in 1998 FDA and the company concluded that it would not be practical to implement the restrictions necessary to ensure the safe use, less than 10 days, of bromfenac and the drug should be withdrawn from the market.

The effectiveness of transaminase monitoring in preventing severe drug-induced liver injury has not been convincingly demonstrated. Transaminase monitoring is ineffective within the tempo of liver injury is such that inexorable progression occurs, even after the drug has been stopped in response to a signal of transaminase

elevation. The foremost requirement that determined the usefulness of transaminase monitoring in preventing frank liver injury is at the time interval between onset of liver chemistry abnormality and subsequent liver injury must exceed the screening interval. Rapid acceleration of liver injury in some individuals may preclude an absolute protective value of standardized periodic transaminase monitoring.

In summary, the sponsor has submitted a risk management plan based on voluntary monthly ALT screening via product labeling. As outlined by the sponsor, the stated objectives for this risk management plan are to facilitate compliance of the monitoring recommendations by health care workers and patients through education and to minimize the risk of severe liver injury. FDA is concerned that it is unlikely that the risk of severe and potentially fatal liver injury will be adequately minimized by the sponsor's currently proposed risk management plan.

The sponsor has not demonstrated that

compliance with monitoring postmarketing would protect patients and, even if full compliance were achieved, that ALT monitoring can prevent serious liver injury with ximelagatran.

In addition, the sponsor has not proposed a strategy to prevent prolonged use of this drug after total knee replacement surgery.

In conclusion, ximelagatran can cause severe and even fatal liver injury in some patients. Initial signs in patients who developed severe liver injury were noted during the first month of ximelagatran use in six patients from long-term trials. The ability of transaminase monitoring to adequately minimize the risk of severe or fatal liver injury remains unproven for ximelagatran.

To date, serum transaminase monitoring in ximelagatran-treated patients has not been demonstrated to be effective in preventing idiosyncratic drug-induced liver injury. Currently, the proposed monitoring plan does not provide assurance of safeguarding the patient

against developing a rapid onset and life-threatening reaction.

I would like to thank my colleagues in the Office of Drug Safety and recognize other primary collaborators on this project, including Directors. Allen Brinker and Claudia Karwoski, and especially my division director, Dr. Mark Avigan.

DR. BORER: Thank you very much, Dr. Gelperin.

Rather than have any questions of Dr. Gelperin at this point, why don't we go on to Paul Watkins, who's sitting to my left here, to talk about drug-induced liver toxicity. And if we have any clarification issues or informational issues for cardiologists who don't know where the liver is, we can do that. Oh, it's somewhere below the heart. Then we will move on to the charge and the questions and have any other discussion within the committee itself.

Paul?

DR. WATKINS: Okay, thanks. I'd like to thank the committee for inviting me here. My

charge is to discuss some principles of drug-induced liver injury that are pertinent to assessing the data that you have. I won't talk specifically about ximelagatran in my short presentation, but would be happy to take any questions that you may have.

Just to frame the discussion, one of the very interesting things about drugs in the liver and drug-induced liver injury, or DILI, as it is called, is that there are many different forms histologically and clinically, and I've listed some of the many different forms of DILI that can occur with drugs. Drugs characteristically tend to have a signature or a characteristic injury they produce which can be any one of these patterns. But one of the observations that's been made is the drugs that have entered the marketplace and been discovered to have more of a liver safety concern than was believed at the time of approval and leading to regulatory action are really almost--you can almost make a blanket statement, none of these types of liver injury but a specific type of liver injury,

which is hepatocellular injury, and these are the drugs that have undergone either withdrawal--we heard about these two--been relegated to second-line status, or received--or there was a communication, usually a "Dear Doctor" letter or direct-to-consumer advertising. And I won't go into them specifically, but with the exception of valproic acid, an anti-seizure drug that's been on the market for a long time and causes microvesicular steatosis, and possibly terbinafine, which has hepatocellular injury but also accompanied usually by a cholestatic component, and based on my experience--and I've been involved with most of these drugs--the issue that got them into trouble was an acute hepatocellular injury progressing to acute liver failure.

Oh, and the other thing I should say, with the exception of acetaminophen, which is a dose-related hepatotoxin, the others would be what we would call idiosyncratic. So 13 of the 16 drugs undergoing those regulatory actions in the last 7 years, the action was because of acute

idiosyncratic hepatocellular injury.

Hepatocellular means the liver cell itself is attacked, breaks open releasing its contents, which includes ALT and AST.

Idiosyncratic--this is a slide that I borrowed from John Senior with permission--apparently has this derivation back in early Greek times, with idios, one's own, self; syn, together; crasis, mixing or mixture. And, therefore, this refers to a person's own mixture of characteristics, factors, nature and nurture--it sounds like John--uniquely. The aspects that make that individual uniquely susceptible to the injury.

Now, the characteristics of an idiosyncratic acute hepatocellular injury, which, again, has been the issue in the 13 of 16 drugs that have undergone regulatory action, this is a delayed reaction, the person has no signs of liver problems, normal liver chemistries for weeks or months, and then it occurs; characteristically has high serum transaminases, ALT and AST, with generally an unremarkable alkaline phosphatase,

modest elevation. If the alkaline phosphatase is markedly elevated, that is then a mixed cholestatic-hepatocellular injury, which is not, with the exception of terbinafine, what we're talking about. Also, it's a rare event, and when the patient becomes jaundiced, as we've heard about, there's a life-threatening injury. And as we heard, this was first pointed out by the late, great Hy Zimmerman, who made this association in a variety of drugs. I've just listed four here from published series. These are reports of postmarketing events. I'm sure you can't all read this, but the point is if you look at the number of deaths that occurred among patients that were jaundiced with these four drugs, the average is around 10 percent. So this is real-world, somebody becomes jaundiced, in general not liver chemistry monitoring, go seek a physician, and have a 10-percent mortality. And his contribution was saying it's sort of independent of a drug. If it's an hepatocellular injury, the mortality is about 10 percent on average if you develop jaundice.

Characteristics of drugs that are capable of causing this idiosyncratic severe liver injury is that in clinical trials they do almost to a man have an increased incidence of ALT elevations greater than three times the upper limits of normal relative to placebo. However, there are many drugs that have ALT elevations such as statins. Heparin is another example, very common. So ALT elevations in themselves are not a concern. With these same drugs, the majority of people who have the ALT elevations are actually not at risk of developing significant liver injury even if they're continued on drug unmonitored.

The concept that has evolved, if you look at this triangle as being all patients being treated with these drugs, the vast majority shown as the bright green can take them totally safely with no reason to believe there's any liver injury whatsoever. There's a subpopulation that develops elevated serum ALTs, yellow triangle, but even with continued treatment, most of those will actually resolve and come back to have normal serum ALT.

The liver adapts, and this adaption process is poorly understood in the NIH research plan for the next five years from the NIDDK, which I helped put input into. Studying this adaption phenomena in animal models is one of the high priority items.

But not everybody adapts. A subset if continued on drug will progress to jaundice, and at least in the real-world setting, 10 percent of those will develop acute liver failure.

This is a slide from a review that I wrote months ago. It's not a real patient, but it's a example of what you would expect in a typical acute hepatocellular injury leading to death from a drug, and like the other slide, what we have is days on drug on the X axis. This was John, Sr.'s. One of his many contributions was deciding to graph the liver chemistries as a function of log of upper limit of normal so you can put all of them on the same axis.

The point here--and I'm losing my pointer--is that serum ALT and--ALT and AST remain normal on the drug for the first month. Then a

little after two months they're up. At this time the serum bilirubin is totally normal. Drug is continued out here beyond day 120. The serum ALT continues to rise. Bilirubin is still normal, but if the injury progresses, then the bilirubin begins to rise. This is because the liver has lost its functional ability, lost too many functioning hepatocytes.

The drug is stopped in this case, but then the injury progresses, and that's actually something characteristic that was referred to earlier, that once you develop this inflammatory response in the liver, it doesn't revert right away and will take a while to resolve.

In this case you can see the serum transaminases are coming down nicely and might be confused for this patient getting better, but in fact there's no liver left to leak transaminases, as indicated by the continued rise in bilirubin.

Now, a patient may or may not have symptoms during this phase when the ALT is up and the bilirubin--before they become jaundiced, which

would be in about here, in most cases they do not, and that's obviously the rationale of monitoring is to catch them at the asymptomatic phase before they go through and progress.

This pattern is more or less similar in all those drugs I showed you on the other slide. However, the time to onset the characteristic rate of upstroke, how quickly it reverses when you stop the drug, vary between one drug or another. But in general you don't in clinical trials that I've been involved with actually have a case of someone who has gone all the way through to a fatal outcome. Therefore, what you're left is trying to assess lesser signals than that. And the reason is in general these are very rare events. You don't treat enough people. You don't treat for long enough. The denominator is really people that have taken the drug for months. Most importantly, once you realize there may be a liver issue, you stop the drug in clinical trials when the serum ALT gets to a certain point, so you don't see the natural history.

So in evaluating liver safety databases the usual thing is to try to find people at various points. How far did they go along in this trial? And that's the basis of this Hy's Rule, that if ALT elevations alone don't mean very much, combining them with bilirubin elevations, even if it's reversible, tells you the drug has this ability to go all the way through.

Just ALT elevations are not very predictive. I mention that. However, the higher they are or if they're accompanied by signs of hypersensitivity, fever, rash, eosinophilia, or symptoms that suggest this has real inflammation systemic symptoms, we get concerned. 8 or 10 times the upper limit of normal is a cut to look at for that. We talked about Hy's Rule. This is the most conservative one with a bilirubin just 1-1/2 times the upper limit of normal, that this is somehow more predictive of a signal. And so what everybody does is they ask for all the cases where ALT was greater than three times and bilirubin was greater than 1-1/2 times, and look at those cases very

carefully.

And what you look for is, is there a cause other than the drug, number one, but number two, is this a hepatocellular injury or is there evidence of cholestasis, elevated alk phos, in which case the bilirubin elevation is occurring at an earlier stage before there is serious liver injury.

So first determine whether each case is consistent with hepatocellular injury and that the drug is the cause. And then what's commonly done, once you have these selected cases after this analysis, is assume irreversible liver damage will occur in 10 percent of these cases. And of course, that's the 10 percent rule really came from post-marketing observations of people who walked into their physician once they were already jaundiced. And as we heard, the only clinical trials data that supports the predictiveness was with troglitazone, where 2 out of roughly 2,000 people had true hepatocellular jaundice, and that would predict around 1 in 10,000. That may be about right post marketing in terms of the liver

events.

The problem with extrapolating this data is there were no criteria for stopping liver chemistries in the troglitazone clinical trials up through NDA submission, so it was up to the individual physician to decide whether they wanted to stop. So things were allowed to progress to a greater stage.

In addition, troglitazone characteristically has a very long tail of recovery. Even ALT elevations took greater than two months to come back to normal, so that stopping the drug, you know, more likely the progressive liver injury. So it's difficult to extract that data back to other drugs.

Then my last comments is--I think they've been made--which is the effectiveness of monitoring really is going to be a function of, number one, if patients are symptomatic. So, for instance, Isoniazid, pulmonologists feel they can follow symptoms reliably, and most public health services don't do routine liver chemistry monitoring as a

safety measure for that. But then it's the rate of upstroke, how quick does it go up? And obviously it goes up very quickly. Your interval would have to be very short. And then when you stop it, how quickly do things return back to normal are kind of the specific issues.

So to finish up, my take-home points are that isolated ALT elevations are difficult to interpret, but if it's greater than 8 to 10 times or associated with symptoms, it raises concern. The highest concern is bilirubin elevations in the setting of a hepatocellular injury, but I think you need to look at the cases carefully to look for high serum ALTs in the presence of a relatively unremarkable alk phos, so you're talking about jaundice due to hepatocellular injury. And then our ability to predict the true risk, especially in the real world from safety databases is imperfect.

Thank you.

DR. BORER: Thank you very much, Paul.

We'll take a couple of minutes in case anyone has any burning questions about these safety

issues. We've had some superb presentations here. But I don't want to dwell on this because we do want to move on to our discussion.

Is that Tom?

DR. PICKERING: Yes. Could you comment on the statements that were made earlier, the 16 out of 18 patients who a rechallenge did not develop additional elevation of ALT, and also that those who maintained on the drug, it appeared to be a transient phenomenon. How would you interpret that?

DR. WATKINS: The fact that you could rechallenge people and not see a return of elevated ALT is reassuring in the sense that that argues very strongly against some sort of immunoallergic or hypersensitivity reaction, so that there would be even a greater reaction the second time with the drug.

It doesn't, however, mean that the elevation wasn't due to the drug, and there are examples of that where drugs that clearly have caused ALT elevations on rechallenge have blunted

or not ALT elevations. And it's presumably part of this poorly-understood adaptive mechanism, where the liver actually adjusts in some way and has a memory or a prolonged memory effect.

And that's the answer to the next question you had which is why is when you continue to treat these people the serum ALT comes back to normal? And as I say, that's a fairly universal finding. So, for instance, with Isoniazid, can cause acute liver failure in some studies of 1 in 1,000 people treated for tuberculosis. The incidence of ALT elevations greater than three times is 15 percent. Well, obviously, that 15 percent, unmonitored, don't go on and develop acute liver failure. The majority of them adapt, and the current thinking is it's a few patients who are incapable of adapting that go on and develop progressive liver injury.

DR. BORER: Steve?

DR. NISSEN: Could you give us an example where Hy's Rule fails? I mean is there out there anything where it clearly, there were people that had--they had elevations of enzymes and

hyperbilirubinemia, where just nobody goes and develops liver failure?

DR. WATKINS: Not that I'm aware of, and of course, I usually get consulted when there clearly is a liver safety issue.

I think the confusion is sometimes if all you do is look at ALT and bilirubin and don't look at alkaline phosphatase, you may be picking people that in fact have a large cholestatic component where jaundice occurs very early in the course of injury, and then you would be not extrapolating appropriately for the risk of irreversible injury. But to answer you question specifically, I'm not aware of any, and I think that's part of the reason why the Agency right now is feeling quite confident about extrapolating Hy's Rule to the real world.

DR. BORER: Tom?

DR. PICKERING: Could you also comment about the statins? Because I think when they were first released there was concern about this issue which seems to have largely gone away. And also, overall in the ximelagatran groups there was no

significantly higher bilirubin levels than in the comparitor groups. Is that of any relevance?

DR. WATKINS: Well, let me answer the first question. In terms of statins, the concern was there was a preclinical model that clearly developed serious liver disease, and those drugs I showed you, in general the preclinical studies have been completely clean. So going into the early statin trials there was already a concern about liver, severe liver injury, and then seeing the ALT elevations carried that concern forward. I think it's pretty clear the risk is quite small now from the statins as a group, and for reasons that aren't totally clear. But there are ALT elevations, as I point out, that don't predict subsequent liver injury.

Now, what I don't know is in the clinical trials of the statins whether there were any Hy's Rule cases. That would be a very interesting question to explore if you just used a very low cutoff like ALT 3 times, bili 1-1/2 times, and I'm sure that's being looked at at current statins, but

in the past, I'm unaware of it.

DR. BORER: Okay. Thank you very much, Paul.

I think what we'll do now is go on to the questions, and we'll have the rest of our discussion in the context of the structured questions before which we need to hear what we're asked to do. So if we can have a statement about the charge to the Committee from Dr. Korvick.

DR. KORVICK: Thank you, Mr. Chairman.

I would just like to point out that for your convenience, we have provided a hard copy of the questions and also we're prepared to project those questions on the screen for everyone to see.

In the interest of time I'm not going to read the questions to you, but point out the areas of interest. As you will see when you read through these, we are very interested in the Committee's opinion about the safety and the data that you've heard presented today. Then we go on to ask you about your opinion on the benefit risk in the three proposed indications that are presented for you.

I would just like to point out that the Committee has been constituted in such a way with the expertise to be able to appropriately address for us this issue of benefit risk evaluation, and that is very important for us to understand. As you've heard earlier today, the FDA and AstraZeneca will be meeting and having further discussions on the risk management program. However, based on your concerns about the benefit risk and these various indications, it is conceivable that further advice may need to be sought from the FDA Drug Safety Committee if it comes to that.

So I think we are very interested in your perceptions on the benefit risk, and we are also interested that you ask the Committee members to vote on all the questions.

Thank you.

DR. BORER: Thank you, Dr. Korvick. I can assure you, you will hear our opinions.

We have two non-voting members on the Committee, Dr. Vega and Dr. Watkins, who can participate in the discussion but not vote. But

I'm going to ask for a vote as well as an opinion if you choose to give one on all the issues listed in these questions. We have a Committee reviewer, Steve Nissen, and a Committee statistical reviewer, Tom Fleming, and for some of these issues I'm going to ask them to go first, and then go around the table, and in others we'll just go around the table.

On the first question regarding safety, what we want is a statement about level of concern from everyone, none, low, moderate or high, for the risk of liver toxicity with the use of ximelagatran in each of the three settings that are noted here, and we'll want an explanation for each of these.

Steve, why don't you start out here?

MR. NISSEN: In my answer, I will lump 1(a) and 1(b) together because they both relate to the longer term use of the agent.

I would consider the risk to be high, and the reasons are that by Hy's Rule, one would estimate approximately a 1 in 2,000 risk of acute liver failure, fulminant liver failure. By actual

observation it's 1 in 2,300. So we have two independent sort of sources of estimation, both of which give about the same estimate. In addition, I'm troubled by the fulminant nature of the liver injury that is seen, that is difficult to predict. Even with monthly monitoring, in 29 days a patient can go from first elevation to irreversible fatal injury.

My judgment from hearing the three cases is that they are all three almost certainly drug related, and so again, I can't make that problem go away with the chronic use, so I do think the risk is very high.

One of the things I did look at as I reviewed this is what the rate was for another agent that was withdrawn, which is troglitazone, and using this methodology, you get about 500 per million patient years for ximelagatran, and that is just about double the rate that was observed with troglitazone. So I think based upon the available data, the estimated risk here exceeds that of an agent that was withdrawn for these kinds of safety

considerations. Now, that says nothing about benefit, but that's my view of absolute risk.

With regard to short-term use, my assessment of the risk would be lower, but I am worried about a couple of things that I suspect the Agency's also worried about. We hear a lot about dose creep when we talk about drugs for arthritis and so on. I'm worried about duration creep here, that, you know, saying to somebody, "You can use this drug for 12 days, but not 13, 14, 15 or longer," and I know my colleagues and I know how they think, and my concern would be somebody's on it, they seem to be doing well, they have prolonged risk of venous thromboembolism, and so they stay on it for 20 or 30 days maybe, not six months.

We don't have a lot of data on the delayed risk profile, what happens if you give the drug for say three weeks or two weeks and then stop it, you know, it there a late phenomenon?

So my risk concerns are lower for short-term use but they don't go away in short-term use because I'm concerned about this duration creep

problem.

DR. BORER: Tom, do you want to address that question?

DR. FLEMING: The only thing that I might add which certainly struck me as particularly noteworthy is in the long-term database with the 6,900 and 6,200 that when we look at Hy's Law and we look at these people who are categorized as severe liver injury, there's a half a percent increase as has been repeatedly noted. And if Hy's Law applies, that is in fact then 1 in 2,000 that would progress to liver failure, transplant or death, which is certainly very significant.

The other thing that I noted was in the third indication listed here in 1(c), what is certainly, what caught my eye was that it's not as clear to me what the risk is, but it's interesting in the 4- to 6-week period at 7 to 1, and I would sure like to know what happens after week 6 here.

DR. BORER: So we need a precise answer, so if you are agreeing with Steve, that means high for (a) and (b), and what for (c)? Tom?

DR. FLEMING: What is my answer for (c)? I mean I agree high on (a) and (b), and (c), I don't know, it's unknown, but I'm concerned.

DR. BORER: Why don't we start at that end of the table with Tom?

DR. PICKERING: I think I would say moderate for (a) and (b). A lot of this depends on the fate of three patients out of nearly 7,000, and of the 37 with "severe liver injury," most of them recovered or died from unrelated causes, and of the 3 cases, my interpretation was that one died from hepatitis B, one probably from drug related and the other one was a mixture. So I think I wouldn't rate it as high as Steve. It's moderate.

DR. BORER: And what about (c)?

DR. PICKERING: (C) I would say low, assuming that it's given for the stated duration.

DR. BORER: I'm sorry. Dr. Vega, you're not a voting member, but if you have any major concerns that you want to raise here, please go ahead.

DR. VEGA: I think given the data I would

say that I would have a moderate level of concern for (a) and (b) and low for (c).

DR. BORER: Ron?

DR. PORTMAN: I would have to agree that (a) and (b) would be high. I think we don't understand very well the injury, the liver injury, and I think that for me, whatever plan for monitoring the company may have, that we will want to see a study to see if that were in fact effective. As far as (c) is concerned, I would rate that low.

DR. BORER: Bill?

DR. HIATT: Pretty much the same conclusions. I think for (a) and (b) it's high. It seems that we have more evidence from this data than other studies about progression of liver disease on to serious consequences. So though the absolute risks are low in the actual clinical trials data, the real risk to the population I think would have to be considered high.

I think for the knee surgery population, it's unknown, but probably moderate at this stage,

and easily quantifiable over a relatively short period of time, you know, 6 months. So my vote there would be moderate.

DR. BORER: Beverly?

DR. LORELL: I think for the two long-term groups for the reasons that have been stated the risk is high. I think for the surgical group as was used in the trial, the risk is low.

DR. BORER: Jonathan?

DR. SACKNER-BERNSTEIN: I would say that even though the sponsor has made the statement that they think that they can reduce the risk to 1 in 10,000 instead of the 1 in 2,000, even if that were the case, I still think as you do the math, that leaves you still at a high risk in letters (a) and (b).

And for (c), one of the factors that we didn't even discuss was the fact that several patients, after discontinuation of drug, developed ALT abnormalities. Since the follow-up was only four to six weeks, and it's been established pretty clearly that the peak rise in these liver enzymes

is between two and six months, I don't see how we allow the absence of safety data to allow us to say that it's no or low risk. I think at the minimum you'd have to say it's a moderate risk, so I'd say moderate for (c).

DR. BORER: Susanna?

DR. CUNNINGHAM: I would also vote high for (a) and (b), and for (c) I would also vote moderate, partly because of the FDA data that Dr. Gelperin presented that the other drugs, people have not kept the dosage duration down, so I think it's likely to creep as Steve said.

DR. BORER: Paul, you're not a voting member here, but again, if you have any opinion to give about this, we'd love to hear it.

DR. WATKINS: Just in regards to (c), the concern that a few patients had elevated transaminases a few weeks after stopping short-term treatment. I think it would be unprecedented for a drug that causes hepatocellular injury or any of the drugs that I listed that underwent regulatory actions in short term to weeks later developed a

problem, that is seen in a few drugs that have cholestatic features like augmentin, where you can stop the drug and weeks later there can be a problem. And even then, that would not generally be thought of as a major medical problem. So it would be helpful to actually see the data on those patients to be sure, but I would be very surprised if any subsequent studies showed that a short-term treatment led to significant liver problems weeks or months later. It would be unprecedented for hepatocellular injury in my experience.

DR. BORER: Thank you.

I would vote high for (a) and (b), but I have to provide a caveat and explanation. It's hard for me to talk about safety without putting it in the context of the relation to benefit. I'll say right now, and it will come up I'm sure from others as we continue this discussion, that warfarin is a very difficult drug to use. There are many, many problems with its use. There are situations and patients in whom it's not practical to consider using it. Having an alternative that

can really markedly reduce risk in certain situations is something that's very attractive to me.

Jonathan Halperin showed a risk to benefit relation slide that was broad strokes, but still suggested there is a population, if Coumadin were not really a practical option, that certainly would benefit more than it would be at risk, the risk of hepatocellular death worse case or liver failure death at worse case we're sort of currently estimating at 1 in 2,000, although that's a total guess because there are so many unknowns here. And the number needed to treat to prevent a major event is 1 in 10 or 1 in 15.

The risk in absolute terms is high relative to what I consider to be the risks of other drugs that I use in patients with cardiac diseases, but you do have to think of it in terms of the relation to benefit.

Nonetheless, I think that the risks of hepatic injury, of liver toxicity with ximelagatran is high in the setting in which it's going to be

used for a long time. Whether that can be minimized with a monitoring program remains to be determined. I don't know that. I think that's something that the FDA is going to have to talk with the company about, and I applaud the potential use of genetic profiling, because as Paul pointed out, it sort of sounds like this is probably not dose related, but be idiosyncratic. And if it is, then you have to find out the characteristics that identify the people at risk.

For the prevention of VTE in patients undergoing elective total knee replacement surgery, I have a relatively low level of concern about safety if the drug were used as it was used in the trial. But as several people have said now, I can't believe that it will be, and therefore, we're going to have an overlap between short-term use and long-term use, and once you get into long-term use or longer-term us, you do begin to worry again about the unknown risks and the potential remediation of those risks by a monitoring algorithm that still has to be determined.

So that's a long-winded answer, but I said high, high and sort of low.

John?

DR. TEERLINK: So I'll say high, high, and the thing that reinforces that for me is the consistency of the data, and the other thing we hadn't talked about was even if you forget about the ALT plus bilirubin, there was the ALT greater than 10 times the upper limit normal being 15-fold higher in the ximelagatran group, so that just reinforces for me the concern in that group.

Prior to what Paul said I had a moderate concern about the post total knee replacement group, the short-term group. When you have an 8-fold or greater increase in--8-fold greater number of patients who have had ALT elevations and no follow-up data to know what happened to those, I was going to say moderate just to help make sure we get that information. If we are confident that those kind of short-term exposures don't tend to result in longer term deficits, then I'd be comfortable saying low.

DR. BORER: Dr. Sjogren.

DR. SJOGREN: I think for (a) and (b) I do agree that the risk is high. However, here's the dilemma: it's high for a small proportion of patients because it is idiosyncratic in nature. Therefore, I hear this drug is good otherwise, you know, probably preferable to Coumadin in many patients, and so when we think about it, we think about the risk, but then we think about the benefit for the other patients that won't develop the fulminant hepatic failure.

So I think although I rate it high for a small number of patients, still I think it would be very important for us to find a way on how to monitor so we can prevent the very bad outcomes, such as transplantation or death.

For (c) I think the risk is low considering what we have discussed.

DR. BORER: Alan?

DR. HIRSCH: It's hard to be at the end of the series and say anything novel, but I will ignore the benefit which I think does probably

exist for this medication, remembering that Coumadin does have high rates of adverse events, and say then therefore with humor that we're following Hy's Law.

For (a) and (b) I think the risk actually, unfortunately, is potentially high, and for (c), I actually think the risk for short-term use is low, but has the problem of "hype's" law, meaning that I do believe that the creep, the duration creep that Steve mentioned is a real issue. There's been so much hunger for a Coumadin replacement, as all of our public advocates have mentioned, that I can't believe that this medication would be used for only the expected duration. The anticipation of it being longer should be expected by all of us due to the hype and hunger for a replacement. High, high, low.

DR. BORER: You've stung me to the quick by saying that you're at the end of the line, so you can start No. 2, which is: Based on currently available data, is it possible to identify patients who are at risk for developing severe liver

toxicity after exposure to ximelagatran?

DR. HIRSCH: Short of some new test, you know, me profiling things that you've mentioned, Mr. Chairman, I think that the greatest predictor was exposure to the drug, was in fact treatment with the data we were shown. Beyond that, and I think if I'm integrating the data correctly, we would anticipate prior liver disease of ALT elevation at the beginning, possibly statin use, small body mass index, and females to be at a somewhat greater risk, although the truth is we need a greater post-marketing exposure to know if these are really true.

DR. BORER: Tom?

DR. FLEMING: Just to refer to two of the sponsor slides, in CS-27 they indicated if you look at ALTs three times upper limit of normal where treatment has a relative risk of 6.8, none of the other prognostic factors had a relative risk of even 2. So it's difficult to really nail down who this population is. And in their slide CS-30 they said there is no patient subgroup identified at

higher risk of developing severe liver toxicity.

DR. BORER: Dr. Sjogren?

DR. SJOGREN: Well, when you confront a group of patients you really don't know who's going to have the idiosyncratic response to the drug, but I would think, like with other medications that we use in liver disease like Imuran(?) or others, we do testing. We initiate the drug, and now with Imuran we do the testing before because we have some markers now, but in the past we did very rigorous testing the first month, and we were able to then discern what patients we needed to take the drug away. So I would think that we now don't know, but once you start the drug you can, not monthly, but probably weekly, monitor those patients for a period of time and then decide who were at risk of exposure to the drug.

DR. BORER: I think that counts as a possibly, a possibly yes.

DR. SJOGREN: Yes, possibly yes.

DR. BORER: John?

DR. TEERLINK: I think I'll have to say

no, and I'll just leave it at that since we've already said.

DR. BORER: Yes. I'm not a hepatologist but my response is really along the lines of what Dr. Sjogren says. I don't want to obviate the possibility or exclude the possibility that there is a monitoring algorithm that could be used. It may be extraordinarily conservative. It may be difficult to apply. I don't know. And I certainly don't know how you would pick out those patients right now. I just don't have the knowledge base to suggest how you could do that, but it seems to me that it might be possible to develop an algorithm that would allow you to at least reduce the risk below what we think it is now in a population that might receive the drug, and I would urge the sponsor and the FDA to work on developing such an algorithm.

Paul, do you have any thoughts about that?

DR. WATKINS: Not about the algorithm, but for none of those drugs that I've listed is there a way to identify what patient is susceptible to the

severe liver injury, and that's one of the reasons the NIH has established this drug induced liver injury network to begin collecting well-defined cases, make a patient registry and get a DNA bank.

In the case of ximelagatran, it looks like there's a clear susceptibility window which suggests to me a genetic component, and I would applaud any efforts the company would do either retrospectively or prospectively to get genomic DNA to help us get some of the answers to these questions.

DR. BORER: Steve?

MR. NISSEN: I appreciated the explanation of the origins of idiosyncratic, and clearly it does in fact apply here, and that's the nature of idiosyncratic drug reaction, is that it is not predictable, and, boy, I sure wish it were because it would turn this whole thing around if somebody could come up with a way to identify. It's a very small number of people to have this problem, but we just can't pick them out.

DR. BORER: Let me, if I may, just modify

what I said a little bit. This question, as it's stated literally says: Is it possible to identify patients who are at risk for developing severe liver toxicity after exposure? And so I guess you have to be a little more precise and tell us whether that identification has to occur before any drug is given, or after some drug is given. If it's before any drug is given, we've heard that there's no way to do it. If it's after perhaps some drug is given, maybe there's a way to identify people who are responding. Maybe there is, maybe there isn't.

MR. NISSEN: Jeff, that's sort of in the next question.

DR. FLEMING: Oh, okay, sorry. Then let's go on to Susanna.

DR. CUNNINGHAM: I'm going to say no, but I'm also going to use this as an opportunity to say that there's little or no, really not much data on ethnicity, diversity in this group that's between 88 and somewhere in the mid 90s, caucasian. And so if there's any further research done on this, I'd

like to encourage the sponsor to look at some ethnically diverse groups, especially African-Americans.

DR. BORER: You know, to point out and get it on the record here, as Susanna's point's very well taken because if you look at the data we have, it sounds as if there is an ethnic difference in response, and that the Asian population did not seem to respond as--with the same likelihood of toxicity as other populations. Whether that's an artifact of sub-analysis or not, I don't know, but it's an important point.

Jonathan?

DR. SACKNER-BERNSTEIN: I would say no, although it's also important that patients who started out with an ALT above two times normal I think in the studies were excluded, so that would be important to include.

DR. BORER: Beverly?

DR. LORELL: I would say it's not possible prior to initiating drug, with that important exception, to identify patients at risk.

DR. BORER: Bill?

DR. HIATT: Just add another note of that, but if you look at the risk factors that were presented, those relative risk increases were really modest, so I'm thinking about positive and negative predictive value around those things which would probably leave a lot of margin for error. So I think those risk factors just aren't strong enough except drug itself to predict a population at risk.

DR. BORER: Ron?

DR. PORTMAN: Well, if it's truly idiosyncratic, then what I'm about to say is incorrect, but as we saw earlier, I mean this is not a fixed dose for patients who have chronic kidney disease, and we saw that as patients' GFR dropped that the prevalence of hepatic enzyme elevation at least went up, and so that's certainly for, as the company admits, for those who are on dialysis it's a risk, and so I think that those patients who have chronic kidney disease--and there are now five stages of chronic kidney disease that

the company may want to look at for dosing recommendations, that those may be at risk for the higher grades of chronic kidney disease.

DR. BORER: Tom?

DR. PICKERING: No, I don't think any of the predictors were strong enough to be of much practical value.

DR. BORER: Any comment, Dr. Vega?

DR. VEGA: No. I agree on what Dr. Watkins said, it's not unique to ximelagatran; it is basically for all potentially liver toxic molecules.

DR. BORER: Having satisfied Alan, we'll now go on to our old way of doing things with Question 3. Did the sponsor study procedures for monitoring and managing patients with regard to liver function adequately minimize the risk of severe liver injury and liver failure in the clinical studies?

We'll start out with Steve as the Committee reviewer, and if anyone has anything to add to his comments, you can. If you just want to

vote on this one, which is probably relatively straightforward, you can do that too.

Steve?

MR. NISSEN: Yes and no. I mean let me see if I can specify what I mean. I was actually a little surprised that only 70 percent of the monitoring that was mandated in the trial was actually done, and I say that because when--I mean I do a lot of clinical trials myself, you know, and those coordinators of ours, you know, they get after the patients if they don't show up for an appointment to have a blood draw. And so this was, in the clinical trial, I would have thought a very optimal setting in which to get a very high rate of compliance with monitoring, and it was only about 69 or 70 percent, and so it does--to me it's a very important question that the FDA is asking here, because if the best that we can do in a controlled clinical trial is 70 percent, then the question is what's going to happen in general use?

And the lowest figure I heard was the troglitazone figure of 5 percent, and so I'm

surprised it wasn't 90 percent in the clinical trial. So that part I don't really understand it based upon my own clinical trial experience. But having said that, I think the 70 percent is sort of intermediate. And so the monitoring procedures were reasonable, but they were certainly not as high as I would have liked to have seen, and probably are going to be a lot lower if it were to be in general clinical use.

DR. BORER: So did they adequately minimize the risk?

DR. NISSEN: I mean it's--you know, no. I mean I think that adequately minimizing the risk would have involved much more intensive and a higher compliance rate. I just don't understand why that wasn't achieved.

DR. BORER: Tom?

DR. PICKERING: I agree, no.

DR. PORTMAN: No.

DR. HIATT: No.

DR. LORELL: I think no. I think it was very appropriate that the sponsor modified their

algorithm for monitoring, but I will agree I was somewhat surprised at the compliance issue.

DR. SACKNER-BERNSTEIN: No.

DR. CUNNINGHAM: No.

DR. BORER: No.

DR. TEERLINK: No.

DR. SJOGREN: I think the protocol was good, but the implementation was not done. So I guess it's no.

DR. BORER: Tom?

DR. FLEMING: No.

DR. HIRSCH: No, but we're replacing now ideally the challenge of monitoring Coumadin with warfarin clinics with the challenge of following ximelagatran with liver health clinics. It's better to be liver than deader.

[Laughter.]

DR. BORER: I was going to start on your end, but I won't now.

[Laughter.]

DR. HIRSCH: It's my last meeting.

DR. BORER: Okay. Do you have any other

safety concerns regarding the long-term use of ximelagatran, for example, cardiac, and perhaps regarding a short-term use of ximelagatran?

Tom, why don't we start with you?

DR. FLEMING: There are two other domains here that I think for me are noteworthy. One is the domain of coronary artery disease and specifically MI, and I'm speaking now first in the long-term use. The slide 0-49 which extends the slide, Table No. 18, that Jeff had called to the attention of all of us, Slide 0-49 the sponsor put up even extended a bit the completeness of the follow up and the MI data that we have in the 6,900 versus 6,200, and there is an excess of half a percent in MIs.

So there is in fact certainly a real indication that there is a relationship here. It was interesting, when we look at the fatal MIs in the SPORTIF III and V trials, in SPORTIF III it was 11/12, but in SPORTIF V it was 10/3, so there were three times as many fatal MIs in the SPORTIF V trial. So it does in fact, to my way of thinking,

look consistent across series of data that there's something here that's real.

In the bleeding domain, whereas the sponsor presented results in the SPORTIF trials indicating lesser--somewhat less, non-significantly less major bleeding, there were still twice as many in this long-term database who discontinued due to bleeding, 83 versus 43, again, another half a percent. In the short-term trial as well, there are, as we have seen, indications of an excess of MIs, 16 versus 4, and major bleeds, 18 versus 10, again consistent with what we're seeing in the longer term.

So I would add those two domains as areas of concern beyond the hepatic toxicity.

DR. BORER: You're forgiven, Alan, you can go ahead.

DR. HIRSCH: Thank you for the forgiveness.

No, I have the same concerns, but I do want to make a position statement. We've been so worried about adverse effects. It's clearly a

positive signal of benefit that's consistent through all the trials for preventing thrombotic events in two extremely vital circulations, the brain and the lungs. Though we have this relative signal of cardiac thrombotic events that concerns me, I believe we might need more data to show net benefit, or we actually probably have data showing net benefit regarding the other thrombotic areas.

DR. SJOGREN: I do have some concerns about MIs. You know, I heard you discuss about it and I am concerned somewhat about it.

DR. BORER: John?

DR. TEERLINK: I also share the cardiovascular concern, and it's a low to moderate level concern because I think it can be addressed in further studies and looked into further, and may be able to be eliminated by some additional data, but for now I think it's an unaddressed issue.

DR. BORER: This is for both short- and long-term, right? I have a couple of concerns but they don't rise to the level of showstopper type concerns, and I have to explain why I say that.

The issue of cardiovascular events is a concern if it's real. And I agree with John. I think that probably the importance of this can be resolved with some additional data, but we have right now is what we have. On the one hand we have some observations suggesting an excess of cardiovascular events, both MIs, small number, low absolute risk and some other generally softer cardiovascular events, and heart failure. These events seem to be excessive in populations in whom they were unexpected, and if they were unexpected, then finding them is less compelling to me than if I had expected them.

But in the situation in which these kinds of events specifically were being looked for as a matter of protocol as efficacy issues, I didn't see that excess. In fact, there was a tendency for things to look better on ximelagatran than on the comparitors. So where I expected ximelagatran to look good, it seemed to look good. Where I didn't expect it to look bad, it maybe looked bad. I don't know how to put all that together.

In any event, the absolute number of excess events seemed to be small, which is why I say I'm not overwhelmingly concerned, but concerned enough to look at little further. There are several confounders that may be involved here. One is the possibly differing pathophysiology of the coagulation system and the cardiovascular system in the different populations, early post-op patients, et cetera, et cetera, versus non-operated patients. We've raised the concern about rebound which I think has been discussed enough, but it still is sitting there as something I'm thinking about.

And then, of course, we have to determine if there really is some excess of events on ximelagatran, whether that represents a toxic effect or a lack of benefit because of, as Steve pointed out, a differing effect on venous versus arterial thrombotic processes. That seems a little farfetched, but it could be.

So I have some concerns, but they don't rise to the level of showstoppers. With regard to the bleeding events, it seemed to me that the more

drug you give in general of an anti-thrombotic, the more likely you are to bleed, and overall these data look that way to me, so that doesn't concern me too much. So I do have some concern, but I would think about it in the context that I just presented it.

Steve?

DR. NISSEN: I guess we're going to skip you, Paul, or maybe we'll come back to you.

First of all, I want to reassure my friend, Tom Fleming, about the bleeding issue, and let me tell you why I'm a little bit reassured about it. That is that I agree with the sponsor and their representatives that the use of Coumadin in this trial was probably more precise and better controlled then we see in the general use. So the fact that Coumadin did pretty well on bleeding is not what we actually see in the real world. In the real world it's a lot sloppier. And so there would likely be some equalization here on the bleeding rates when you consider how drugs are generally used, particularly Coumadin, are used in real life

where the monitoring just isn't as good as we'd like it to be.

However, I have considerable concerns, more than others, about the cardiac, and let me tell you why. Yes, the absolute numbers are low, but in the short-term trial the exposure duration is very short, and so if I look at an event rate of the magnitude that we saw for myocardial infarction with 12 days of exposure, it starts to look a lot worse, and it maybe looks even a little bit scary there as you sort of think about it. It is statistically significant.

Now, p-values don't mean that everything is biologically significant, but it sure gives you the bias that it probably is. So when I see a statistically significant excess of cardiac events, and when the magnitude of the events is high for the duration of drug exposure, it makes me worry. And I think it would need to be explored before it would be safe to use that drug in a population of old people who are undergoing knee replacement and hip replacement, have a lot of concomitant

cardiovascular risk factors, and I know what these people look like because I look at them. A lot of them are going to have coronary disease. And so I think we just don't know, but it doesn't look promising in terms of the cardiovascular risk.

DR. BORER: Paul, I didn't mean to skip over you. If you have any comment? No?

Susanna?

DR. CUNNINGHAM: I agree with Steve.

DR. BORER: Jonathan?

DR. SACKNER-BERNSTEIN: I agree with Steve about the risks, and I would say that I feel reasonably similar to him about the cardiac risk. I think that it's fair to pull in a paper that Bob Temple wrote a few years back, where he was quoted in that paper saying that a signal with a p-value of .1, potentially showing a safety risk when you're looking at a database even post hoc, is a signal that's worth enough of a concern that it nearly needs to be addressed formally. So I think that this level of a signal, this kind of p-value, means it's something that really deserves some

future attention.

I would also say that the long-term a-fib population is a concern in two respects. One, I agree that the manner of management of Coumadin was much better than seen in clinical practice, but I would also expect that the management of liver risk is better than will be seen in clinical practice. So all we can do is really compare apples to apples and say in this trial, this is how the warfarin was managed, this was how the liver was managed. Let's just balance the risks between the two.

And that also becomes important when you start to look at the kinds of patients seen in clinical practice who have atrial fibrillation. I don't know the demographics perfectly, but I know that there's a huge proportion of a-fib patients over 75, and I know this data a little bit. But if you look at a typical patient who's 75 or 80-years-old, unless they have a creatinine down at about .7 or .8, they're going to have a creatinine clearance that's very, very different than the creatinine clearances of the patients in these

trials, and you're going to see patients treated with this drug that have calculated creatinine clearances of 30 to 45 cc's per minute. That's an area where we don't know what the risk/benefit ratio is and there really aren't sufficient data. I think it's an area that if you're going to be advocating this drug be considered for atrial fibrillation, really have to do a primary analysis in people who have impaired renal function.

DR. BORER: Beverly.

DR. LORELL: Thank you, Jeff. My feelings about the cardiovascular risk in long-term use are more similar to yours than to Steve's. I think that that very small apparent absolute increase is in somewhat a hypothesis generating. I don't see it as being an extremely strong or hard signal that there is an increased risk.

My thoughts about bleeding are similar to yours, Steve. I agree with you on that.

To my mind, the short-term signal I think may be a real issue. As I questioned earlier today, I think it relates to a more generic problem

that all of us around the table have seen, interventional cardiologists certainly see. We know that the post-surgical period for any kind of lower-extremity or hip surgery is a period of prolonged tissue damage and inflammation, and we know enough in 2004 to realize that is a milieu where there is a higher risk of vulnerable crack rupture, of acute coronary syndrome and infarction. So to me that signal of a possible, quote, "rebound," I don't look at so much as rebound, but being the more generic issue of how you manage aspirin correctly and fastidiously in post-surgical patients who have risk factors for coronary disease period. And I think that's a more generic issue.

So that's a little bit of a long-winded answer, but I did want to make the comment that I look at it somewhat different as being a narrow rebound issue as opposed to a broader issue of the importance of using aspirin carefully in this population.

DR. BORER: Bill?

DR. HIATT: I think there is a predictable

bleeding risk, and I'm not really concerned about it because it matches the pharmacology of the drug, it's related to levels in the circulation. So I'm really not terribly concerned about the bleeding risk.

I agree with everybody else around the table, there may be a cardiovascular risk, and I have two questions about that. One is: were those events adjudicated, the MIs? I don't remember if we asked that question.

DR. SHETH: The events in the SPORTIF trials, SPORTIF III and V, and the events in the ESTEEM trial were pre-specified and adjudicated, and the SPORTIF trials did not demonstrate a difference with that comparitor, and you know the results of the ESTEEM.

DR. HIATT: Yes.

DR. TEERLINK: Thanks for clarifying that. I think that was a point that if we really want to believe that there's a cardiovascular signal, I would really want to have some hard data, so I'm not yet fully convinced that there is.

I think the other challenge that we brought up earlier, if there is such an increased risk, to try to quantify that might be a difficult thing to do in a population for whom you're not expecting a lot of events. And what I'd ask is not an assessment of the mean event rate difference between drug and placebo, but the 95 percent competence interval, the upper end of that competence interval around that risk. And where would you set that? So I think to say there might be something there leads you to the next question, how would you then go quantify that, and what level of risk would you be willing to accept if in fact it's there?

DR. BORER: Ron?

DR. PORTMAN: I think the bleeding is an issue, particularly in the advanced CKD population, but--and I also would like an answer to my question related to the CKD stage and the cardiovascular complications. I am concerned about that, but I would agree with you that it's not really a showstopper. I think it's an opportunity. If we

can figure out the mechanism of why this seems to be happening, it would be really fascinating, and perhaps come up with ways to manage that.

DR. BORER: Do you want an answer now to the question you raised?

DR. PORTMAN: If she has it.

DR. SHETH: Yes. We did manage to--

DR. BORER: Just a quickie.

DR. SHETH: Okay. 0-50, please. I'm sorry, I don't have my screen in front of me. Here we go. Calculated creatinine clearance on the right-hand side, normal renal function, mild renal impairment, moderate and severe, and whether or not patients had an MI, yes or no. Ximelagatran, warfarin, placebo.

And you see that for patients without renal impairment the incidence is about 40 percent across, 44, 37 and 40. For patients in the mild renal impairment group it's 39 for ximelagatran, 37.5 for warfarin and 43.8 for placebo.

Then if we take a look at moderate, it's 11 percent for ximelagatran, 25 percent for

warfarin and 15 percent for placebo. And in the severe group the numbers are too small.

DR. BORER: What are those numbers in parentheses?

DR. SHETH: The numbers in parentheses, I believe, are the percent.

DR. BORER: Percent of what?

DR. SHETH: But what I don't have--I'm sorry. Just understand that this is not the percent over the total population. This is the percent of patients who had normal renal function and had an MI, so the denominator is not the 6931. It's the percent of the column total. Sorry. Thank you.

DR. BORER: Okay. Ron?

DR. PORTMAN: That's not what I would have expected, but that's interesting. Thank you.

DR. BORER: Tom?

DR. PICKERING: One thing about the bleeding of concern is the absence of any antidote. You can't give these patients vitamin K if they come in with a massive bleed. I guess you just

have to wait and hope.

With regard to the MI, I'm not that concerned. The numbers were small. It was in EXULT A but not really in EXULT B, and I was reassured by the ESTEEM and SPORTIF data. So I think there may be something there, but it's not something that would really have much influence on my overall decision.

DR. BORER: Dr. Vega?

[No response.]

DR. BORER: We've now finished Section I. We have not all that much time, so I'll ask to give shorter answers, and I am the most egregious non-doer of that, so I will shorten my answers too.

Short-term use. Now we're talking about benefit risk, specifically short-term use, prevention of VTE in patients undergoing elective total knee replacement surgery.

No. 1. Do you recommend additional safety studies with longer follow-up to address the possibility of delayed occurrence of liver toxicity following short-term use?

Steve?

DR. NISSEN: Briefly, I'd like to see exposure up to, say, 30 days, with another three months of follow-up because I think that that kind of duration creep is likely to occur in clinical practice, and so we would need to know exactly what happens if you get 30 days of exposure over the next, say, three months thereafter.

DR. BORER: Okay. Alan?

DR. HIRSCH: Agreed.

DR. BORER: Tom?

DR. FLEMING: Agreed.

DR. SJOGREN: Agreed.

DR. : Agreed.

DR. BORER: Me too.

DR. CUNNINGHAM: Me too.

DR. SACKNER-BERNSTEIN: Agreed, but I would urge that if the comparitor is warfarin, that actually the starting doses are according to the ACCP guidelines of perioperative treatment, starting at 5 to 10 milligrams instead of 2-1/2 as were done in this study.

DR. LORELL: I agree.

DR. HIATT: I do too, and if I had that information, that would resolve my major concern about approvability for that indication.

DR. BORER: Ron?

DR. PORTMAN: I agree.

DR. PICKERING: Yeah.

DR. BORER: No. 6. Regarding the potential risk of myocardial infarction/coronary artery disease with short-term exposure ximelagatran (mean 8 days) in patients undergoing total knee replacement, do you recommend further studies to assess the risk of acute MI/CAD? If yes, what type of studies do you recommend?

I think Bill discussed this already. Do you have sufficient information from our comments about that question, or do you want us to go through that again?

DR. KORVICK: I think it might be helpful to vote, and then if there's a specific design that you wanted to vote on, to just make it crisp, because the discussion was long. I think just

crisp it up.

DR. BORER: Okay. Steve, can you crisp it up?

DR. NISSEN: Very crisply. Again, I'll suggest a design, which is because there's a statistically significant p-value in this short-term population, I can't make this go away without additional data. Therefore, I would suggest studying patients that are at high risk, patients that have had a prior MI or have known vascular disease, that is, arterial vascular disease, and try to confirm or refute, and adjudicate the events carefully. That doesn't have to be a huge population because the higher risk group that you study is going to have a higher event rate and therefore is going to accrue more events. But I think you can target a high-risk population and answer the question in this surgical group.

DR. BORER: Does anyone have any other opinions besides what we heard? Jonathan and then Beverly.

DR. SACKNER-BERNSTEIN: As I said before, I think that it is possible that the risk of infarction is related to the fact that these patients are untreated, and as Beverly said before, have a pro-inflammatory state in surgery. I would argue that the trial should be one in patients who appear to be low risk, who are not on cardiovascular medicines, because that's the only way you're going to address the signal that we see so far.

DR. BORER: Beverly?

DR. LORELL: I disagree. I don't feel that there is an indication for another study with short-term exposure. I do feel there is a need in education after approval and in labeling to remind physicians to use aspirin appropriately, as current guidelines indicate.

DR. BORER: Any other opinions? Alan?

DR. HIRSCH: I'll try to be creative. I believe like Steve the signal requires some additional data, but it is very challenging to design and offer a design that's practical. This

is a tantalizing molecule that looks like it should have therapeutic use. I'd like to define the population which is clearly safe. The average 25-year-old or the 35-year-old at low risk, that has a very low risk of MI, would be tantalizing to use this medication, and so I would do a pre hoc risk assessment before the orthopedic procedure and define risk by pre *hoc parameters, Framingham parameters, whatever you'd like.

DR. BORER: Yes, Norman?

DR. STOCKBRIDGE: Quick question for Steve. Do you have any idea what dose you'd want to use in this new trial?

DR. NISSEN: I assume we would just test the 36-milligram dose because isn't that the dose that's being requested here?

DR. STOCKBRIDGE: You have some sense that that was a sensible thing for them to do?

DR. NISSEN: Yes. I mean I don't--maybe I missed something.

DR. STOCKBRIDGE: Are you in fact trying to confirm a phenomenon or are you trying to figure

out how to minimize the effect?

DR. NISSEN: Oh, I see. Well, first of all--

DR. STOCKBRIDGE: Haven't had a maximized benefit.

DR. NISSEN: I understand what you're saying. I see a signal which is a statistically significant excess of events that may be a false signal, and therefore, I am looking for a study that will confirm or refute that the doses used in the short-term trial will result in excess short-term cardiovascular risk.

DR. STOCKBRIDGE: So if you get a yes/no answer, you're still not going to know what to do about it without studying dose.

DR. NISSEN: You will not know what to do about it, but I guess I think the risk is high enough that we're getting a false signal here, that there really isn't any increased risk; that I am looking for a confirmatory study that would indicate that there is, because if we could make that excess risk go away, it would increase my

comfort level with the approvability for the short-term indication.

DR. BORER: I'll add just one point here, and that is that I don't know that it's an appropriate use of resources to do another study in people for 8 days. I think that Steve's earlier point is the important one. We're concerned really not about 8 days but about the protracted use that will probably be the model in clinical practice. So I would want to see the study that you suggested earlier, which I think would provide information about whether these unexpected results are repeated in a post operative population or not, and I'd probably use the dose that the sponsor has suggested is effective.

There are questions that can't be answered if we use that design, but my intuition is that that will provide us with the most information and the key information that we need to be able to know about the most important risk which is liver toxicity if the drug is used in a more prolonged regimen.

DR. HOUN: And that 30-day study, you're saying you're recommending it pre-approval?

DR. NISSEN: I am. I would not be comfortable without additional data.

DR. HIATT: Could I comment on that? I'm sorry. Go ahead.

DR. AVIGAN: I was just going to ask another study design question, which is, remember the comparitor was warfarin in the 8-day study. Would you, in the safety study, as for a basis of comparison want to look again at warfarin for the longer duration, or what would be the comparitor, and how would you construct the trial?

DR. BORER: I'll take a stab at that, and then people can disagree. I think that warfarin is a reasonable comparitor because it's used commonly clinically. I don't believe that the statements we heard or read about the comparison being unfair are really germane. This is a recommended treatment by a consensus panel, even though it's not an approved indication. It is used clinically. Such a study would provide us with a great deal of information,

and the fact that warfarin doesn't get you to your therapeutic level so fast is a problem. It's a problem in the use of warfarin. So in fact, that comparison provides us with useful information. If the sponsor chose to use low-molecular weight heparin followed by warfarin, that would be fine too, but I wouldn't find it unacceptable to look at warfarin alone.

Bill?

DR. HIATT: This is analogous to the discussion on cilostazol several years ago, where a drug is being approved for symptomatic indications that may or may not be a signal of excess mortality, but the event rates were very low.

I think what has to happen here is you have to look at this putative MI risk, look at the confidence interval around the difference between drug and warfarin, and then look at the--which has got to be large now, and then ask the question: how many patients do you need to shrink that confidence interval so the upper limit end of the confidence interval is below some threshold. What

risk are you willing to accept if it's real, 25 percent, 50 percent? I mean I think you have to get rather specific about how to address this question, because then it would be simply a number of patients needed to study to look at the confidence interval around any putative risk in this particular area. So I would just play with those numbers and set that up.

Now, the question is, do you want to do that before or after approval? It depends on your experience in that area.

DR. BORER: Which brings us really to the next question. I'm sorry? Okay. I thought I could get away with that.

[Laughter.]

DR. BORER: Okay. Tom, yes or no on Number 6? Do you recommend further studies to assess risk of acute MI/CAD? If yes, what?

DR. PICKERING: No.

DR. BORER: Ron?

DR. PORTMAN: Yes, the same as in No. 5.

DR. BORER: Bill?

DR. HIATT: Yes.

DR. BORER: Beverly? Actually, you already gave your opinion. And so did you, Jon.

DR. LORELL: I do, however, advocate doing the study for roughly 30 days to understand the liver issue.

DR. BORER: Jonathan, you already voted. Susanna? Oh, you did? Sorry.

DR. CUNNINGHAM: No. It would be yes if I did.

DR. BORER: It would be yes. John?

DR. TEERLINK: Yes, with moderate risk cardiovascular patients followed for at least 30 days of treatment and followed for three months at least.

DR. SJOGREN: No.

DR. FLEMING: Yes.

DR. HIRSCH: Yes.

DR. BORER: I said yes, but the 30-day study.

Based on the currently available data, do you conclude that the benefits of ximelagatran for

short-term use for prevention of VTE in patients undergoing elective total knee replacement surgery outweigh its risk? So this is the sort of approvability question, and the question about whether the study we're all talking about needs to be done pre-approval or post-approval can be inferred from the answer to this.

Why don't we start at that end of the table? Tom?

DR. PICKERING: I would say no to this one on the grounds that it was marginally better than warfarin for the venography endpoints, but I think the optimal standard of care would be low molecular weight heparin which has not been compared against, and there was no suggestion that the major events like PE and MIs were reduced.

DR. BORER: Ron?

DR. PORTMAN: Based on my answers on 5 and 6, I would have to say no.

DR. BORER: Bill?

DR. HIATT: Technically no at this point, but I think I said earlier, if that safety data

were available, I think they proved their primary endpoint, the validity of that, but it's a positive study. So if the safety issue can be resolved, then I would vote for approval.

DR. BORER: Beverly?

DR. LORELL: That's precisely my answer as well.

DR. BORER: Jonathan?

DR. SACKNER-BERNSTEIN: I would also vote no because the risk really hasn't been defined adequately to establish a risk/benefit ratio.

DR. BORER: Susanna?

DR. CUNNINGHAM: I agree, and I don't think the benefit's large enough.

DR. NISSEN: I'm sorry, but I'm answering a little bit longer here.

DR. BORER: You're allowed. You're the Committee reviewer.

DR. NISSEN: I know. This is a little tougher question. I want to make sure I get on the record why I'm voting the way I am. First of all, in terms of benefit what we have actually is excess

risk for the heart events. If you take the composite of the things that you really care about, death, pulmonary embolus and MI, there are more events in the ximelagatran arm than the comparitor arms in the short-term studies. So the proof of benefit for the things that really are the most important is simply not there, it goes the wrong way.

Secondly, we really don't know what happens if you give this drug for longer, and I have to believe that it's going to be given for at least up to 30 days after an event like this. So now we have the added problem of not really knowing what the risk is of a 30-day exposure over the next three months.

Third point. Warfarin is not burdensome for 30-day administration. We've got a drug out there--I mean I heard all the arguments about the guy in Montana, but, you know, they're much more applicable to somebody who's on it for years than somebody who's on it for 30 days. It's not a big deal to take warfarin for 30 days, and so I don't

think we have a deficit in clinically available alternatives, and that's why we need to be more secure in our information about what's going to happen when this agent gets out there.

I'm very worried about the duration creep, and I'm very worried that if we let the genie out of the bottle for this very limited indication, it would be very hard to put it back in again. So before I'm willing to let the genie out of the bottle, I want to make sure I know what the liver risk is in a 30-day exposure, and without knowing that, I can't be comfortable with the agent.

DR. BORER: I agree with Steve. It's important for me to say that my intuition is that this drug is useful for short-term use and probably for long-term use if we could deal with the toxicity issue a little bit better, but I am concerned that I'm basing that intuitive judgment on my belief about pathophysiology and my inferences about what the natural history would be on that basis rather than on a consistent result with heart events and pseudo surrogates.

So I'm a little concerned about that. I would like to know more about the safety with the 30-day business, and therefore I don't--although I think ultimately this drug should be approvable for the indication, I don't think we have sufficient information right at this moment to allow that to happen.

John?

DR. TEERLINK: Jeff, you skipped Paul again.

DR. BORER: I'm sorry. Paul?

DR. WATKINS: No, no, I have nothing to say.

DR. TEERLINK: I share your enthusiasm for the medicine, and hope that it will someday be able to be used for many of these indications, although now I can't say that it would be appropriate for this indication for two reasons: because I'm not convinced of the endpoint in terms of how it played out with being a surrogate, and secondly, the risk I don't think it well enough defined at this time.

DR. SJOGREN: I agree. My answer is no.

DR. FLEMING: I would like to give some very brief specifics to justify my answer. I think Jonathan Halperin's discussion of saying in the Indication 2 that we should focus on what does the data show in the aggregate on the primary endpoints, major bleeds and death. He didn't actually do that, although I did for this knee replacement surgery indication. If you start at deaths it's 10/4 in the wrong direction. If you're adding PEs and MIs now you're capturing what I would consider to be the most significant major events; it's 31/14 in the wrong direction. If we add, as he did, major bleeds, 2 of which were fatal, it's 49/24 in the wrong direction. We're still at a doubling of the rate. If we move on and add symptomatic DVT, it's still 68/49 in the wrong direction with a 40 percent excess. If we move on, guided by Tom Pickering's summary of the stated guidelines that some would at least include asymptomatic proximal DVT and we add those in, it's still in the wrong direction. It's 111/105. What's left is the asymptomatic distal DVT, and in

my view that's at best a non-validated surrogate.

So as we look through what are really the most significant events, they're in the wrong direction, and even including everything other than asymptomatic distal DVT, there's still not even a positive relationship. So I think guided by Dr. Halperin's way of looking at this, I think it is in fact not established to be favorable benefit to risk in this setting.

DR. BORER: Alan?

DR. HIRSCH: It's hard to follow Tom.

I would say no, at the current time I don't have adequate data yet to be confident that risk is worth the benefit. But I would like to say I think there is a potential role for this as a therapeutic molecule in this indication and we're here to opine. I think we haven't probably the adequate data to know whether this putative surrogate marker of thrombosis in the infrapopliteal segment really is asymptomatic, and I suspect, with a well-designed trial, one might conceive of an outcome where the signal of adverse

events is less than we anticipate and the relative therapeutic symptomatic benefit might be measurable. So the answer is no now; more data needed.

DR. BORER: Now we go on to the long-term use. Again, I think that we've heard a great deal here, but for the record we'll go around the table. Based on currently available data, do the benefits of ximelagatran for secondary prevention of VTE for 18 months after six months of standard treatment for an episode of acute VTE outweigh the risks for this indication?

We discussed the risks, but now we have to give a specific answer about the weighting of the benefits and risks.

Steve?

DR. NISSEN: This gets much tougher for me, and let me say what I think hopefully will not be viewed as excessively harsh, but if you have an agent that has serious risks of toxicity that are fatal toxicity like liver failure in a range that's similar to what we've seen in drugs that had to be

withdrawn from the market, then you're going to have to show superiority over existing therapies. And so for any of the long-term indications--I've thought about this very hard in the last couple of weeks--I'm convinced that to overcome the current burdens of the liver failure problem we need to see unequivocal superiority on outcomes of importance, that equivalence is not equivalent when you have a 1 in 2,000 potential risk of fatal liver injury. And so I obviously think we're not there yet.

DR. BORER: Tom?

DR. FLEMING: You're answering Question No. 8? So Question No. 8 relating to the long-term use?

DR. NISSEN: Yes.

DR. FLEMING: You just threw me with your statement about the equivalence, so I wasn't quite following that.

DR. NISSEN: Let me actually clarify that just--

DR. FLEMING: Which is an issue of No. 10.

DR. NISSEN: Let me just clarify why.

Because we have data for 8 which is superiority data over placebo, and I answered it the way I did deliberately, because basically to make 8 approvable I would want to see superiority over another anticoagulant therapy, even for 8 where we have placebo data. That was why I answered that way.

DR. FLEMING: This too for me is the hardest question, and I will articulate later the pros and cons as I'm looking at them, but I'd surely, in this case, like to hear my clinical colleagues' judgments about those first if you don't mind coming back to me?

DR. BORER: Alan?

DR. HIRSCH: I'll simply echo more or less what Steve said. We need an active comparitor and superiority. The trial design, when it was created, was appropriate. Currently need a different comparitor.

DR. SJOGREN: I agree. I don't think we're there yet.

DR. BORER: John?

DR. TEERLINK: I think the study is very impressive for demonstrating that we should anticoagulate patients long term. Now the question is what agent should we use? That's why it's no for now, but perhaps yes later.

DR. BORER: I don't think that we have data sufficient for approval for this indication now because the risk is of concern and it's not well defined, and we don't know yet whether we have an algorithm that might acceptably minimize the risk to patients who get the drug. So I'm concerned about that.

I can't agree that the bar has to be set at superiority in efficacy to Coumadin because Coumadin has problems too. But before I could wholeheartedly favor approval, which I cannot now for this indication, I would like to see minimization of risk to a greater extent than we've seen, as well as the kind of efficacy that we've seen because I think as John just said, this represents a practice pattern that isn't now generally followed, and these data suggest that it

should be.

Paul, do you have any? No. Steve?

Steve, you spoke already.

Susanna?

DR. CUNNINGHAM: I don't think I have much to add except I don't think the public is ready to accept liver failure. Livers are hard to come by, and it's really not a complication they would be enthusiastic about.

DR. BORER: Jonathan?

DR. SACKNER-BERNSTEIN: I'm convinced that it was better than placebo. I'm also convinced that the study was not designed in keeping with the consensus guidelines that exist that recommend, at least in the year 2001 when they were published, that these patients probably were treated with Coumadin for two brief a period of time before they were enrolled in the trial, and therefore, in a study design they were studying a scenario that really is not relevant to best practices. These patients probably, as best I can tell from the guidelines and their characteristics, should have

been treated with Coumadin for at least a year in most or at least a lot of cases before being then randomized to a new agent or placebo. So I would say no, there's not sufficient data.

DR. LORELL: This was also a very tough one for me. I thought this study was very powerful in demonstrating the benefit of secondary prophylactic therapy in this group compared with what is certainly the general practice of not treating, at least in the United States. I also agree that with the issue of the specter of very severe and fulminant liver toxicity, although it is rare in absolute terms, it's disastrous if it occurs to a single patient and their family. I would like to see a comparitor study against Coumadin, applying the algorithm, the revised algorithm as if it were being used in a larger population. I'd like to see some evidence that whatever algorithm is proposed, which will look different, I'm sure, than what we've so far, some signal that it might be working.

DR. BORER: Bill?

DR. HIATT: I would vote no. And I think the arguments are very well articulated and I can't add anything to them.

DR. BORER: Ron?

DR. PORTMAN: I think Coumadin is a problematic drug, and I think this one has lots of potential advantages, but I would like to see a study where the company uses whatever algorithm they're going to come up with, and see what it can do to reduce the liver toxicity.

DR. BORER: Tom?

DR. PICKERING: Just to be different, I would vote yes. There was substantially less pulmonary emboli in the patients who were treated, and it's all very well to say that these patients should be given Coumadin, but in reality they're not. And there was no excess of bleeds. And I guess I'm rating the liver toxicity issue slightly lower than some of the others.

DR. BORER: Now we go on to the final--I'm sorry? Did you want to say something? Oh, yes, I'm sorry.

DR. FLEMING: Actually, I would have been comfortable skipping me here on this one, which is uncommon for me, but I really have difficulty with this.

I try to look at things quantitatively, and the major things that I'm seeing are evidence per 200 patients of about 6 or 7 prevented pulmonary embolism as a significant positive effect, and against that is, per 200 patients, what seems to be by our best estimate, one additional MI and one additional severe liver injury. And I have trouble balancing those pros and those cons.

I'll abstain.

DR. BORER: That's okay, because we're going to No. 9 and you're number one.

Is the non-inferiority margin of 2 percent compared to warfarin adequate to ensure that ximelagatran is non-inferior to warfarin with respect to efficacy? If no, what should the non-inferiority margin be for the indication of prevention of stroke and systemic embolic events in patients with atrial fibrillation?

DR. FLEMING: Well, these are complex issues, and I'd like to begin by thanking Lloyd Fisher, John Lawrence and others for some very thoughtful analyses on what is intrinsically a really difficult issue to handle in a most informed and unbiased way.

So beginning with the first part of the answer to Question No. 9, I definitely concur with the sponsor that a non-inferiority design is proper here in this setting. I think they did the right trial in the context of a non-inferiority study being done.

The 2 percent margin that was put forward was, in essence, based on an expected background rate of 3.1 percent for warfarin, for its event rate, and there was, inappropriately, when that was proposed, no adjustment for several factors. The first is the constancy assumption, critical factor. I'll come back to that. The second is they didn't adjust for the fact that their estimate of efficacy of warfarin itself was variable and not precisely known. They didn't adjust for the need to preserve

a fraction of the warfarin effect, such as half of the warfarin effect.

And, of course, this part they didn't know in advance, that the actual rate wasn't going to be in the neighborhood of 3.1 percent, it was going to be 1.16 percent. And that's certainly very significant. If you could justify an absolute increase of 2 percent and the baseline rate was 3.1 on warfarin, that would be a relative 67 percent increase. That, to me, is pretty substantial. And whether that is in fact too liberal a margin we could debate, but I don't think it's debatable that it's way too liberal a margin when the background rate is 1 percent, because now going from 1 to 3 is a relative 200 percent increase.

Just to give you a sense about why I think it's unjustifiable to have used such a margin, the actual data they had in SPORTIF V said there were excess events, 51 against 37. If there actually had been 2-1/2 percent versus 1.16, rather than a 1.61 against 1.16, it had been 2-1/2 against 1.16, that's 79 events against 37. If these data had

shown primary endpoints in excess, 79 against 37, you still would have satisfied the 2 percent margin. Is that clinically relevant? I struggle thinking that patients wouldn't care if warfarin would have had 37 strokes and Exanta would have had 79, and we still wouldn't have been calling that clinically relevant.

By the way, if we look at it as a relative risk, that relative risk would have been statistically significantly increased with a Z statistic of 4, and yet it would have satisfied their margin. So the 2 percent margin absolute, absolutely doesn't in fact make clinical relevant sense or statistical sense in the context of now applying it in the setting where you're going to have a very much lower rate of events in the active comparitor arm than what you were anticipating in the trial design.

In fact, just to close, in that example I gave, the actual data would have been consistent with a relative risk on warfarin against Exanta of .32, which would have been bigger--actually, that's

consistent with what placebo would have been, and yet you would have satisfied that margin.

So what is in fact an appropriate--the second part of the question--what would be a proper non-inferiority margin? Let me start by answering this by essentially saying, what are the factors that have to guide the choice of the non-inferiority margin? The first is it has to be a difference what you can allow that you would say is in fact not a clinically important or clinically relevant difference, i.e., we're willing to have a somewhat lesser efficacy here of Exanta than warfarin to a level that patients would consider to be an acceptable level of loss of efficacy. Of course, what motivates a more flexible approach there is when you have a much safer intervention, much more convenient to apply or more cost effective. Those are the factors that would influence that decision.

There are also many other factors. One of them is this constancy assumption that I referred to, and I want to talk a bit more about that right

now. When you are, as Dr. Fisher pointed out earlier on, when you're making an assessment of efficacy in a non-inferiority trial and you're looking at the efficacy against placebo, there are really two things that you're looking at. You're looking at the efficacy of Exanta against warfarin and warfarin against placebo, and the latter comes from historical evidence. And they provided six trials.

The question is: is the estimate of efficacy of warfarin in those six trials a reliable estimate of what the efficacy of warfarin is in the Exanta trial? That's the constancy assumption. Well, why wouldn't it be?

There are several reasons why it might not be. Were the populations the same in those six trials as in the SPORTIF trial? Was supportive care the same in those trials? In fact, if supportive care in a U.S. setting in the SPORTIF V trial was more enhanced, you could readily expect that the additive effect of warfarin to that supportive care could be less.

What about issues of how the outcome was assessed? All of these are things that influence the validity of the constancy assumption. One thing that makes me worry a lot about the validity is if you look at the statistical analysis that was provided by the FDA in Table 1 on page 7, the listing of the event rates in the warfarin arm in the six historical trials reflect much higher rates of events than in the SPORTIF V trial. It certainly is a smoking gun for suggesting that the validity of the constancy assumption is at best uncertain.

There are other issues as well when you do a non-inferiority trial. You have to make sure that the active comparitor was delivered in a way that maximized its efficacy, because the best way to look equal to something that's an active comparitor is to deliver the active comparitor in a way that's not particularly optimally delivered. I suspect that probably isn't a key issue in this case.

And then there's the issue of blinded

assessments. What was also apparent in this FDA review is not only was the SPORTIF V trial showing a lesser effect as the blinded trial, but in the six warfarin trials, where two were blinded, those two also showed lesser effects. So that adds, obviously, some additional complexity.

A second issue that you have to consider when you define them--or a third, I guess, because the first was clinical relevance and the second was a validity of the constancy assumption, is you've got to take into account the uncertainty or the variability in the estimate of the active comparitor's effect, and you have to take into account how variable were those estimates of efficacy across trials?

Next issue is the issue of blinding, and how in fact do we think that influences our overall estimates is something we have to take into account.

And finally, I think--and it actually emerged from this Committee many years ago--there is a sense or a standard that if you're going to

replace a standard therapy, it's not enough just to be better than placebo. You really in fact need to be preserving a substantial fraction, at least, and I think what's emerged is, 50 percent of the effect. You need to be preserving that.

So with those as criteria, where do we go? What do we do? The analysis that the briefing document for the sponsor provides, as well as in their slide CE 35, basically said let's estimate the efficacy, and they called it a "paper placebo." Let's estimate the efficacy of Exanta here by saying there's two pieces here. We know the relative risk, even though it's unfavorable, is 1.39 when you look at Exanta against warfarin, but warfarin is so good its relative efficacy is .36. If we take the product of those two pieces we should be getting a paper estimate of what the efficacy is of Exanta against placebo, and that's .5, and that comes out to be a very positive impression for a result.

There are important strengths to that analysis. First of all, it's based on relative

risks instead of absolute differences, and in this setting I think that's a more robust way to analyze the data. It also is taking into account the variability in the estimate of warfarin's effect.

But there are several issues that are not taken into account in that analysis. The first of them is it's not taking into account the level of variability that's occurring in these estimated effects across the six warfarin trials. The FDA, in attempting to address that, used a random effects model to address that issue. It doesn't take into account the uncertainties generated by the fact that four of the six trials weren't blinded when you're estimating warfarin's effect. Importantly, it doesn't take into account two other things. It doesn't make any accommodation for the uncertainty about the validity of the constancy assumption, and it also doesn't address the fact that we have to preserve half of warfarin's effects. So while those analyses looked impressive at the beginning, there are several critical issues that aren't addressed.

In essence, what is a proper approach? Steve talked about dose creep and duration creep, so I'll talk about bio-creep.

[Laughter.]

DR. FLEMING: A common term that is used in the non-inferiority setting is bio-creep. What's bio-creep all about? Well, suppose I have a standard intervention whose efficacy is reasonably well understood. Now I go to generation two and I show I'm not meaningfully worse than generation one with non-inferiority. But let's suppose I'm liberal, like I use a big margin, so my estimate actually is I am somewhat worse by estimate. Well, Sponsor 3 comes along with a new product. Which one are they going to use for non-inferiority? I think I'll probably choose the second generation one, and let's do non-inferiority again with a fairly lenient margin. Two or three generations of this, and what do we really know about efficacy any more? That's bio-creep.

In essence, to address bio-creep, one has to have rigorous margins, as the ICH guidelines

clearly indicate. In my words, it's treacherous when you're implementing a strategy that can declare non-inferiority when your actual point estimate of the relative efficacy of the experimental with the active control actually favors the active control. If you have such a lenient margin that you can be estimated to be worse, and yet you're still satisfying non-inferiority, you're setting yourself up for a setting of bio-creep.

In essence, the FDA I thought did a marvelous job. In fact, my kudos to John Lawrence and colleagues for really nailing down all of these issues.

On page 9 they define several possible margins that could be used to try to address these issues, and the first point I would argue is the margins based on the risk ratio or relative risk I think are in fact the most appropriate to be used in this setting. These particular approaches that are defined here not only use the relative risk at the bottom half of this table, but appropriately

adjust for the variability in the estimate of the active comparitor's effect. They also adjust for needing to preserve half of the efficacy. And they also, by using the random effects model, adjust it for the variability.

But they gave you several choices, and those several choices are based on two additional factors. Essentially the more liberal choices say the margin could be in the neighborhood of 1.56 to 1.65, meaning that you would satisfy non-inferiority if in a relative risk sense your point estimate was sufficiently favorable that you could rule out you had a 65 percent increase or excess in the rate of stroke. By the way, from a clinical relevance perspective, how could you have a margin bigger than that? I would struggle with justifying from a patient's perspective that it's okay to have stroke rates be more than 65 percent higher. I even struggle with whether that in fact is sufficiently rigorous.

The key point here is that those two estimates, 1.56 and 1.65, they're called the

Holmgren approach. A variation of this is the Rothman approach. We see these used at other advisory committees. These methods do not make any accommodation for the validity of the constancy assumption. So basically you better be darn confident that the estimate of the efficacy of warfarin in those six trials is precisely accurate for what the efficacy of warfarin is in the SPORTIF trials even though there could be different populations, different assessment, and different supportive care.

Generally I have great concerns about that, especially when you show me the event rates. The event rates in warfarin are much higher in those six trials than in the SPORTIF V trial. So I would far prefer the approaches that are used that are called the 95/95 that adjust for the uncertainty about the constancy assumption, and those are margins in the neighborhood of 1.23 to 1.38.

My last point is they differ only by whether you really would include all of the trials,

and this is an issue that's always a struggle. Which of those six trials are relevant to the context in which the SPORTIF V trial was done? Maybe none of them fully, but some of them more so than others. The one that in particular looks to be problematic is the EAFT trial that was done in patients where you had recent TIAs and strokes and you have very high event rates. So if you drop those out your margin would be 1.23 rather than 1.38.

But if you actually take the approach that I only believe the placebo-control trials, then your margin is 1. What does that mean, your margin is 1? It means you actually have to show superiority. Unless you show superiority, you haven't adequately established efficacy.

In closing, where am I on this? My sense is I am not sure about whether we can include all six or only have to look at the two that are the placebo-control trials. My sense of the margin should be based on the relative risk estimate here, and the proper margin is somewhere between 1 on the

conservative side, meaning you have to show superiority, up to about 1.4. Something in that range seems to be aggressive but potentially justifiable factoring all of these issues.

DR. BORER: Let me ask you one additional question, Tom. I'm inferring from what you said specifically that the Rothman approach that Lloyd showed us, that suggests that you are likely to have preserved at least 71 percent of the warfarin effect really is not something that you would accept as a valid analysis here because of all the things you said?

DR. FLEMING: Well, it's a variation of analyses that are shown in the briefing document. It has one plus that I liked, i.e., what he was showing today relative to what was in the briefing documents. I think was a step in the right direction of actually addressing needing to preserve half of the effect. So that analysis was getting into that, whereas the analyses that the sponsor provided in the briefing document didn't.

But what that analysis still didn't do is

it still didn't address the variability that existed among these six comparitor trials for efficacy. It didn't address the issue of do we trust all six of those given that only two of them are blinded trials. It didn't address, really importantly from my perspective, there's no adjustment made for the constancy assumption. So if you're going to trust that estimate you've got to be thinking those estimated effects of warfarin in those six trials are exactly what warfarin is going to do in the SPORTIF V trial in spite of the fact that the estimate of the efficacy--of the event rate in the warfarin arm in SPORTIF V was only about one-third. And actually, if we go back to Jay Harrow's answer to Steve earlier today about why do III and V differ, his answer was, well, there's a whole lot of differences in these historical control trials of warfarin effect. I'm saying don't play that card too hard because that's the very issue that makes the validity of the constancy assumption.

If you believe that the difference in the

risk level of an event rate on warfarin is going to influence warfarin's efficacy--and I think that's a valid thing to think--then I can't trust these six estimates that come from higher warfarin background rates when I'm projecting the efficacy of warfarin in SPORTIF V. I don't know if I can, but that's an issue of concern.

The last thing that he was doing today--it's statistically valid but I really worry about it--is he was putting together in a clever way the pooling of the data from the two trials, and the analyses that I'm giving are basically--what I've been discussing is looking at the definition of the margin as you assess each of these two trials individually.

So that's some of the differences or issues that weren't addressed in that analysis that concern me, as I would look at--I would favor--I think John Lawrence's analysis was outstanding. I think the analysis--basically, I don't think I've added a nickel to what he already did. I just explained it. I think those analyses lay out the

issues in an excellent way and in my belief you have to address the concerns that he raised in his summary.

DR. BORER: Can I ask, do you want us actually to vote on this issue or can we just go on to the next question?

[Laughter.]

DR. PICKERING: Could I ask a question?

DR. BORER: Yes, Tom.

DR. PICKERING: My understanding is that the analyses basically ignored SPORTIF III and said let's just focus on SPORTIF V. So my question is, if you included SPORTIF III how much does this change these errors of margin, because obviously it went in a different direction?

DR. FLEMING: I was sticking to Question 9, which basically just said, formulate the margin of what would be an appropriate margin in this setting. Question 10 gets into part of what you're talking about in my view, which is, all right, with this as a background, how do we assess the strength of evidence in SPORTIF III and SPORTIF V? So I was

going to get into that when I got to Question 10

DR. BORER: Steve?

DR. NISSEN: I just had to make one comment. First of all, that was fabulous, and I always learn a lot from you. But there also is a clinical context, and all of that assumes, it's all oriented around the issue of efficacy, and in deciding on a design for the future, which is really partly what we're talking about, is you can't separate efficacy and safety because the efficacy question has a safety component, namely that if two therapies have equal safety, you did a great job of telling us how to set the margins for non-inferiority for efficacy. But that to me isn't the question that we now face, that the standard would have to be modified for what would constitute adequate evidence of efficacy if we know certain things about adverse safety consequences. I don't know if I'm making sense to you or not, but I think you can't--I think it was an absolutely right on if you had two therapies that were equally safe.

DR. FLEMING: I believe I follow what

you're saying, Steve, and if so, I agree with you, and it was one of the first things that I had mentioned, as I said what are the criteria I would look to in defining a margin? The first criterion that I would look to is: from a clinical perspective, what level of excess risk could be allowable before to a patient this would be an unacceptable level of excess? That should be an important criterion. And that does need a subjective assessment of what are the other elements of the benefit to risk profile that this intervention provides?

If I was looking at thrombolytic and I could get rid of intracranial hemorrhage risk, I might have a little more of a margin I'd allow on mortality in that type of setting. If there is in this setting a judgment that the level of safety profile is substantially enhanced, I can understand a willingness to allow a somewhat larger element to the margin.

So there are two separate domains that really should define the margin. One is a clinical

relevance aspect that is really a rigorous fair assessment of how much worse can this be in the efficacy measure in the context of overall benefit to risk? And the other is very much a statistical issue of what is the scientific evidence that we have to truly allow us to conclude that we are effective when we don't have the luxury of doing a direct comparison in the randomized trial? We're having to rely on the historical data. There are two pieces, and I always say a chain is as strong as its weakest link. The weakest link in most non-inferiority analyses is the uncertainty about the strength and the reliability of the evidence of the active comparitor against the placebo.

DR. BORER: We'll move on to the final question, which is: Based on the currently available data do you conclude that the benefits of ximelagatran for long-term use for prevention of stroke and systemic embolic events in patients with atrial fibrillation outweigh its risk?

Steve, you can go ahead and start.

DR. NISSEN: Again, I'm going to be

short-winded rather than long-winded because I think people want to catch planes.

You know, I think I've made it pretty clear that I think it's no, and--

DR. HOUN: Can I just interrupt and let the two departing members vote on the record?

DR. BORER: They did. They both voted no.

DR. CUNNINGHAM: Susanna Cunningham, no.

DR. HIATT: No. William Hiatt votes no.

DR. NISSEN: And to directly answer Tom's question about where to set that margin if this development program continues, the margin is 1.0. In other words, I'm setting that margin, knowing what I know about safety, that at a very minimum that a future trial would have to show superiority in order to compensate for what I think is a pretty well-defined increase in risk of a very serious toxicity.

DR. BORER: Tom?

DR. PICKERING: I would say yes. Viewing it in the sort of relatively narrow confines of the trials, but looking at the greater population of

patients who currently are not getting any treatment and who have a prospect of getting treated if this drug is approved, I would say the benefits--there are substantial benefits that outweigh the risks.

DR. PORTMAN: No, for the same reasons as the last long-term trial.

DR. BORER: Beverly?

DR. LORELL: No.

DR. SACKNER-BERNSTEIN: I would say no also, realizing that there seems as though there are a number of patients whose long-term status in the SPORTIF trials are unknown because they withdrew from the study, not just withdrew from study medication. So, no.

DR. BORER: Paul, do you have any comment to make? No.

DR. BORER: Okay. I reluctantly vote no, primarily because of the arguments that Tom has made. Like Tom, I believe that there's a place for this drug in this population. I think we need to know more about the risk. We need to define it

better, and we need to be able to minimize it better than we have, just as I said about the other long-term issue. So I agree with Steve about the risk/benefit concern here. But I'm primarily concerned that I'm not secure that we know that we've actually preserved the degree of warfarin-related benefit that we nominally think we did from this study. I'd like some reassurance on that, and we may not get that without another trial.

Having said that, I don't think that we need, as I said earlier in another context, that we need to show superiority. I think there are enough good reasons why an alternative to warfarin would be a good thing so that if we understood the risk and we could minimize it by some reasonable algorithm in a way that would be acceptable to us--and I can't define that here--that equivalence would be sufficient if we could be sure it was equivalent. So I would vote no on that basis.

DR. TEERLINK: I share your reluctance to vote no. I think it's a potentially very useful

therapy in this patient population and would help a great deal of patients who are not being helped at this time. But my concerns about the safety remain unaddressed at this time, as well as the need to show true equivalence to warfarin. I think I'm probably between you two, Steve and Jeff, that I don't know if I'd make it 1.0 and I don't know where I would put that line. It would have to be fairly stringent.

DR. BORER: Dr. Sjogren?

DR. SJOGREN: I agree with you and John, and I vote no.

DR. BORER: Alan?

DR. HIRSCH: The reluctant no again, but with a comment. There is a pressing need for such a therapeutic molecule as you've said, and the goal to decrease both stroke as well as DVT and pulmonary embolus is required with such molecules, but this database for this particular medication doesn't permit me to vote yes quite yet.

The addition of a new molecule doesn't mean that treatment intensity would have increased

for the public health advocates. That's a function of education, guidelines and care management pathways, not drug approval, per se.

DR. BORER: I think we've answered all the questions. Oh, Tom, didn't you vote?

DR. FLEMING: I don't think so, but I'll be brief.

DR. BORER: Sorry.

DR. FLEMING: I will be brief on this. I look at these two pivotal--well, I look at these two studies. I look at V as being the pivotal study and III as being the supportive trial. Largely with the blinding and open label rationale for that, but also the V study done in the U.S. I think is particularly relevant to a U.S. regulatory action.

For the reasons that I discussed, I don't think, in fact, I believe quite clearly that the SPORTIF V trial did not establish efficacy. The SPORTIF III trial, even though it is open label and has that (?)-arity, so to speak, it has a favorable estimate. I'm uncertain that I would require

superiority, but I do believe that I would require nothing more lenient than an upper limit on the order of 1.4 or so. That would, however, be a criterion that the SPORTIF III trial does meet, and so ultimately whether SPORTIF III is viewed as positive is influenced by how important is blinding, the blinding issue in assessment of reliability of results? How important is it that four of the six warfarin trials weren't blinded? And how important is it that the uncertainties about the hepatic toxicity makes, as some have argued, one to want to be much more stringent in terms of how you would look at this.

Ultimately though, it's a strength of evidence issue as well. I want SOE 2, the strength of evidence of two trials, and at best here I'd say we have one. So that's the rationale for my view of no.

DR. BORER: I was off by 26.5 minutes, but I think we've answered all the questions. Thank you very much.

DR. NISSEN: Jeff, can I just say one more

thing unrelated?

You know, this is your last meeting as chair, and I guess I wanted to express, on behalf of a lot of us who have served with you over many years, appreciation for the great leadership and balance you have provided to the Committee, and I think everybody--that all the stakeholders here owe you a debt of gratitude for the fair and evenhanded way you've run this Committee over the years I've certainly been involved. So my thanks.

[Applause.]

DR. BORER: Thank you very much. And we'll close the meeting.

[Whereupon, at 5:28 p.m., the Advisory Committee was adjourned.]

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