FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Cardiovascular and Renal Drugs Advisory Committee

NDA 22-406, rivaroxaben oral tablets

(10 milligrams)

Thursday, March 19, 2009

8:01 a.m.

Marriott Conference Centers

UMUC Inn and Conference Center by Marriott

3501 University Boulevard East

Adelphi, Maryland

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P R O C E E D I N G S

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DR. LINCOFF: In the interest of staying on time for plane rides this afternoon, I think we'll get started. It's 8:00. I'm Michael Lincoff. I'm an interventional cardiologist and director of clinical research at the Cleveland Clinic, and it's my privilege to be the acting chair of today's meeting.

There is a text that I'd like to read to start the meeting.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings; however, the FDA will refrain from discussing the details of the meeting with the media until its conclusion.

Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

I'd like to now go around and ask each of the committee members to introduce themselves and tell us your affiliation and specialty so we understand where you come from. If we could start with Jonathan, Dr. Fox.

DR. FOX: My name is Jonathan Fox. I serve as the industry representative to the committee. I'm a cardiologist in clinical development with AstraZeneca.

DR. PAGANINI: Emil Paganini. I'm a critical care nephrologist out of Cleveland, Ohio.

DR. BLACK: I'm Henry Black at the New York University School of Medicine. I'm a preventive cardiologist and specialist in hypertension.

DR. VENITZ: Jurgen Venitz. I'm a clinical pharmacologist at Virginia Commonwealth University.

DR. SWENSON: Erik Swenson. University of Washington. I'm in the pulmonary and critical care medicine section there.

DR. McGUIRE: Darren McGuire, UT Southwestern, general cardiology.

DR. FOGEL: Ron Fogel, gastroenterologist.

DR. KRENZELOK: I'm Ed Krenzelok. I'm a clinical toxicologist from the University of Pittsburgh in the Pittsburgh Poison Center.

DR. NEATON: Jim Neaton, University of Minnesota, biostatistician.

DR. MAYOR: Michael Mayor, orthopedic surgeon with the Dartmouth

Hitchcock Medical Center in Hanover, New Hampshire.

DR. WOLFE: Sid Wolfe. I'm a general internist. I am with the health research group of Public Citizen.

MS. FERGUSON: Elaine Ferguson. I'm the designated federal official.

DR. GAGE: Brian Gage, associate professor, Washington University, and director of the anticoagulation service.

DR. SKINNER: My name is Harry Skinner. I'm a professor emeritus of orthopedic surgery, bioengineering, mechanical engineering, and I'm in private practice, do hip, knees replacement.

DR. GROSS: Peter Gross, professor, New Jersey Medical School, and chief medical officer at Hackensack University Medical Center. I'm an infectious disease specialist.

DR. KRANTZ: Good morning. My name is Mori Krantz. I am a general cardiologist at University of Colorado.

DR. McCORMICK: I'm Paul McCormick, professor of neurosurgery and Columbia University in New York City.

DR. KAUL: Sanjay Kaul, Cedars-Sinai Heart Institute, Los Angeles, general cardiologist.

MR. DUBBS: Bob Dubbs. I'm a non-scientist, non-physician patient representative and I'm pleased to be here.

DR. TORNOE: Cristoffer Tornoe, clinical pharmacology,

pharmacometrics, FDA.

DR. LU: Min Lu, medical review from division of medical imaging and hematology products.

DR. RIEVES: Hi. I'm Dwaine Rieves, director of the division of medical imaging and hematology products.

DR. DAL PAN: I'm Gerald Dal Pan, the director of the office of surveillance and epidemiology at FDA.

DR. PAZDUR: Richard Pazdur, FDA, office of oncology drug products.

DR. LINCOFF: We now have the conflict of interest statement with Elaine.

MS. FERGUSON: The Food and Drug Administration is convening today's meeting of the Cardiovascular and Renal Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found under 18 USC 208 and 712 of the Federal Food, Drug and Cosmetic Act is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this

committee are in compliance with the federal ethics and conflict of interest laws.

Under 18 USC 208, Congress had authorized FDA to grant waivers to special government employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's service outweighs his or her potential financial conflict of interest.

Under 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular government employees with potential financial conflicts when necessary to afford the committee's essential expertise.

Related to the discussions of today's meetings, the members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 USC 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teachings, speaking, writing, patents and royalties and primary employment.

Today's agenda involves discussions of the new drug application NDA 22-406, rivaroxaben (Xarelto), oral tablets, 10 milligrams, for the proposed indication for prophylaxis of use in deep vein thrombosis and pulmonary embolism in patients undergoing hip replacement surgery or knee replacement

surgery. Rivaroxaben was originally developed by Bayer Healthcare Pharmaceuticals, an affiliate of Bayer A.G. Bayer Healthcare and Ortho-McNeil, Inc., a Johnson & Johnson company, have an agreement to jointly develop and market rivaroxaben.

This issue is a particular matters meeting during which specific matters related to rivaroxaben (Xarelto) will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

With respect to the FDA's invited industry representative, we would like to disclose that Dr. Jonathan Fox is serving as a non-voting industry representative acting on behalf of regulated industry. Dr. Fox's role at this meeting is to represent industry in general and not any one particular company. Dr. Fox is employed by AstraZeneca.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusions will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with any firm at issue.

I would like to, at this time, recognize Karen Riley from the FDA

press office. Karen, can you stand. Thank you.

DR. LINCOFF: All right. So just a brief outline of how the morning and is going to run. We're going to start with brief remarks by Dr. Rieves, the director of the division. We'll then have a 90-minute of various sponsor presentations, and we'll do that without questions or interruptions.

We'll have a 20-minute period after that, before the break, for questions directed at the sponsor, after which the FDA will then have their series of presentations for approximately an hour and 15 minutes, and then we'll have questions for the FDA.

We have what I think will be ample time in the afternoon as well for questions to the sponsor and the FDA, so with -- that we don't get to in the morning. And then we'll conclude the day with direct discussion of the questions that the FDA has posed to us.

With that, I believe that Dr. Rieves has initial remarks.

DR. RIEVES: Good morning. We welcome you to this meeting. We're especially appreciative to the cardio-renal advisory committee because just a few months ago we brought another challenging product to you, a diagnostic product, so we're bringing quite a spectrum of products, so we really appreciate the open-mindedness and diligence, particularly of the standing members of this committee.

Today we're going to talk about rivaroxaben, an oral anticoagulation drug under development in five major settings. Highlighted in yellow here is

the setting for discussion today, use of the drug in the prophylaxis of deep vein thrombosis and pulmonary embolism among patients undergoing hip or knee replacement.

Ongoing studies are assessing the drug in several other indications, including the use in the secondary prevention of DVT and PE as part of the treatment of an index thrombis, the prophylaxis of DVT and PE among hospitalized medically ill patients, the prevention of thrombotic complications in patients with atrial fibrillation, as well as the use of the drug in the treatment of acute coronary syndrome.

The field of oral anticoagulation development has several notable features, as highlighted here. Warfarin, the only currently approved agent, is administered in a dosage regimen that is generally titrated to achieve certain anticoagulant parameters, such as the INR. The drug's anticoagulant effects are specifically reversed by vitamin K administration and, as we all know, warfarin has a broad range of clinical uses.

The second bullet here highlights the experience with ximelagatran, an investigational oral anticoagulant that was discussed at this committee in 2004. The ximelagatran NDA proposed use of the drug for prophylaxis of DVT and PE in the setting of knee replacement surgery, as well as its use among patients with atrial fibrillation.

During that review, the committee and review team noted a number of concerns, but particularly the finding of hepatotoxicity in the atrial

fibrillation studies, a finding that was not readily observed in the shorter duration knee surgery prophylaxis studies.

Ximelagatran was not approved in the United States, but was approved for the knee surgery usage in other countries. Subsequently, the drug was withdrawn from marketing because of further evidence of hepatotoxicity.

In contrast to warfarin, rivaroxaben is proposed for use with no dose titration to achieve any specific level of anticoagulation. The drug has no specific reversal agent for its anticoagulant effects, although procoagulant products may assist in handling bleeding complications.

In our discussions today, we may hear the hip and knee prophylaxis studies referred to as short-term studies, which may help distinguish them from the extended dosing or the long-term studies.

As background to our discussion, I highlight two of the major categories of DVT/PE prophylaxis in hip and knee replacement surgery. Chemoprophylaxis is a term occasionally used to refer to the use of drugs to prevent the thrombotic events, and FDA has approved three drugs specifically for this indication. However, other drugs are also sometimes used in thrombotic prophylaxis.

Mechanical prophylaxis generally refers to the use of certain devices to lessen the risk for thromboses, such as intermittent pneumatic compression or, in very uncommon situations, the use of a vena caval filter, other methodologies.

Practice guidelines variably recommend the use of both chemo and mechanical prophylaxis, depending upon risk factors and feasibility considerations.

Today's discussion is notable in that FDA's preliminary review supports rivaroxaben efficacy based upon a decrease in the occurrence of total venous thromboembolism, or VTE, which is a composite primary end point that includes clinically symptomatic events as well as asymptomatic imaging outcomes.

Today our review team will also provide a few comments regarding exploratory analyses of only the symptomatic VTE events.

The main challenge during the review has predominantly related to safety questions and how the answers to these questions impact the overall risk and benefit considerations. Hence, we're coming to this committee today requesting perspectives regarding three main safety topics which relate to the risks for bleeding with the drug, consideration of whether or not the data provide a signal of severe hepatotoxicity, and finally considerations of the role of the ongoing, the extended dose, the long-term studies' data in the assessment in the risks and benefits associated with the prophylaxis use of the product.

We look forward to a vigorous discussion, and I return the podium to our Chair.

DR. LINCOFF: Thank you. Now we'll move on with the sponsor's

presentation, so -- starting with Dr. DiBattiste.

DR. DiBATTISTE: Good morning. Mr. Chairman, members of the complications, ladies and gentlemen, my name is Peter DiBattiste. I am the cardiovascular therapeutic area head for Johnson & Johnson Pharmaceutical Research and Development. And today it is my privilege to introduce you to rivaroxaben, a novel oral anticoagulant.

Rivaroxaben has been developed to support the following proposed indication. Rivaroxaben is indicated for the prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip replacement surgery or knee replacement surgery.

Rivaroxaben was discovered in the laboratories of Bayer Healthcare and is being codeveloped through a joint research program between Bayer Healthcare and Johnson & Johnson Pharmaceutical Research and Development.

Rivaroxaben is the first oral direct factor 10a inhibitor. Factor 10a catalyzes the conversion of prothrombin to thrombin. Rivaroxaben acts on factor 10a directly; that is, it does not require any cofactors.

As illustrated here, rivaroxaben fits directly into the active site of factor 10a, the site that cleaves prothrombin to thrombin. Rivaroxaben inhibits not only free factor 10a, but also accesses clot-bound factor 10a.

By virtue of where it acts in the coagulation cascade, rivaroxaben inhibits thrombin generation as opposed to blocking the activity of thrombin that is already present.

The rivaroxaben clinical development program is comprehensive. The primary focus of today's discussion will be on the development for VTE prophylaxis after total hip or total knee replacement.

To better characterize the safety profile, we will also share additional longer-term safety data.

The ATLAS ACS phase 1 study, a six-month placebo-controlled study of 3,491 patients, has been completed and unblinded. Over 2200 patients in this study were treated with rivaroxaben. In addition, as Dr. Rieves noted, phase 3 programs are ongoing in the other populations listed here.

These other programs include a mix of short and longer-term treatment studies. Already, there are unblinded safety data for over 4,000 patients who have been exposed to rivaroxaben for three months or longer that contribute significantly to our understanding of rivaroxaben's long-term safety profile.

The schedule for the upcoming presentations is shown here. Two of the presenters, Dr. Richard Friedman and Dr. Paul Watkins, are external experts in orthopedics and hepatology respectively. In addition, other external experts in hepatology, cardiology, clinical pharmacology and risk management are present today and available to address specific questions that may arise.

I'd like to now introduce Dr. Richard Friedman. Dr. Friedman is a practicing orthopedist and clinical professor of surgery at the Medical

University of South Carolina, and will present an overview of the current state of thrombosis prophylaxis in joint replacement surgery.

Dr. Friedman.

DR. FRIEDMAN: Thank you and good morning, and I appreciate the opportunity to speak before you. I am a practicing orthopedic surgeon in Charleston, South Carolina. I've had an interest in thrombosis prophylaxis in total joints for over 20 years. I would like to give you a real-world opinion and perspective in terms of what goes on for prophylaxis in total joints. I wish to note that I'm a consultant for Johnson & Johnson and am compensated for my time.

So the first question to answer is why do we prophylax our patients? First and foremost is to prevent pulmonary death and secondly to prevent non-fatal PE. But in addition to that, there are other acute events we want to prevent, and that's mainly deep vein thrombosis, both proximal and distal.

In addition to those acute events, there are chronic conditions that we also want to prevent long-term. If you develop a symptomatic DVT, your risk of recurrence at one year is 10 percent, and obviously we want to prevent that. At three years, if you've developed a symptomatic DVT, your risk of chronic venous stasis disease and post-thrombotic syndrome is as high as 24 percent. And should you have symptomatic non-fatal PE, you have a high risk of developing chronic pulmonary hypertension down the road as well.

So in addition to the acute events of PE and DVT, there are some

long-term events that we are trying to prophylax our patients for as well.

If we don't prophylax, what is the incidence of DVT and PE in our patients? This is a compilation of control studies and placebo arms over the past 35 or 40 years. For the DVT, these are venographic rates, and for the PE these are symptomatic rates.

You can see in total hip arthroplasty as high as 57 percent. In total knee arthroplasty, DVT will occur in up to 85 percent of patients. The proximal rates are higher in hips than knees, and knee clots tend to be more distal, and you can see fairly significant rates for PE and, in the early studies in the early days, you had death rates up to 2 percent in total hip arthroplasty and 1.7 percent in total knee arthroplasty. So these were patients coming in for elective joint surgery for non-malignant conditions, and 1 to 2 percent were dying of a fatal PE.

In the United States, there are over 300,000 total hip and 500,000 total knee arthroplasties done every year, and this number is rising exponentially as the baby boomers age. The predictions are that by the year 2030, over 1-1/2 million total joint arthroplasties will be performed in this country every year.

Currently, patients are admitted the day of surgery, have their procedure and, on average, go home at 3.1 days after surgery. In fact, at our institution, 27 percent of patients are going home at day two. So it's clear that VTE prophylaxis has now become mainly an outpatient event and an

outpatient issue that we have to deal with.

If you look at comparisons between the United States and the rest of the world with regard to hip and knee arthroplasty, we published two papers in the last two years looking at a large registry of over 15,000 patients. We found that patient demographics were similar between the United States and the rest of the world, with the small exception that United States patients tend to be, as we say, morphologically challenged. They tend to be a little bit heavier.

The surgical procedures, the techniques and outcomes are similar. Whether you look at joint registries or you look at individual studies published in medical journals, the outcomes are very much the same across the board.

There are some variations in length of stay, and those tend to depend more on the socioeconomic conditions in that country and the particular health care system. Some European countries keep their patients in the hospital two weeks regardless of medical need, just because that's the way they're set up and that's the way they are funded.

Low molecular weight heparins tend to be the most commonly used anticoagulants across the world. Aspirin and warfarin are used almost exclusively in the United States and have almost zero use in the rest of the world.

And if you look at VET rates for both DVT and PE, while there are

regional variations even within the United States, and a bit from country to country, overall the rates are fairly similar worldwide.

This graph here demonstrates the cumulative incidence of symptomatic DVT and PE currently. This is our data found from the registry and, in fact, similar data was published by White in the United States back in 1998, and the curves are almost identical. And what you can see is for total hip arthroplasty the symptomatic events rise for about the first month or so, and then they level off around 1-1/2 percent, and for knees the curve is much steeper early on and then it levels out a little bit sooner, closer to 2 percent.

So understand that if your patient is going home on post-operative day three or four down here, the vast majority of symptomatic events that are going to occur are going to occur on an outpatient basis. They're not going to be occurring in the hospital.

So there's clearly a need for out-of-hospital prophylaxis that is safe and efficacious. DVT and PE are the most common and potentially serious complications following total hip or total knee arthroplasty. As studies have shown, compliance with the American College of Chest Physicians, or ACCP, guidelines are less than optimal.

There are drawbacks to currently available agents that limit their use, as we found in our GLORY registry. We know that almost all patients in the U.S. receive at least some form of prophylaxis after surgery. However,

full compliance with the guidelines in terms of type of prophylaxis, the duration, the start time and the dosage was achieved in only 47 percent of total hip patients and 61 percent of total knee patients. And I would suggest to you that orthopedic surgeons tend to do one of the better jobs in terms of prophylaxis compared to our other medical specialties, but I would say we're clearly not doing as well as we could be.

If you break this out for the two most common agents used, both in the U.S. and worldwide, low molecular weight heparin and warfarin, you can see for the low molecular weight heparin the rates were 63 percent for hips, 72 percent for knees -- but these numbers dropped off significantly for warfarin, only 33 percent for hips and 48 percent for total knee arthroplasty.

What agents are available? Well, for oral agents we have warfarin. It's been available about 55 years. And, again, the advantages are that it's an oral agent -- it's a pill -- and, when used correctly with the proper INR range of 2 to 3, it is efficacious. However, there are significant disadvantages to warfarin that limits its use for orthopedic patients.

Patients, when they go home, require twice, and sometimes three times a week blood draws, so generally a home health nurse is coming out to the house to do that. There are food and drug interactions that will either potentiate or inhibit warfarin's effect, so their INR may get bumped up above 3 -- they may be at risk for bleeding -- or it may get knocked down below 2 and then they are not protected against a clot.

There is a variable response. I can give the same doses to five people, look at them on day five and have five different ranges from a low number below 2, some above 3, and some in range.

There is slow onset and slow offset, and that has clinical implications, and certainly if the INR gets too high, there are potential bleeding complications as well.

For the injectable agents, we have the low molecular weight heparins and fondaparinux. Advantages include that these agents are used as a fixed dose. There is no monitoring and also no dose adjustment required. There are not the same types of food and drug interactions that you see with warfarin, and numerous studies in clinical use over the past 20 years have demonstrated these agents to be safe and efficacious.

Disadvantages include the fact that they are injectables and require either the patient, a family member or some other health care professional to provide the injection on a daily basis.

There is also sequential pneumatic compression, or SCDs or IPC, as was mentioned. Advantages include the fact that they have been shown to be somewhat efficacious in knees if worn continuously for 19 hours a day. They clearly have no effect on bleeding and are safe.

Disadvantages include the fact that they have not been shown to have the same efficacy in total hip arthroplasty, they are not efficacious if worn for 13 hours a day or less, they are really restricted to in-hospital use, and

again, if patients are going home on post-op day three, on average, there is not that much of a role.

In addition, we mobilize our patients very rapidly. A lot of times the morning cases and getting up in a chair that afternoon. They are up the next morning at 7:30, 8:00, dressed, eating breakfast and starting to walk. And, clearly, when they're being transferred from bed to chair, getting up and walking, they cannot have these devices on.

So with early physical therapy, rapid mobilization, early discharge, there's limits to pneumatic compression usage today.

So, in summary then, there are important clinical needs that exist in DVT and PE prophylaxis for total hip and total knee arthroplasty. There are symptomatic and asymptomatic events that are clinically important, and there are significant costs associated with the management of patients who develop a DVT or PE compared to the cost for prophylaxis. There are significant inconsistencies that exist between clinical practice and published guidelines. And the deficiencies of existing therapies therefore create the need for new agents with improved efficacy, more convenient dosing and administration, and do not have the requirement for anticoagulation monitoring. Thank you very much.

Now I'd like to introduce Dr. Gary Peters who will give you the clinical rivaroxaben development program. Thank you.

DR. PETERS: Thank you, Dr. Friedman.

It is my privilege to present the rivaroxaben development program results today. Our development program has been extensive. In phase 1, over 50 studies have been conducted with over 1100 participants exposed to rivaroxaben. Our clinical pharmacology data show that rivaroxaben has no food effect with a 10-milligram dose and has predictable pharmacokinetics and pharmacodynamics, with a limited potential for drug-drug interactions. This supports fixed dosing with no need for laboratory monitoring.

Four phase 2 dose finding studies in hip and knee replacement surgery were performed with over 2200 patients on rivaroxaben. The phase 3 RECORD program consisted of four studies, RECORD 1 and 2 after hip replacement, and RECORD 3 and 4 after knee replacement. These studies were conducted globally and randomized almost 13,000 patients with over 6100 assigned to rivaroxaben therapy.

I will now briefly summarize our phase 2 dose finding program first, then review the design and results of the phase 3 RECORD program.

In the phase 2 hip and knee replacement dose finding studies, both once and twice daily dosing regimens were explored, using a wide dose range. There were no apparent differences in either efficacy or safety between the once and twice daily dosing regimens.

Efficacy was not strongly related to rivaroxaben dose, although a decrease in proximal DVT events was observed with increasing doses. Bleeding events did increase with increasing doses in all studies, but the event rates

for rivaroxaben doses of 5 to 20 milligrams were similar to those with enoxaparin.

Based on the information available from the clinical pharmacology and the phase 2 studies, a dose of 10 milligrams once daily was selected as the most promising one for evaluation in the phase 3 RECORD program.

Differing views of the relationship of rivaroxaben dose to bleeding events are presented in the two briefing books which you received. I will try to clarify this situation using the post-operative major bleeding event data from the once daily dosing study 11527.

The primary safety analysis was for dose response in this study, the green line, and this was statistically significant. The numbers of events are small for each individual dose group and are likely not the best estimates of the event rate for that group.

For example, the one event for the 10-milligram dose, a rate of .7 percent, does not fit with the occurrence of three events with the 5-milligram dose, so it's likely an underestimate of the true event rate. Similarly, the rate of 4.3 percent at the 20-milligram dose level is likely an overestimate based on the dose response curve. The greater than four-fold increase in major bleeding events with a doubling of rivaroxaben dose stated in the FDA briefing book is based on these individual group event rates.

Looking at the dose response curve, the estimated rate for the 10-milligram dose group is 2.2 percent, and for the 20-milligram group is 3.1

percent, an increase of about 50 percent.

I believe you will see a similar presentation from the FDA later that shows exposure response data and comes up with a very similar estimate.

An increase of this magnitude or less is also supported by the any-bleeding event end point data from this study and by our twice daily dosing studies.

Based on this data, rivaroxaben exposures of less than two-fold are considered to be acceptable, while exposures greater than a two-fold increase may need to be avoided. We are committed to working with the agency to agree [sic] this threshold and elucidate it in our label. Let's move on to the RECORD program.

RECORD 1 was a double-blind hip replacement study. Randomization occurred the day before surgery, day zero, and surgery was on day one. Enoxaparin dosing started on day zero the evening before surgery. Rivaroxaben dosing was started six to eight hours post-operatively. The duration of dosing was 35 days post-operatively for both drugs, with bilateral venography scheduled for the day after the last dose, day 36. All subjects were to be followed an additional 30 days after the last dose of study medication.

The primary efficacy analyses were prespecified for the treatment phase. Events in follow-up were collected and were analyzed separately. All the key end points, both for efficacy and for safety, were centrally adjudicated by independent committees.

This enoxaparin 40-milligram extended dosing regimen is recommended in the American College of Chest Physicians guidelines and is approved in the United States. In fact, it is the only regimen approved for extended use after hip replacement.

RECORD 2 was also a hip replacement study, and the only difference from RECORD 1 is that active enoxaparin dosing was stopped at day 12. This is a standard duration of enoxaparin dosing that is still commonly used in clinical practice, and it is approved in the United States.

RECORD 3 was a knee replacement study. The main difference from the hip replacement studies is that the duration of dosing is now for 12 days, with venography scheduled for day 13. Follow-up was planned for day 42. Enoxaparin 40 milligrams once daily is commonly used in the United States after knee surgery based on its demonstrated efficacy after hip replacement, especially in the outpatient setting where once daily injections are more convenient for the patient. However, this regimen is not approved in the United States for this indication. It was agreed with the FDA that this study would support the United States approval if it showed superiority to enoxaparin.

RECORD 4 was also a knee replacement study and was the same as RECORD 3 except that the enoxaparin dosing regimen is now 30 milligrams twice daily started 12 to 24 hours post-operatively. This is the approved enoxaparin regimen after knee replacement in the United States.

The primary efficacy end point in each individual RECORD study was a venography-based assessment of total VTE. This is the composite of all DVT events, both asymptomatic and symptomatic, distal and proximal, non-fatal PE events and all deaths.

The prespecified main secondary efficacy end point was major VTE, which is the composite of proximal DVT events, both asymptomatic and symptomatic, non-fatal PE events and VTE-related deaths, which are fatal PEs.

Symptomatic DVT, PE and death were expected to occur at a low frequency in each individual study, and the studies were not powered to detect differences for these events. Therefore, a prespecified analysis, pooling these events across the studies, was planned to increase the precision of the estimates of the rivaroxaben treatment effect. Pooling of all four studies is supported by the similar study designs and the identical event ascertainment and adjudication processes.

The primary end point for this pooled analysis was the composite of symptomatic VTE -- that is, DVT and PE events -- with all deaths. This composite was not an end point in the individual studies, but it's not unusual to construct a difference composite end point for a pooled analysis compared to the individual studies.

Importantly, all subjects in the safety population are included in this analysis since there are no exclusions related to available venography.

The next slide summarizes the analysis populations. The only

requirement for inclusion in the safety population was to have received at least one dose of blinded study medication. This population was the primary one for the pooled symptomatic events, efficacy analysis and for most safety analyses.

To be included in the ITT populations, you had to be eligible for the safety population, have the planned surgery, and have an adequate venogram for the end point, or a confirmed DVT or PE event. These populations were used for the individual study and the pooled subgroup efficacy analyses.

The safety population had the most subjects, 97 percent of those randomized to each treatment group. All three populations had balanced numbers in the rivaroxaben and enoxaparin groups.

Summary demographic characteristics for the hip and knee studies are shown here, along with totals for the entire program. A wide range of patient characteristics was present in both types of surgeries and reflects the spectrum of patients seen in clinical practice.

Now we will review the primary and secondary efficacy end point results for each study, followed by the analyses of symptomatic events pooled across the studies.

For total VTE, the primary analysis was for differences in absolute event rates between the two treatment groups. Analyses of relative differences were also calculated as supportive. The per-protocol population was used for non-inferiority testing in RECORD 1, RECORD 3 and RECORD 4, and

each study easily met its prespecified non-inferiority margin.

Superiority testing in the ITT populations of all four studies showed that the upper limits of the absolute risk difference confidence intervals excluded the vertical solid line of no difference. This indicates that rivaroxaben prevents more total VTE events than enoxaparin in both hip replacement and knee replacement and against all the enoxaparin dosing regimens tested, into the 30-milligram twice daily regimen in RECORD 4.

The results for the per-protocol and ITT populations were consistent with each other, as were the results for the prespecified main secondary efficacy end point of major VTE. For major VTE, statistically significant reductions were seen in RECORD 1, 2 and 3, with directionally consistent, although not statistically significant, results in RECORD 4.

Prespecified total VTE subgroup analyses are displayed here, with the overall pooled RECORD 1 to 4 odds ratio shown at the top in blue. Being to the left of the no-difference line indicates fewer events with rivaroxaben compared with enoxaparin.

The effects of rivaroxaben on total VTE events were consistent across all the subgroups examined with all the point estimates favoring rivaroxaben over enoxaparin.

For the pooled symptomatic VTE or death primary end point analysis, across the studies, this showed that rivaroxaben reduced symptomatic events compared with enoxaparin. The hazard ratio was .42, indicating a relative

reduction of 58 percent that was statistically significant with a P-value of less than 0.001. The absolute difference of .76 percent was also statistically significant.

All the components of this composite favored rivaroxaben. Reductions of 50 percent were observed for both PE and death separately.

The cumulative event rate for the end point of symptomatic VTE or death over time in the hip replacement studies is shown in this Kaplan Meier figure that includes both the treatment and follow-up phases. Two points are important to note. The first is that the curves begin to separate early after surgery and continue to separate during the entire treatment phase, through day 42.

This indicates that the symptomatic events were truly independent of the venography procedure performed around day 36. The second point is that there is no loss of the separation between the curves during the follow-up phase. This indicates no rebound excess of venous thromboembolic events after discontinuation of rivaroxaben.

A similar pattern is seen after knee replacement surgery with early and continuing separation during the treatment phase and no loss of benefit during the follow-up phase.

Before moving to the safety results, here is a summary of the three efficacy end points, total VTE, major VTE and symptomatic VTE or death, presented on a relative scale for all four studies pooled and for the hip and

knee studies separately. All these comparisons favor rivaroxaben and are statistically significant.

For the pooled RECORD 1 to 4 studies, the relative risk for total VTE of .46 is very close to the symptomatic VTE or death hazard ratio of .42. This shows the consistency of the results for the venography-based and the clinically based assessments.

The efficacy results for rivaroxaben are very clear. All four RECORD studies showed statistically significant reductions in total VTE and parallel reductions in major VTE. The pooled analyses of symptomatic events were also statistically significant in favor of rivaroxaben. The efficacy results were consistent across the end points, across the studies, across subgroups and across analysis methods.

The efficacy results are also compelling. Substantial reductions were seen for all three end points and, to our knowledge, rivaroxaben is the first agent to show reductions in symptomatic events beyond what is achieved with enoxaparin, a drug already known to be highly effective compared with placebo.

Now we move to the safety results for the RECORD program where we will review the three prespecified areas of interest: bleeding events, cardiovascular events and hepatic events. These three areas occur in the context of the following overall summary of adverse events.

13 deaths occurred at any time in the rivaroxaben group, including

during the follow-up period compared with 25 deaths in the enoxaparin group. Low rates in both groups with an absolute difference of .19 percent and a confidence interval just extending to no difference.

Treatment-emergent serious adverse events and adverse events leading to permanent discontinuation of study drug were also less frequent for rivaroxaben compared with enoxaparin.

The first area of special interest was bleeding event, which are a concern for any anti-thrombotic drug. Bleeding events were recorded by the investigators and then independently centrally adjudicated in a blinded fashion according to prespecified definitions. In each individual study, the primary safety end point was major bleeding events, analyzed the same way as for the total VTE primary efficacy end point, using absolute risk differences.

For the pooled analyses, the four bleeding event end points shown on this slide were prespecified without identifying any one as primary. These end points were analyzed the same way as the primary pooled efficacy end point of symptomatic VTE or death with a time to first event hazard ratio approach.

Major bleeding events were defined as those events that were fatal, that occurred at a critical site, like intracranial or spinal, that, if they were at an extra-surgical site, were associated with a decrease in hemoglobin of greater than or equal to 2 grams per deciliter, or transfusion of two or more units of blood. If they were at a surgical site, they had to be associated with re-operation.

In RECORD 1 there were six major bleeding events in the rivaroxaben group and two events in the enoxaparin group, an absolute difference of .18 percent with a hazard ratio of about 3, with a wide confidence interval due to the small number of events.

In RECORD 2, with the same rivaroxaben dosing regimen as in RECORD 1, the number of events was one in each group.

In RECORD 3, there were seven events on rivaroxaben and six events on enoxaparin, while in RECORD 4 there were ten events on rivaroxaben and four events on enoxaparin, giving an absolute difference of about .4 percent and a relative difference of about 2.5, with a wide confidence interval.

The types of major bleeding events that were seen in the studies are shown on this slide. There were 24 events for rivaroxaben and 13 events for enoxaparin in the pooled safety population. There were two fatal bleeding events that occurred in the rivaroxaben group, but only one received active study drug. This is consistent with the FDA introduction to the questions for today which describes one fatal bleeding event with rivaroxaben.

These two events are included in the overall death summary, showing 13 deaths with rivaroxaben and 25 with enoxaparin.

The on-therapy rivaroxaben death was a fatal gastrointestinal bleed after six days of therapy in a patient also receiving two concomitant prescription non-steroidal anti-inflammatory drugs and an over-the-counter medication containing aspirin.

Critical site bleeding events occurred in three patients on rivaroxaben, one perioperative spinal hemorrhage in a patient that also did not receive active drug, one adrenal hemorrhage and one retinal hemorrhage. In the enoxaparin group, five patients had critical site bleeding events, four spinal hemorrhages and one subdural hematoma. One of the spinal hemorrhages and the subdural hematoma required surgical evacuation.

There were eight versus one extra-surgical site bleeding events having hemoglobin drops and transfusions. All of these were gastrointestinal tract bleeds, including the one fatal bleed mentioned earlier. There were 12 versus 7 surgical site bleeds requiring re-operation.

One way to get a better estimate of the bleeding risk with rivaroxaben is to include more events so that a more precise estimate is possible. Adding the non-major clinically relevant bleeding events to the major bleeding events increases the event rates and is shown here.

Now, with more events, the absolute and relative differences are more consistent across the studies. Each study shows a modest increase in this bleeding event end point for rivaroxaben compared with enoxaparin.

Another approach for estimating the bleeding risk, given the relatively low event rates is to pool the results across the studies similarly to what was done for the symptomatic VTE events.

For major bleeding events pooled across the studies, the absolute increase with rivaroxaben compared with enoxaparin was about .2 percent, two

cases per 1,000 patients treated. The relative difference was 84 percent.

For the bleeding event categories with more events, the absolute differences are consistent and range from a low of about .4 percent to a high of about .6 percent. The relative differences were from a low of 8 percent for the any-bleeding event category to a high of 31 percent for the major bleeding events combined with surgical site events.

For the major bleeding events combined with non-major clinically relevant bleeding events, the hazard ratio of 1.25 was statistically significant with a P-value of 0.039, and there were consistent trends present for the other end points as well.

The results of the prespecified subgroup analyses for the major combined with non-major clinically relevant bleeding events are shown here, with the hazard ratio for the pooled RECORD studies at the top in blue. Being to the right of the no-difference line indicates an increase for rivaroxaben compared with enoxaparin.

Most of the subgroup point estimates and confidence intervals were consistent with the overall increase of 25 percent. This includes subgroups with known increased rivaroxaben exposures, like older age individuals, those with moderate renal impairment, and those who were considered fragile.

Similarly for the any-bleeding event end point, the subgroup point estimates and confidence intervals were consistent with the overall increase of 8 percent, with no groups appearing to be at particularly high risk.

Overall, the data show a modest and consistent increase in bleeding risk for rivaroxaben compared with enoxaparin, mostly for non-major clinically relevant bleeding events. Such an increase is not unexpected, given the better efficacy results observed.

Bleeding events are important to the patient and to the physician. We have looked for combinations of factors that might increase the bleeding risk with rivaroxaben, including those that would be based on increased rivaroxaben exposures. The data available from the RECORD studies shows that subgroups with known increases in rivaroxaben exposures of about 50 percent have documented efficacy benefits with bleeding risks that are similar to those of the overall population; that is, there is little or no bleeding risk in these subgroups.

These subgroups include those patients who are considered fragile, who are older than age 75 or who have moderate renal impairment.

We are proposing that patient populations where rivaroxaben exposures would be increased by more than two-fold should be handled by labeling and education instructions rather than by a reduced dose.

One example is the use of the strong cytochrome P453A4 and P-glycoprotein inhibitor ketoconazole which increases rivaroxaben exposures about 2.5-fold. We recommend that rivaroxaben not be administered concomitantly with ketoconazole.

Another example is moderate or severe hepatic impairment where we do

not believe that patients with cirrhosis and impaired liver synthetic capacity should be receiving rivaroxaben.

The situations where rivaroxaben exposures greater than two-fold would occur are estimated to affect only a few percent of patients. This is based on the pharmacokinetics of rivaroxaben and the use of concomitant cytochrome P453A4 inhibitors in the RECORD program. We can show some of this data during the question and answer, but in the interest of time, we weren't able to show this in the main presentation.

And we do look forward to further discussions with the agency on the best approach for managing these situations where rivaroxaben exposures are substantially increased.

Our second prespecified area of interest was for the cardiovascular events of myocardial infarction, ischemic stroke and cardiovascular death. These events were identified by the investigators and then independently centrally adjudicated in a blinded fashion by an external panel of cardiologists.

For the evaluation of potential rebound effects, only subjects who received active study drug were considered. In this population, the number of on-therapy events was 13 for rivaroxaben compared with 25 for enoxaparin; the number of off-therapy events was 17 for rivaroxaben compared with 14 for enoxaparin, indicating no rebound increase in thrombotic events after stopping rivaroxaben.

The number of ischemic strokes was numerically higher for rivaroxaben, but this increase does not appear to be consistent with a generalized rebound hypercoagulable state that would be expected to increase myocardial infarctions and venous thromboembolic events as well.

For the third prespecified area of interest, hepatic events, there was heightened concern for rivaroxaben based on the previous experience with the oral direct thrombin inhibitor ximelagatran. Therefore, the liver safety has been -- liver safety has been evaluated systematically and comprehensively in the rivaroxaben program, including the review of individual liver cases of interest by an external liver advisory panel.

Dr. Watkins and I will review the liver safety data in detail, including the presentation of some individual cases of interest by Dr. Watkins.

Rats, mice and dogs have comparable metabolic profiles to humans. This supports the appropriateness of each species for safety evaluation. Rivaroxaben exposures were at least 29-fold higher than the human exposures with the 10-milligram dose, a good margin for evaluating potential adverse effects.

All the non-clinical findings related to the liver were below the thresholds for adverse liver effects estimated by an FDA working group. Therefore, they do not indicate that the liver is a target organ of toxicity, according to the published FDA criteria.

Consistent with this assessment, clinical development of rivaroxaben progressed without any limitations other than routine liver laboratory testing, and the non-clinical findings do not indicate that rivaroxaben has the potential for causing drug-induced liver injury in humans.

The FDA introduction to the questions for today highlights a rate of serious alanine aminotransferase increases for rivaroxaben of .3 percent compared to .2 percent for enoxaparin. These serious adverse events are shown in this slide where the number of cases for rivaroxaben is 17, .27 percent, for both the treatment-emergent analysis and the treatment plus follow-up analysis.

For enoxaparin, the number of treatment-emergent cases is 11, .17 percent, and the total number of post-baseline cases is 14, .23 percent.

Four of the rivaroxaben adverse events had their onset before the start of rivaroxaben dosing, so really cannot be due to rivaroxaben. If these cases are removed, the number of cases with rivaroxaben is 13, which is very similar to either the 11 or the 14 events with enoxaparin.

Also, the any adverse event data -- that is, including both the serious and the non-serious adverse events -- shows a reduction in reports of ALT elevations for rivaroxaben compared with enoxaparin.

ALT levels were regularly measured in the RECORD studies using a central laboratory. This data provides a more reliable and comprehensive evaluation of the effect of rivaroxaben on ALT levels, and is shown here.

ALT levels greater than three times the upper limit of normal were about 1.2 percent less common in the rivaroxaben group compared with the enoxaparin group, about 2.5 percent for rivaroxaben compared with 3.7 percent for enoxaparin. Since enoxaparin is known to cause transient elevations in ALT levels, this observation is expected.

Also as expected, at higher ALT thresholds the rates are more comparable between the two treatment groups, and there is no indication for any increase with rivaroxaben at any ALT threshold.

The combined occurrence of ALT greater than three times the upper limit of normal, with total bilirubin greater than two times the upper limit of normal in the RECORD studies is shown here.

There were ten cases in each treatment group using the broadest possible screening. This screening identified cases from both central and local laboratory measurements that were either concurrent -- abnormalities occurring in the same sample -- or non-concurrent, abnormalities occurring in samples from different days.

Two of the cases in the rivaroxaben group actually occurred immediately post-operatively but before the administration of active rivaroxaben. Therefore, the number of cases after the start of rivaroxaben dosing is eight versus ten.

For concurrent cases only, with both central and local laboratory measurements, there were nine rivaroxaben cases and eight enoxaparin cases.

With only central concurrent laboratory measurements, there were nine cases, .15 percent, in the rivaroxaben group, and seven cases, .11 percent, in the enoxaparin group.

These are the numbers that are mentioned in the FDA introduction for the questions today. If we consider the cases that started after rivaroxaben dosing, the number is identical in both groups, at seven in each.

The ATLAS ACS TIMI 46 study is central to the evaluation of rivaroxaben because this studied a six-month duration of rivaroxaben dosing and is placebo-controlled, so it's a key study to evaluate the liver safety of rivaroxaben.

This study was a phase 2 double-blind dose finding study. The rivaroxaben total daily dose range was from 5 to 20 milligrams, with more than 85 percent of the patients receiving doses of 10 milligrams or higher. The randomization ratio was 2-to-1, with over 2300 patients assigned to rivaroxaben and over 1100 to placebo. The planned duration of dosing was for six months, and monthly liver laboratory testing was done.

For perspective, the liver injury signal with ximelagatran was first detected in a phase 2 atrial fibrillation study of 257 patients, with a duration of dosing of 12 weeks. This signal was then subsequently confirmed in every longer-term study done after that.

The ATLAS ACS study is more than 10 times larger, with twice the duration of dosing compared to that ximelagatran study.

ALT levels greater than three times the upper limit of normal were observed in about 3.7 percent of the over 2200 rivaroxaben-treated subjects, and in 4.6 percent of over 1100 placebo patients, rates that are similar.

At higher ALT thresholds, the rates were also comparable between the two treatment groups.

This figure shows the cumulative incidence rate for ALT elevations greater than three times the upper limit of normal over time with confidence intervals for selected time points. There is an initial increase in both groups in the first week to about 2 percent which probably reflects the effects of the initial ACS event and associated heparin therapies. Then the curves remain parallel and similar throughout the remaining six-month treatment and 30-day follow-up periods to day 210 where over 1400 rivaroxaben and 700 placebo patients are still included in the analysis.

These data are important because ALT elevations are a sensitive marker for drug-induced liver injury. So no differences between rivaroxaben and placebo over a six-month period indicate that rivaroxaben would not be expected to cause drug-induced liver injury.

The occurrence of combined ALT with total bilirubin cases for all completed phase 2 and 3 studies with a planned dosing duration of 35 days or less is shown in this slide. Most of the cases come from the RECORD program, and the overall incidence rate is .16 for rivaroxaben, with over 8,000 exposed patients, with a very similar rate of .14 percent in the comparator group.

Excluding the two cases I mentioned earlier that occurred before rivaroxaben dosing, the rates are identical at .14 percent.

Similarly, the number of cases of combined elevations for all the phase 2 and phase 3 studies, with planned dosing durations longer than 35 days, and for which we know the treatment assignments, are shown here. The incidence for rivaroxaben is .09 percent with over 4600 exposed patients, which is very similar to the comparator group of .1 percent.

For comparison, the data from the ximelagatran long-term dosing studies are now added. This drug had a clear signal with an incidence of combined cases of .53 percent, more than six times the comparator incidence of .08 percent. Also, I would point out that our database of over 4600 patients is larger than the troglitazone database at the time of its approval.

These data for rivaroxaben, for both durations of dosing, show no excess of cases of combined ALT with total bilirubin compared with control groups that are not associated with drug-induced liver injury. This is consistent with the absence of any increased ALT levels compared with placebo in the ATLAS ACS study.

Dr. Watkins was involved as an FDA consultant in the review of the ximelagatran data. He has not been involved in the assessments by the rivaroxaben liver advisory panel during the conduct of our studies and was asked to provide an independent review of our currently available liver data which he will now present. Dr. Watkins is from the University of North

Carolina.

Dr. Watkins.

DR. WATKINS: Good morning. I'm a hepatologist with a long-standing interest in drug-induced liver injury. I'm involved in a number of national and international research efforts in this area, including the NIH-supported drug-induced liver injury network where I serve as chair of the steering committee.

By way of disclosure, I own no stock in J&J or Bayer. My only relationship is that of a consultant, compensated for my time.

Now, as you heard, this is the second oral anticoagulant to come before this committee, the first being ximelagatran. I have a research interest in this compound and can talk about many aspects of it, but I just want to point out that the structures are not similar between ximelagatran and rivaroxaben, their targets are different and the metabolism is different. Ximelagatran is a pro-drug that needs to be converted to the active anticoagulant, whereas rivaroxaben is not.

I know of no scientific reason why these two molecules should share a liver safety profile.

So in my outline I'm first going to review patients who died after experiencing liver injury in the rivaroxaben trial program. I'm then going to review how I approached the evaluation of liver safety in the clinical trial database. And then, in that light, I'm going to present the liver safety data

from the RECORD trials and also the ATLAS trial because I do think it makes some important points. And then I'm going to end with my conclusions, but the goal of my presentation is actually to give the committee the data and to context to arrive at your own conclusions.

So listed here are the six patients who died within 30 days of experiencing a significant liver injury defined as a serum ALT exceeding three times the upper limits of normal, accompanied by a serum bilirubin exceeding two times the upper limit of normal.

There were no such deaths in the RECORD clinical trials, and these are all the deaths fitting these criteria across all completed and ongoing clinical trials for rivaroxaben, blinded and unblinded.

Also listed here in the second column is the study names and the randomization schedules of these trials.

You can see that there were four patients in the phase 2 and phase 3 clinical trials who received rivaroxaben and then, in addition, one patient receiving placebo and one patient receiving enoxaparin. I'm not going to discuss the enoxaparin or placebo-treated patients or the first patient listed, the rivaroxaben patient in the EINSTEIN trial who clearly died of gastric cancer metastatic to the liver.

I will discuss the three deaths which are the three deaths that are referred to in the FDA briefing document as possibly related to rivaroxaben.

The first was a French woman with advanced COPD and known congestive

heart failure who suffered multiple pulmonary emboli and was put into the EINSTEIN trial. She then had a very classic clinical course for ischemic liver injury, so-called shock liver, and this is a condition where the liver does not get a sufficient blood flow for a sufficient period of time to kill liver cells.

As you will see in one of the slides that will be shown in the FDA's presentation, this patient had a very rapid fall in serum ALT -- actually at the half-life of serum ALT, which is about 48 hours, which is classic for this condition of not having enough blood flow and having it then restored.

In addition, she had renal failure and liver biopsy showing zone 3 necrosis, which is, again, characteristic for this condition.

The issue was that there was no documented episode of hypotension in this case, and one pathologist initially felt that this must be related to rivaroxaben on that basis.

However, ischemic hepatitis is well-established in the medical literature to occur in the absence of documented systemic hypotension. In fact, I believe that was first described by Dr. Willis Maddrey, who is one of the consultants here today.

And after this pathologist reviewed the case, together with the experienced hepatologist, he concurred that ischemic hepatitis was the likely diagnosis. And I agree with the consensus statement shown on the slide. This patient most likely had an ischemic injury leading to hepatocellular necrosis

in the setting of multi-organ failure. There is a distant possibility, albeit much less likely, for a role of rivaroxaben in the initiation or worsening of the event.

This woman died, actually of a cardiac death, not as a result of liver failure, which is typical for shock liver.

The second patient was a woman from Czechoslovakia with metastatic uterine cancer who received rivaroxaben in a phase 2 study. And this patient had an acute hepatitis B infection. The issue here was that, at autopsy, little inflammation was observed in the liver, and the pathologist who performed the autopsy concluded that drug toxicity was more likely than hepatitis B infection on that basis.

This is the graph of this patient's liver chemistries, and I'm going to display the clinical course of patients in this way several more times. The X-axis reflects the days from surgery, and the various liver chemistries are shown as fold upper limits of normal on the log scale along the Y-axis. The color key for individual parameters is shown. ALT is shown in green and bilirubin in blue. The treatment interval is defined by the vertical dotted lines.

So, at first glance, this looks like a treatment-related event, normal liver chemistries prior to starting drug, rising on treatment. But this patient had detectable hepatitis B surface antigen in her serum at baseline when all other hepatitis B markers were negative. And during the

course of the liver injury, the patient converted to IGM positive for hepatitis B core antibody, which is characteristic of an acute hepatitis B infection.

This case has been reviewed by a number of experts in viral hepatitis, including Dr. Eugene Schiff, who is here today, and all agree this was a case of acute hepatitis B.

An experienced and highly respected liver pathologist felt that the paucity of inflammatory cells in the liver biopsy at autopsy could be attributed to autolysis after death.

Because hepatitis B is not usually a fatal condition, a logical question was whether rivaroxaben might somehow accelerate or worsen the clinical course of hepatitis B infection once it occurs. I am unaware of any data that would support this hypothesis.

At autopsy it was noted that there was little regeneration of the liver, and it may be that this was the result of the six rounds of chemotherapy the patient received just prior to entering the study.

Another thought was that rivaroxaben might somehow increase susceptibility to viral hepatitis, and there was another case of acute hepatitis B which occurred in the still-blinded ROCKET trials. The treatment of this individual was unblinded and it was discovered that this patient was receiving warfarin and not rivaroxaben.

And I think this points out that acute viral hepatitis does occur in

clinical trials, and this is probably more common in clinical trials conducted outside the United States.

The final patient that is -- of the three patients discussed in the FDA briefing document was a 79-year-old German woman with a history of hypertension and Parkinson's disease, who sustained a cholestatic liver injury. And the issue was whether this contributed to her death. Her clinical course is shown on the next slide.

This woman had a total hip replacement without incident and received rivaroxaben for only seven days. Her liver chemistries were entirely normal throughout treatment and for about two weeks after treatment. Then, 39 days after her last dose of rivaroxaben, she went to her family doctor due to loss of appetite, weight loss and brown urine. Her liver chemistries revealed marked cholestatis, and you can see that her serum alkaline phosphatase started at five times the upper limit of normal and peaked at ten times the upper limit of normal, which is very high.

An ultrasound showed a gallstone in her gallbladder, although the common bile duct was not enlarged, and the patient underwent an ERCP examination.

No biliary obstruction was found, but a sphrincterotomy was performed, and this patient then developed acute pancreatitis, presumably due to the procedure, and then experienced the stormy course depicted here and died two months later.

She had an autopsy and the causes of death were listed as sepsis, bronchopneumonia, cholecystitis and acute pancreatitis. The liver did not show necrosis, and her prothrombin time was essentially normal, shown here, when last measured, about one month before her death. This is incompatible with liver failure.

The patient received a seven-day course of Bactrim for a urinary tract infection right after receiving rivaroxaben treatment, and Bactrim is estimated in the literature to rarely cause a cholestatic hepatitis.

It is also not possible to exclude a role for rivaroxaben here, but there has been no indication from the clinical trials that rivaroxaben can cause a cholestatic injury -- for instance, looking at alkaline phosphatase between treatment and comparator.

It should be noted that a cholestatic injury -- that during a cholestatic injury, the patient becomes jaundiced early in the evolution of the injury and before there is significant dysfunction of the liver. And, in general cholestatic liver injury is not the serious health threat that a hepatocellular injury is. And this woman here died of -- did not die with liver failure.

So I conclude that it is unlikely that rivaroxaben-induced liver injury causes these deaths.

And I'd now like to tell you the approach I used in evaluating liver safety. And I'd first like to say at the outset that it's never possible, at

the time of FDA approval, to say that any drug will never have a liver safety concern in any patient. It's not possible. But there is now a growing consensus on approach to take in evaluating clinical trials database, and that's the approach that I used.

A traditional way to -- approach is to examine the incidence of elevations in serum ALT over various limits expressed as fold upper limits of normal -- and you've seen these data before from the RECORD trials. And as you can see, elevations in serum ALT exceeding ten times the upper limit of normal were rare and balanced in both treatments.

At lower cutoffs, enoxaparin treatment was associated with greater incidence of ALT elevations, and this is expected since enoxaparin is known to be capable of causing low-level ALT elevations.

And there are other drugs like enoxaparin that can produce ALT elevations in some patients, even reasonable high ALT elevations, yet have no risk or a very low risk of liver injury.

And this is the reason why it's considered the most reliable indicator of liver liability in a clinical trial. It's not just ALT elevations, but the simultaneous elevations of ALT plus bilirubin, which indicates a dysfunction of the liver. And a convenient way to examine ALT and bilirubin elevations in a clinical trial is shown on the next slide, and the data depicted in the next slide, is not data from rivaroxaben-treated trials.

This tool is called eDISH which stands for evaluation of drug-

induced serious hepatotoxicity. It was developed at the FDA, largely by Dr. Dal Pan, based on insightful observations made by Dr. Senior, who is also in attendance. And I believe it actually represents a major advance in organization of drug safety.

This particular eDISH plot appeared in the journal article noted and depicts data from an actual phase 3 clinical trial of a drug that's now known to be capable of causing serious liver injury. The identity of the drug was not revealed in the journal. However, based on published data, the data from the long-term ximelagatran clinical trials would look very similar to this.

And I'm going to take -- it's important to understand this slide because all the rest of my talk is based on it, and a good deal of the FDA's presentation I believe will also be based on it. So I'm going to walk you through it.

Each of these points represents a single individual in the clinical trial. The peak serum ALT is shown along the X-axis, and the peak serum bilirubin is shown along the Y-axis as fold upper limits of normal on log scales.

The treatment group is shown by the red triangles and the control is shown by the green circles. Four quadrants have been defined by the black lines corresponding to three times the upper limit of normal for serum ALT and a line corresponding to two times the upper limit of normal for bilirubin.

The right upper quadrant, which I will highlight, includes all

patients with serum ALT greater than three times the upper limit of normal, but who also had an evaluation in serum bilirubin greater than two times the upper limit of normal. And this combination of laboratory abnormalities is recognized, as I said, to be the most reliable indicator of a drug's potential for serious liver injury.

And this is based on an observation by Dr. Hyman Zimmerman years ago that patients with hepatocellular jaundice due to a drug have at least a 10 percent mortality, and that's why this quadrant is labeled Hy's law range.

Now, of course, patients can have other reasons than the study drug to end up in this quadrant, such as passing a gallstone or developing viral hepatitis. But in this case of this particular drug, the imbalance in this quadrant is so obvious you can argue you don't need to do causality assessments to know that this drug has a serious liver liability.

Now, in addition to an imbalance in the Hy's law quadrant, you will note that there is also a clear treatment imbalance in the right lower quadrant; that is, those patients with ALT elevations greater than three times the upper limit of normal but not also having elevations in serum bilirubin.

And Bob Temple at the FDA first noted that drugs capable of causing clinically important liver injury characteristically produced ALT elevations, and this is why this quadrant is labeled Temple's corollary range.

An imbalance between treatment and comparator in Temple's corollary quadrant does not in itself constitute a clear liver safety signal because

drugs -- heparin and derivatives, for instance, are examples of drugs that will do this.

However, imbalance in this quadrant has been reliably present with drugs capable of causing hepatocellular injury even when examination of the Hy's law quadrant is unrevealing.

This is because, with serious hepatocellular injury, ALT rises before bilirubin because it is much more sensitive to hepatocellular injury. In other words, individuals move like this on the plot over time. Patients in the Temple's corollary quadrant may never progress to the Hy's law quadrant because, for instance, their drug could be stopped before there's injury progression or because the liver completely adapts to the liver injury despite continued treatment.

In fact, the current concept behind severe hepatocellular injury is that it results from at least two hits, the first being stress to hepatocytes manifested by a rise in serum ALT that most patients will recover from whether or not the drug is stopped.

However, with drugs capable of causing clinically important liver injury, a subset of these Temple's corollary quadrant patients won't adapt to the stress and will march on to clinically important liver injury if treatment is continued.

The important point from this slide is that in evaluating a liver safety database, one searches for an imbalance between test drug and

comparator in both the Hy's law quadrant and in the Temple's corollary quadrant, and an imbalance in each is expected for a drug capable of causing clinically important hepatocellular injury.

So now, with this background, let me go to the eDISH plot for the RECORD -- combined RECORD studies. And you can see this is not the pattern expected for a drug with serious liver liability.

I've highlighted here the Temple's corollary quadrant and listed the numbers and percentages of patients receiving rivaroxaben and enoxaparin, and you can see that there are less rivaroxaben-treated subjects here, so Temple's corollary is not satisfied. But interpretation is confounded because enoxaparin, the comparator, is known to cause ALT elevations. You know, that is, there might have been a higher ration of rivaroxaben to comparator-treated patients in this quadrant had another comparator been chosen in the trial; that is, a comparator that doesn't cause ALT elevations.

Now I've highlighted the Hy's law quadrant, and I'd like to blow it up to make things clearer. Each subject is labeled with their assignment number -- and I'm sorry if this is too small for some people to see, but you have the printouts. You can see that there are ten patients treated with rivaroxaben and ten patients treated with comparator here.

However, one subject receiving rivaroxaben and two subjects receiving enoxaparin never met both biochemical criteria at the same time. And it makes sense to drop these. And the FDA analysis did as well -- so

there's the original ten and ten. Dropping these results in nine rivaroxaben-treated patients and eight enoxaparin-treated patients.

The FDA analysis did not include one enoxaparin that I've included here who qualified based on local but not central labs -- and I'm going to show you data from this patient later.

The next step, having done this, is to determine which of the remaining patients fulfil the criteria for what's called the Hy's law case, and these criteria are shown on the next slide.

Number one -- these are individuals in the Hy's law quadrant -- that the liver injury should be hepatocellular in nature, and that's defined in the document as having a peak serum alkaline phosphatase less than two times the upper limits of normal. An elevation in alkaline phosphatase, as I stated before, indicates a cholestatic component to the injury which typically causes the bilirubin to rise early in injury, before there's significant liver dysfunction, unlike a hepatocellular injury.

Cholestatic injury does not generally represent a great health threat to the patient -- as great a health threat as hepatocellular injury. For example, the widely used antibiotic Augmentin is an example of a drug that typically causes a cholestatic injury.

The second point is that there should be no more likely alternative cause for liver injury other than the drug. And number three, there should be evidence that the drug causes more frequent ALT elevations greater than three

times the upper limit of normal than suitable comparator; that is, the imbalance in treatments in the Temple's corollary quadrant that I discussed earlier -- and again, this criteria can't really be applied to the RECORD trial because the comparator causes ALT elevations.

Now, I should point out that this draft guidance and these three criteria reflect the consensus of not just the individuals at the FDA that put this together, but also experts from academia and industry who had ample opportunity to weigh in through the now closed public comment period and two meetings that were actually organized by Dr. Senior.

So I'll now show you what happens when you apply the first two criteria to those subjects in the Hy's law quadrant. This is a slide we left moments ago, and if we exclude those patients with peak serum alkaline phosphatase exceeding two times the upper limit of normal, the field is reduced to five rivaroxaben-treated patients and six enc-treated patients.

The next step is to look for other, more likely causes for the observed injury; that is, criterion number 2. And these are the two patients highlighted with the highest serum ALT values, one receiving rivaroxaben and one receiving enoxaparin. I'm going to show you those.

This is the rivaroxaben-treated patient, and you can see, at first look, this would be very compatible with a drug-induced liver injury. Liver chemistries rising remarkably during treatment and resolving after discontinuation. But, on evaluation, this patient unequivocally experienced

an acute hepatitis C infection. Serum obtained before treatment tested negative for virus by both polymerase chain reaction and antibody, and both of these tests converted to positive during the course of the injury. So this patient can be excluded.

This is the patient with the highest peak serum ALT during enoxaparin treatment. Again, looks exactly like a drug-induced liver injury. However, this patient had decreased congestive heart failure, and the most likely diagnosis was ischemic hepatitis, or shock liver, the condition I talked about before.

So we can drop these two patients, resulting in four remaining rivaroxaben and five enoxaparin-treated patients.

Next, these two rivaroxaben-treated patients had their only qualifying values of ALT and bilirubin before they actually received the drug. So the drug could not possibly have been responsible. And you'll remember that three out of the four RECORD trials, rivaroxaben was started about 20 hours after enoxaparin or placebo injection, and these events occurred during that interval.

There were no comparable events in the enoxaparin-treated -- there were no events in this quadrant in the enoxaparin-treated patients during this interval. So I think its -- intent to treat analysis would include them, but I think it's reasonable to exclude them.

So that results in two rivaroxaben and five enoxaparin patients.

I'll just say two of the remaining enoxaparin patients, it was unlikely to be drug-related. One had passed a gallstone, for instance. So we can drop them. And we're left with two rivaroxaben and three enoxaparin patients.

I'll now show you graphs of the liver chemistries of both of these rivaroxaben-treated patients and two of the three enoxaparin patients.

This rivaroxaben-treated patient had unremarkable liver chemistries during his ten-day treatment course and at the end of the course. However, about a month and a half later, when he returned for a scheduled follow-up, his ALT was noted to be over 1,000, and his serum bilirubin was around 3 milligrams per deciliter.

He was apparently asymptomatic at this time, and follow-up serum ALT measurement two weeks later was entirely normal, and this was confirmed.

The event was not attributed to study drug, and the patient did not undergo an evaluation, so such things as viral hepatitis serologies were apparently not performed.

It would not be typically for a drug to cause a hepatocellular injury with unremarkable liver chemistries at the end of treatment. This is more common with cholestatic injuries, which this individual did not have. Nonetheless, a role for rivaroxaben cannot be excluded, and it was unfortunate that there wasn't a more complete evaluation of the event.

This is the other remaining patient randomized to rivaroxaben. You can see that although there was a time when both the ALT and bilirubin just

qualified him to be in this quadrant, the serum bilirubin actually peaked several days before the serum ALT peaked, and this is not the pattern of hepatocellular jaundice. And at that first peak, actually, unconjugated bilirubin exceeded conjugated, suggesting it was related to blood transfusions or blood resorption.

Here is the one remaining patient randomized to enoxaparin treatment. The clinical course, again, consistent with drug-induced liver injury. And it's interesting to note, of the 20 cases in this quadrant, this was the case considered to be most likely drug-related during the blinded assessments by the hepatology experts.

And this the other one I'm going to show -- the final -- the remaining patient. This patient, who qualified based on local -- this is the one who qualified based on local laboratories. Serum ALT and AST spiked to about ten times the upper limit of normal, and these transaminase elevations were confirmed locally.

This would be a pattern consistent with drug-induced liver injury and adaptation with continued treatment.

So I think what these cases with enoxaparin -- since enoxaparin has not been associated with serious liver injury -- show is that a small fraction of patients who were undergoing major joint surgery will end up in the Hy's law quadrant without a clear explanation of why. We can speculate it's the anesthesia, perioperative antibiotics, non-steroidals combined with the heme

load from transfusions and blood resorption -- so really the issue is, is there an imbalance between the comparator in this quadrant -- with comparator? And as I showed you, there is not.

So, to summarize, in the RECORD trials there is no imbalance between treatments and clinically important liver injury. Temple's corollary is hard to interpret, since enoxaparin was the comparator. But, as correctly pointed out in the FDA briefing document, the RECORD studies are relatively short-term, and drugs have turned out to have serious liver safety issues that first manifest ALT elevations after one month -- you could question whether it's a little before one month or not.

And this is why I think the ATLAS trial experience is relevant. That's what I'm going to discuss next.

As stated by the sponsor, this was a six-month randomized trial for acute coronary syndrome with over 2,000 patients receiving rivaroxaben, 1,000 receiving placebo. 80 percent completed six months of treatment. So this is longer-term exposure data with a true placebo for comparison.

And this is the eDISH plot from that trial. And you can again see this is not the characteristic pattern expected. There are not more rivaroxaben-treated patients in the Temple's corollary's quadrant or in the Hy's law quadrant. And the fact that there is no difference with true placebo in the Temple's corollary quadrant suggests that rivaroxaben does not cause ALT elevations with six months' of exposure and that the drug, therefore,

would not meet Temple's corollary.

Looking at this data another way, the data would suggest that rivaroxaben is incapable of producing the first hit to hepatocytes in the multiple-hit hypothesis.

I have mined these data in every way I can think of to search for a reason that might obscure ALT elevations caused by rivaroxaben, and I've been unsuccessful. Things I considered included a possible imbalance in cardiac and thrombotic events between the two treatment arms that could have increased the incidence of ALT elevations in the placebo arms. But removing the individuals with these events did not change the conclusion.

I considered that there might be an imbalance in treatment of drugs that can cause ALT elevations -- for instance, statins -- but I could find no evidence of such an imbalance.

I considered whether there was more bleeding in the rivaroxaben-treated group that may have caused iron deficiency anemia, because this condition is reported to cause a modest reduction in serum ALT. But there was no difference in hemoglobin -- hemoglobin analysis was unrevealing.

I even searched the literature for a mechanism whereby 10a inhibition might cause a reduction in serum ALT or might somehow be generally hepatoprotective, but could not find such a mechanism.

So, in summary, no deaths were likely attributed to rivaroxaben liver injury, particularly the three deaths that are at issue. No imbalance

was found in clinically important liver injuries between rivaroxaben versus enoxaparin in the RECORD, or versus true placebo in the ATLAS clinical trial. And there's no evidence of increased ALT elevations relative to placebo in the ATLAS trial.

And one obvious question is, is the six months enough? I believe there is no example where it took longer than six months to show a drug produced ALT elevations.

So, in conclusion, I hope I've given you the data and the framework to arrive at your own conclusion, but my conclusion, which is shared by the other experts here, liver experts, is that there is not -- a liver safety signal is not evident in the clinical trials database for rivaroxaben. Thank you.

DR. DiBATTISTE: In the RECORD clinical program of over 12,000 patients, the single risk clearly identified as related to rivaroxaben was bleeding. As noted by Dr. Watkins, no signal has been identified across the programs for liver injury.

We acknowledge, though, that no clinical trial program, even one of this size, is large enough to identify rare events and, in addition, clinical trials do not completely characterize the safety profile in clinical practice.

We also acknowledge the potential for use outside of the labeled indication. The safety surveillance and risk management plan I will now share with you addresses these issues.

The foundation of our safety surveillance and risk management plan will include the routine activities listed here. In recognition of the identified and potential risks we just discussed, though, a number of additional enhanced activities are proposed for both risk assessment and risk minimization. Let me briefly describe each of these.

We're going to do what we refer to as enhanced pharmaco-vigilance, which means that whenever we get a report for an event of special interest, we will reach out proactively to try to get complete case information.

A post-marketing observational study. This 15,000-patient observational study is already underway in Europe in total hip and total knee patients, collecting data in real-world practice.

A post-marketing utilization study will capture reliable drug utilization data from three estimated databases covering inpatient and outpatient care in the U.S., and in addition, IMS prescription tracking will capture near real-time prescription data by specialty and duration of treatment.

On the risk minimization side, we plan targeted education activities which will include specific programs for health care providers and third-party payers which are expected to drive appropriate use in the right patient for the right duration of treatment.

A patient package insert will be distributed to every patient with every prescription describing the indication, appropriate duration of

treatment and risks in patient-friendly terms. And this will be facilitated by our drug packaging strategies.

Rivaroxaben in the retail setting will be distributed only in blisters in cartons of 12 or 30 designed specifically for the surgery, hip or knee replacement.

These elements comprise a broad strategy for risk management, and we expect them to result in both timely assessment of identified and potential new risks, and in appropriate risk mitigation.

We'll be happy to address any questions on these or other aspects of the risk management program in the Q&A.

So we're in the home stretch. So far you've heard a lot of information about rivaroxaben, including detailed characterizations of efficacy and safety in the phase 3 program. What remains is to analyze the benefit-risk for rivaroxaben in VTE prophylaxis in total hip and total knee replacement.

There is no single method or collection of end points that is universally accepted for the assessment of benefit-risk. Identification of the correct end points for comparison can be particularly challenging.

We've done a number of analyses with different methods and different approaches addressing the issue from multiple perspectives, each of which has its own particular strengths.

We will present the excess number of events approach, as we believe

it most clearly demonstrates the public health impact. I'll present the four different comparisons shown on this slide.

This analysis compares total VTE, the primary efficacy end point in each of the RECORD studies, with major and non-major clinically relevant bleeding, a key safety end point. Total VTE event rates in the pooled RECORD population are listed in the two orange bars, clinically relevant -- in the top two orange bars, and clinically relevant bleeding in the lower orange bars.

Total VTE across the pooled population occurred in 9.4 percent of enoxaparin-treated patients and in 4.3 percent of rivaroxaben-treated patients. Clinically relevant bleeding occurred in 2.6 percent of enoxaparin-treated patients and 3.2 percent of rivaroxaben-treated patients.

If one considers the impact in a hypothetical population of 10,000 patients, these event rates would translate into the absolute numbers of events illustrated in the teal section of each bar.

Treatment with rivaroxaben would result in 504 fewer total VTE events, the difference illustrated in pink. And at the same time, treatment with rivaroxaben would result in an excess of 64 clinically relevant bleeding events.

Direct comparison of these measures of benefit and risk yield a total of 440 fewer events with rivaroxaben therapy.

Said in another way, for every clinically relevant bleed resulting

from rivaroxaben therapy, eight total VTE events are prevented. This ratio suggests a highly positive benefit-to-risk for rivaroxaben.

This benefit-to-risk, particularly in this end point, was examined across multiple subgroups, including those with increases in exposure, and the results were largely consistent across these subgroups.

On this slide, major VTE events are compared with major bleeding, using the same methodology. It is important to note that this comparison, major-major, was the prespecified comparison for benefit-risk in each of the RECORD study protocols.

As illustrated here, in a population of 10,000 total hip and total knee replacement patients, treatment with rivaroxaben would result in 205 fewer major VTE events. At the same time, treatment with rivaroxaben would result in an excess of 18 major bleeding events.

A simple comparison of these excess events reveals a total of 187 fewer events on rivaroxaben compared with enoxaparin. Said in another way, for every major bleeding event resulting from rivaroxaben therapy, 11 major VTE events are prevented. This ratio, again, suggests a highly positive benefit-to-risk for rivaroxaben.

To drill down even further, we next compared the composite of symptomatic VTE and death with major bleeding events. And here we see the results of that comparison. Again, in our 10,000-patient population, treatment with rivaroxaben will result in 76 fewer symptomatic and death

events, while causing 18 additional major bleeds, again, indicating an overall favorable benefit-risk for rivaroxaben.

In thinking about the 800,000 total hip and total knee replacement surgeries that take place annually in the U.S., treatment with rivaroxaben could potentially result in a reduction of 6,000 symptomatic VTE and death events annually.

One potential shortcoming of direct comparisons like this is that they imply that events being compared are of similar importance and don't take into account varying degrees of severity of the events comprising the end points.

In this comparison on the screen, we compared symptomatic VTE and death with major bleeding. In order to get a more complete understanding of the importance of these events, we evaluated a number of characteristics as identified by the investigator that are shown here.

As you'll see, symptomatic VTE events were longer in duration, were more likely than either major or non-major clinically relevant bleeds to be considered serious, require remedial treatment, persist at the time of study end, and occur remote from the immediate perioperative period. All of these taken together support the tenet that VTE events are of greater clinical importance than both major and non-major bleeds.

A somewhat different approach to the assessment of benefit-risk is an analysis of serious adverse events. Reporting of SAEs is mandatory in

clinical studies. The criteria for seriousness are well-established and include death, conditions that are immediately life-threatening, that require hospitalization or prolongation of hospitalization, that result in a significant and/or persistent disability, cause a congenital anomaly or are considered an otherwise important medical event. SAEs include both efficacy and safety events.

In the RECORD studies, investigator characterizations of SAEs were done blinded to treatment assignment. In the RECORD program, 6.6 percent of rivaroxaben-treated patients sustained SAEs, compared with 8.5 percent of enoxaparin-treated patients. Translating these to our population of 10,000, treatment with rivaroxaben results in 194 fewer serious adverse events, again, indicating an overall favorable benefit-risk.

All of these analyses, then, demonstrate an overall favorable benefit-risk profile for rivaroxaben compared with enoxaparin. As noted earlier, though, there is no uniform agreement regarding which comparisons are more reasonable to assess benefit-risk. For that reason, we have displayed all of the end points identified in the prior comparisons on this slide.

The efficacy parameters are identified in blue, safety in orange, and those outcomes that incorporate both efficacy and safety are in green.

As you can see, comparing any of the efficacy end points with any of the safety composites yields an overall reduction in events with rivaroxaben treatment.

In addition, the measures that capture both efficacy and safety, death and serious adverse events, also reflect the consistently favorable benefit-risk with rivaroxaben.

So, in summary, we have presented data demonstrating that when used for prophylaxis of DVT and pulmonary embolism in patients undergoing total hip or total knee replacement, rivaroxaben, administered as a once daily oral fixed-dose regimen of 10 milligrams, results in statistically significant and clinically meaningful reductions in total VTE, major VTE and symptomatic VTE versus a highly effective comparator, that rivaroxaben is well-tolerated with modest increases in bleeding, as noted by Dr. Watkins that no liver signal was apparent in the RECORD studies or across the program to date.

And, finally, considering all of the data in total, treatment with rivaroxaben has a compelling benefit-risk compared with enoxaparin in the prophylaxis of VTE in patients undergoing total hip and total knee replacement.

Members of the committee, in a short time you'll be asked to weigh in on whether you have sufficient information to assess rivaroxaben safety and whether the clinical data demonstrate a favorable benefit-risk for rivaroxaben in the prophylaxis of DVT and PE in patients undergoing total hip and total knee replacement. On balance, considering all of the information we've shared today, we believe that the public health benefits clearly outweigh the risks, and that rivaroxaben represents an important new treatment option for

physicians and patients in this indication. Thank you.

DR. LINCOFF: All right. We'll take now about a 20-minute -- 15- to 20-minute period for questions for the sponsor, and then we'll take a break. I'd appropriate if we could have you raise your hand, and we'll keep a list here so that -- and try to go around and get everybody in the sequence that they indicated.

So I think Dr. Kaul --

DR. KAUL: Thank you, Mike. My questions are directed at the rationale for pooling the trials together. I was particularly struck by the disparity in the primary end point event rates in the RECORD 1 and 2 and 3 and 4. For example, you have a 3.7 event rate in enoxaparin in RECORD 1 versus 9.3 in RECORD 2 -- these are the same populations, same procedure.

Similarly, in 3 and 4, we have a two-fold difference, 10.1 in 4 and 18.9 percent.

A related question is, what was the purpose of using the different treatment durations in RECORD 2? I mean, were you trying to differentiate a treatment effect amongst the two regimens? Or were you trying to differentiate a treatment duration differential effect irrespective of the treatment agents?

DR. DiBATTISTE: Let me ask Dr. Peters to address both of your questions.

DR. PETERS: So I'll start with the second question first. The --

all four studies have somewhat -- are complementary to each other and were designed to look at somewhat different aspects of current therapy. The RECORD 2 study was designed to look at extended rivaroxaben, 35 days, which is -- the data in the literature does support extended dosing after hip replacement; that's recommended by ACCP -- versus some countries it's not approved, although it is in the U.S., and many patients still receive, as standard therapy, a short, two-week course.

So that study, if you will, is kind of a dosing strategy question of extended dosing with rivaroxaben versus standard practice that's currently done in various places around the world, including the United States.

DR. KAUL: So should you add that if you have unequal treatment duration -- if you wanted to add data from that, you should have used a matched treatment duration comparison.

DR. PETERS: So, actually, just to follow up on that -- and we'll come back to the event rates -- if we could show the sensitivity analyses that show the active control pool.

We looked at the data in various ways. I presented the primary analysis for the pooled symptomatic VTE or death. But we also did look at excluding that placebo control period from the RECORD 2 study for the phase 3 data, the sensitivity with active control.

And we also looked at just the first 12 days, which was a common therapy duration across all four studies. We also looked at including the

follow-up period as well, to capture all of those events.

So if we could show that slide. And then the next one, actually, if we can come back, after this, to the core slide with the primary end point results to address some of the questions about the end points. Slide on.

So here you see the first row is the primary analysis for the pooled analysis, so this is all four studies safety population, the hazard ratio of .42. If we include the follow-up period, the hazard ratio is .49. If we look at just the first 12 days, which is active versus active, all four studies, the hazard ratio is .48. And if we look at the active control, which just excludes the placebo control period of RECORD 2, you can see with all of these analyses we have highly statistically significant results.

Actually, the next slide on.

So here are the end point rates that you're commenting on from the primary analysis. Now, we didn't pool the total VTE events other than for the subgroup analyses to increase the event rates when we're looking -- you know, splitting things by subgroups.

So if the question is about pooling, that's really about the symptomatic event analysis, VTE and death. But just to comment on your questions about the different rates, in RECORD 1, it was extended rivaroxaben versus extended enoxaparin. So you might expect that the RECORD 1 enoxaparin rate, which was 3.72 percent, would be lower than a shorter duration in RECORD 2, which was 9.32 percent.

The rates in rivaroxaben for both of those studies are right around 1 to 2 percent with the same rivaroxaben dosing regimen. So I think those rivaroxaben rates are very consistent. The differences between RECORD 1 and 2 for enoxaparin reflect the different durations of therapy.

RECORD 3 and 4, it's harder to make cross-study comparisons, at least for the enoxaparin rates. The rates for rivaroxaben were about 7 percent and about 10 percent, so again, relatively comparable, although lower in RECORD 4. And then in RECORD 4, as you point out, the enoxaparin -- it is the higher dose. The rate is about 10 percent, which is lower than the 18.

Part of that may reflect the cross-study differences. Part of that may reflect some variation between studies. Part of that may reflect the higher enoxaparin dose in that study.

Regardless of which regimen of enoxaparin we compared against, we were statistically significant in each of these studies for the primary end point.

DR. KAUL: Well, it seems like to me that the only two pure trial that you can readily justify a pure comparison is RECORD 1 and RECORD 4. And the overall primary event rate in RECORD 1 was 2.4 percent, and compared to 8.5 percent in RECORD 4. And I'm not even sure whether you can combine 1 and 4 because they are two distinct populations with respect to the primary event rate, nearly a four-fold difference.

DR. PETERS: Right. But, again, we didn't combine the total VTE

event rates. If you look at the symptomatic events, those rates are much more comparable across all four studies. And there was actually no evidence for statistical heterogeneity across the studies when we looked at that.

DR. LINCOFF: Do you have the data, total VTE -- I understand -- I'm sorry, symptomatic VTE? I understand it was prespecified to be only for the combined analysis, but to show that.

And also, because of the difference in symptomatic VTE versus the total VTE, do you have data regarding the rates of follow-up or adequate venography by study? You've given it overall, but was it the same by the studies -- across the various studies?

DR. PETERS: So your first question is for the symptomatic event rates by study?

DR. LINCOFF: Right. I mean, are they -- are they comparable?

DR. PETERS: If we could go to the backup one for the results for all three end points by study, because that will have the symptomatic VTE and the backup -- in the core backup slides. It will be a little bit of a busy slide, the Forrest plot.

DR. LINCOFF: While they're getting that, can you just summarize, if you recall?

DR. PETERS: This study will -- slide on.

So here's the symptomatic VTE or death for the treatment phase, which was the primary treatment phase by study, and then pooled across the hip

and knees. So you can see the event rates for enoxaparin range from a low of .67 percent in RECORD 1 to the highest rate is 2.1 percent in RECORD 3. So about 1 to 2-1/2, 3 percent.

And for the rivaroxaben rates, they're all less than 1 percent, with the lowest being .41 in RECORD 2, and the highest being .79 in RECORD 4.

So in all four studies, the symptomatic VTE or deaths were reduced versus the enoxaparin regimen they were being compared against. Again, the studies weren't powered for these kind of event rates on an individual study basis. You can see all of the point estimates do favor rivaroxaben.

When we do the prespecified pooling of hip and knee -- of hip for RECORD 1 and 2, knee for RECORD 3 and 4 -- and then all four studies together, all three of those analyses are highly statistically significant with hazard ratios that are very close to each other. For the two hip studies the hazard ratio is .43; for the two knee studies, .42. And then pooled 1 to 4 was the .42 overall.

And you had a second question --

DR. LINCOFF: Just -- and you don't necessarily have to show the data, but if you can, that would be great. Were the rates -- to differentiate between the total VTE and the symptomatic, were the rates of venography, adequate venography, similar in all four studies, or were there systematic differences among the studies that might explain some of the variability?

DR. PETERS: Okay. So we can show RECORD -- if we could show the

venography availability rates for the four studies. We do have that data. Here's RECORD -- so slide on.

Here you can see the analysis populations by study for RECORD 1 to 2 -- and then we can pull up the slide for 3 to 4. So if you're looking at the safety population, that was very consistent across all four studies, it being in the upper 90 percent. If you look at the MITT valid for total VTE, which was the superiority population for total VTE, you can see in RECORD 1, that was 69 percent, very close in RECORD 2 at 69 percent for the two hip studies. And now for the two knee studies, RECORD 4 did have that poorest venogram availability rate -- slide on.

For RECORD 3, the rate was 67 percent, and for RECORD 4 it was 61 percent.

So the knee studies were a bit poorer than the hip studies, but again, it was balanced between enoxaparin and rivaroxaben in each group, and they are within the range of what you see in the literature for venography availability.

DR. LINCOFF: Dr. Fogel.

DR. FOGEL: Thank you. To understand whether the liver status of the study population is similar to that of the general population, I'd like to know what the liver exclusion criteria were. I'd like to know whether you measured alcohol use, and whether you did any pre-procedure assessment of liver status.

DR. PETERS: If we could have the inclusion/exclusion, to just read it verbatim -- slide on.

So the first was the specific criteria, which is the third bullet down. So the exclusion was clinically based, significant liver disease, with some examples given. For example, acute hepatitis, chronic active hepatitis, cirrhosis. There were no laboratory-based exclusions in any of the RECORD studies.

Also, there were no specific exclusions regarding alcohol use. We did record it, but I don't believe we have any slides to be able to show that.

And your third point was?

DR. FOGEL: Whether you did a global assessment of liver status before study initiation.

DR. PETERS: We did not, other than general history, medical -- physical exam and medical history findings. So we do have -- we do know that people reported a medical history of having had hepatic disease of -- relatively low of about 3 percent or so.

DR. LINCOFF: Dr. Gross?

DR. GROSS: I have a question on slide CC-24. And I have some questions about the comment that there's no need for dose adjustment. The curve shown on slide CC-24 is not a flat line, but a shallow rising line, and the denominators are between 100 and 200. And for a low incidence of bleeding, you may have a denominator problem to determine the dose.

The fact that the 10-milligram dose seemed to have the lower incidence of bleeding may be a statistical fluke because your denominator is not high enough.

And the reason I'm asking the question is it may have an impact on who bleeds and who doesn't. And, really, why not pick the 5-milligram dose, or even a lower dose? I don't understand, unless you have more data than this that has not been shown, how you picked the dose. And it might also affect patients with renal failure or mild liver failure.

DR. PETERS: So a little more information about why we selected 10 rather than 5 -- slide on.

Here, from the same study in the same format is the major VTE. So this was not the primary end point, but it was a prespecified secondary end point in this study. And you can see the dose response curve here in green was statistically significant, P-value was 0.0072. So there is evidence that major VTE events would increase as you -- that they decrease as the dose increases.

And looking at -- again, looking at the individual cells is problematic, as you point out, because the sample sizes are small, the number of events are relative small. But we did have eight events in that group with a rate of 8.5 percent. Three events -- one to three events in all of the other groups. So that group did seem to stand out and is, obviously, driving that dose response curve.

So we had this data, we had one other phase 2 study that had a very similar pattern where there was an increase in major VTE events at a 5-milligram dose. It was two-and-a-half twice a day. So this was the primary reason that we were reluctant to take the 5-milligram dose into the phase 3 program.

As far as -- if we could show the adverse event data for all four for bleeding and efficacy pooled across all four of the studies as well. Because this summarizes, at least from the investigator perspective -- slide on.

Here, from the investigator perspective -- so this is adverse event data across all four studies -- so now you're getting to bigger sample sizes of 4 to 500 per group, and larger numbers of events.

So you can see, for any reported treatment-emergent bleeding event, the rate was 10.1 percent at 5 milligrams. It went up to 11.3 percent -- so about a 1 percent increase at 10. And then to about 13 percent at 20 milligrams. So a relative shallow dose response curve there.

And then for reported events -- again, not adjudicated, but reported events of DVT or pulmonary embolism, again, it looks like the 5-milligram dose is not as effective as the other doses. And once you get past 5-milligram, the efficacy curve is -- does appear to be very flat. There's very little difference between the 10 doses up through the 60 milligrams.

DR. GROSS: Have you looked at renal function and liver function in

the patients who did bleed to see if that might be an indication that, in the future, there should be some dose adjustment based on kidney function?

DR. PETERS: Now, liver function -- if we could pull up the major and non-major clinically relevant bleeding for -- by renal function.

Hepatic function is -- we did not measure hepatic function, and I'm not sure what measure you would use to try to assess hepatic function. As I said, very few people had a medical history of hepatic disease. They were having elective surgery so, I mean, their liver synthetic function was normal in virtually everyone. Slide on.

This shows the major and non-major clinically relevant bleeding end point for the safety population -- so this is all four studies pooled. And this is the end point that had a 25 percent increase in risk, pooled across the whole population.

So you can see, looking at the event rates, that in the enoxaparin group, the rate for the greater than 80 milliliters per minute is 2 percent. And then the two higher groups, it's about 3 percent. In the less than 30 mills per minute, a few people snuck into the protocol. They were supposed to be excluded because of the enoxaparin dose adjustment that's required for severe renal impairment.

And if you look at the rivaroxaben rates, it's 3 percent in the normal renal function in the middle group with moderate renal impairment. And then slightly numerically lower, but probably really the same, in the group

with 30 to 50 milliliters per minute.

So this is one of the subgroups. And if we could show the efficacy figure that corresponds with this, because I think it's informative.

This is one of the groups that we did look very carefully at and did not see evidence for an increase in bleeding risk as renal function decreased, even though we do know that their exposures would be about 50 -- now, there is a gradated increase in exposure which we saw in the phase 1 and we see in the phase 3 with the prothrombin time measurements.

So if we could have the efficacy data just to finish for this population -- slide on.

So here you see the efficacy data for this group -- and again, starting with the enoxaparin group, the rate was about 9 percent in the best renal function, the normal renal function. Then it goes up to about 9-1/2 percent and actually up to 14 percent in the group with moderate renal impairment.

So, actually, even though we know in enoxaparin exposures as well will be increasing as renal function decreases -- these are -- the people with poor renal function are at high risk for thrombotic events, so they have an event rate of almost 14 percent.

Looking relative to rivaroxaben, we see rates of 3 percent up to about 6 percent -- I can't really read the slide. So we're better -- we have fewer total VTE events than enoxaparin in each of these three groups. So

we've shown good efficacy versus enoxaparin in all three renal function categories, a little increase in bleeding. So the benefit-risk is highly favorable in the moderate renal function impairment group.

And I think this also illustrates a point that I'm not sure that exposures are the only thing to be considered because we know the rivaroxaben group and poor renal function does have increased exposure, but their absolute event rate is also higher.

So groups with higher exposures may be higher risk for thrombotic events, may be higher risk for bleeding events. So it's important to look at those groups, where we have enough data -- and we have about 400 people in each treatment group for the moderate renal impairment here. So it's important to look at the actual risk-benefit for groups that might have increased exposures rather than assuming that the exposure-response relationship is the same across all subgroups of patients.

DR. LINCOFF: We have a list here now of about six or seven people, and we are running behind. So we'll probably go another five minutes or so. I emphasize that we have ample time in the afternoon for questions, both to the sponsor and to the FDA. But to kind of stay to the schedule, we'll try to get through what we can in the next five minutes or so.

Dr. Krenzelok?

DR. KRENZELOK: Thank you very much. I'm trying to get a little bit of a perspective, Dr. Peters, on the safety analysis with respect to

compliance. So in your presentation you stated that every patient had to have at least one dose of the drug, of the study drug versus the other drugs. And I'm just wondering what percentage of the patients failed to receive the whole course of therapy. So I'm trying to put this safety thing in perspective.

Were there a lot of patients that just got one or two or three doses of drug, which would have sort of a minimizing effect on safety versus -- adverse events versus -- what percentage received the full course of therapy of each of the drugs?

DR. PETERS: If we could show the treatment completion information -- I'll just comment on that while we're waiting.

So it is important, when I was talking about the liver events -- three of the four studies, the enoxaparin dosing started the evening before surgery. So that was about, on average, 13 hours presurgery. Rivaroxaben started six to eight hours later. So there was a window of about 20 hours where some of the liver cases occurred before actually getting any rivaroxaben, and then actually were not elevated while they were on rivaroxaben therapy.

RECORD 4 is the opposite. Rivaroxaben started six to eight hours; enoxaparin started the next morning.

So that -- it is important to remember those windows between the different studies.

If we could actually go to the slide that was up here just before

this one was the right slide. It looks at treatment discontinuations. Slide on.

So here is the -- for the pooled studies again, looking at the whole population, completed treatment was about 90 percent, so a little less than 90 percent of both groups. And this would mean that they completed the assigned duration of therapy, so 35 days in RECORD 1 and 2, and the 12 days, plus or minus two days, in RECORD 3 or 4.

DR. LINCOFF: Dr. Neaton?

DR. NEATON: I want to come back to the primary end point and the amount of missing data, which is substantial, as a consequence, largely of the venography not being there, 30 to 39 percent. And so while it's reassuring that the percentages are similar in the two treatment groups, that's only partially reassuring, as I'm sure you know, because there may be different reasons for not getting that venography.

Can you kind of shed any light on what type of sensitivity analyses have been done to convince us that that missing-ness is not really something important that we should be paying attention to?

DR. PETERS: So if we could have the slide -- slide on.

So before going through these, just do want to comment that we did look -- again, the amount of missing data was equal in the two groups, and we did look at the -- and that primarily is due to the venography. There were a few people who missed the surgery. There were a few people who were excluded

from the ITT populations because the evaluations were outside of the prespecified windows. But the vast majority of the missing data is related to either not having the venography done, or it was done but it wasn't -- you weren't able to read the venogram. So that's important to remember.

Also, the symptomatic event analyses, which lined up very closely with the primary end point, in terms of relative reductions, do not have the problem with missing data because we included everyone in the safety population.

So having said that, these are the five methods that we used. In each individual protocol we did assign some different scenarios -- we called them optimistic, realistic and pessimistic -- where we imputed values for the people who were missing data.

We also expanded the ITT population by looking at the investigator-reported events, rather than just centrally adjudicated, and widening the windows for inclusion to include all the venographies we had.

We did look at treatment effects, taking the centers and taking the best centers and grouping them into highest validity tercile, and looking at the worst centers. And you do see the highest validity terciles get up to about 90 percent of valuable data, and the worst are in the 50 percent range.

We looked at a method, composite end point method reported in the literature. And then we also did look at the rates of -- VTE rates that would be required for rivaroxaben in the missing data population that would be

needed to negate the superiority.

So we have slides for all of these. They all very strongly support the primary end point results.

DR. NEATON: I saw the data that you cited for a couple of these bullets in your reported. Have you looked at kind of characteristics of patients at entry, apart from center that you looked at, that were related to the missing-ness?

DR. PETERS: We did, and there are some, as you would expect -- I don't remember all of them off the top of my head, but, for example, older individuals were more likely to not have venography done. And heavier individuals, where it might be technically more difficult, were a bit more likely.

So there were some baseline characteristics -- actually, center -- you know, some centers are better than other centers. So when you look at centers, there are some differences there.

And then there are some -- so we did look at some of those reasons -- and, again, it was very -- the reasons were very balanced between the two treatment groups.

DR. NEATON: Patients that had a high probability of getting the data, kind of based on characteristics apart from center, are the results comparable?

DR. PETERS: I would say the closest to that is probably the

validity tercile analysis because that would group the people and the centers that were good at -- at least it would group the centers that were very good at doing the venography. So -- slide on.

So here's, again, the pooled data across the RECORD 1 to 4. We also have it by individual study. And you can see the lower tercile, the rate -- the odds ratio was .5, the middle tercile was .33, the upper tercile was .44. No strong statistical evidence for any heterogeneity.

And, again, the best tercile was approaching 90 percent of the people in those centers did have the venography done, and it was a valuable -- you know, and the lower tercile was significantly poorer than that. So we don't see much evidence for a difference according to -- at least this analysis of missing data.

DR. LINCOFF: All right. I think we're going to break here. We do have a list -- McGuire, Wolfe, Venitz, Skinner, Kaul and Paganini -- which we will come back to after the FDA's presentation. So we will not forget.

I'd like to cut this a little shorter than 15 minutes, so we'll take a break. Panel members, please remember that there should be no discussion of the meeting during the break amongst yourselves or with any member of the audience.

I'd like to restart at about 10:25. So about a ten-minute break, if we could. Thank you.

(A recess was taken from 10:16 a.m. until 10:33 a.m.)

DR. LINCOFF: Okay. At this point, we'll now move on to the FDA presentations, starting with Kathy Robie-Suh, medical officer.

DR. ROBIE-SUH: Good morning. My name is Kathy Robie-Suh, and I'm a medical team leader in the division of medical imaging and hematology products. I will give a brief introduction of the FDA presentation of rivaroxaben, and provide some regulatory background.

As outlined here, following my introduction, Dr. Min Lu will present her review of efficacy and safety of rivaroxaben for the indications. Then Dr. Qing Xu will comment on statistical aspects of the efficacy analysis. Next, Dr. Kate Gelperin will discuss hepatotoxicity concerns for the drugs. And, finally, Dr. Christoffer Tornoe will present clinical pharmacology findings related to the need for rivaroxaben dose adjustment in certain patients.

Hip and knee replacement surgeries are very common in the United States, with hundreds of thousands of the procedures being performed yearly, as has been mentioned earlier. The rate of thromboembolic events, or VTE, in patients undergoing these surgeries has been estimated at 40 to 60 percent in the absence of prophylaxis, with rates being higher in knee surgery than in hip surgery.

Events consist mainly of venographically detected deep vein thromboses, DVT, most of which are asymptomatic and do not appear to be clinically important.

Clinically important DVT, which may lead to symptomatic pulmonary emboli and death following these surgeries are uncommon, occurring at a rate of 1 percent or less of all detected VTE. Because of the low rate of symptomatic DVT and PE, VTE prophylaxis studies have generally relied upon using imaging, venography, to detect all DVT and, thereby, to provide sufficient numbers of events to assess drug effects. And this approach, and has been mentioned, commonly leads to substantial percentages of patients been non-evaluable by venography or missing -- not having a venography done, and leads to missing data of about -- upwards of 30 percent sometimes as has just been mentioned in this current case.

Studies have indicated that occurrence and detection of proximal DVT has greater clinical importance than distal DVT.

FDA has approved three drugs for the prophylaxis of VTE in major hip and/or knee surgery. These drugs are enoxaparin sodium, or Lovenox, daltaparin sodium, or Fragmin, and fondaparinux sodium, Arixtra.

Enoxaparin and fondaparinux are approved for use in both hip and knee replacement surgery, and daltaparin is approved in use only in hip replacement surgery. All three drugs are administered subcutaneously, and no drug is recommended for a treatment duration beyond 35 days for these indications.

My final slide highlights particular issues that might be considered when interpreting the results of the submitted studies for today's

application. With respect to efficacy, venographic outcomes have been the precedent for assessment of primary end points in clinical trials of VTE prophylaxis, and this approach has been used in planning the rivaroxaben trials.

With respect to safety, we note that enoxaparin, the comparator drug in the RECORD studies, is known to be associated with transient liver enzyme elevations with or no apparent clinical consequence.

As has been presented, rivaroxaben also causes elevations. And also note that the studies tested a fixed 10-milligram dose of rivaroxaben, with very limited representation of certain special populations at risk for increased exposure and potential increased bleeding risk.

Finally, I cite the following regulatory considerations. Several drugs are already approved and available for prophylaxis in elective hip and knee surgery. If approved, rivaroxaben would be the first oral anticoagulation approved for these short-term uses.

Furthermore, this would be the first oral anticoagulant approved for any use since the approval of warfarin.

Certain factors, such as the convenience of an oral anticoagulant might result in a special potential for extended prophylaxis use, or for use of the drug in other settings, as reflected in the clinical uses for warfarin. However, the safety and efficacy of rivaroxaben for these other uses and longer durations is not known and will be evaluated in the ongoing clinical

studies for these other indications.

Now, Dr. Lu will present findings of the FDA efficacy and safety review. Thank you.

DR. LU: Good morning. My name is Min Lu. I'm a medical reviewer in the division for medical imaging and hematology products. I will summarize the major findings from the rivaroxaben NDA that are mostly relevant to today's discussion.

Our review has focused on four major questions, as outlined here. Firstly, does rivaroxaben show efficacy for the proposed indication? Our main safety questions are, does rivaroxaben increase bleeding compared to enoxaparin? Does the drug increase the risk for hepatocellular? And, lastly, is the risk for thrombotic cardiovascular event increased after rivaroxaben discontinuation?

As previously noted, the proposed indication is for the prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip or knee replacement surgery. The proposed dosage regimen is a 10-milligram tablet once daily with a recommended duration of 35 days for patients undergoing hip replacement surgery and 14 days for those undergoing knee replacement surgery.

Rivaroxaben is under development for five indications. Confirmatory clinical data are completed only for the hip and the knee surgery indication. Clinical studies are currently ongoing to assess the drug's use in other

indications. Several of these ongoing studies assess the long-term safety and efficacy of rivaroxaben.

The clinical development program is summarized here. Approximately 18,000 patients participated in 64 completed clinical studies. As previously noted, the four RECORD studies are the main confirmatory data source for the proposed hip and knee surgery indication. The ongoing clinical studies provide us some information, although the data are limited, preliminary, and are largely blinded for treatment assignment.

As previously mentioned by sponsor, one study are mentioned later. That study we have not received the complete study report and result.

As of six-month safety update for the NDA, approximately 10,000 patients had been exposed to rivaroxaben for one month; about 6,000 patients had been exposed to rivaroxaben for six months in these studies.

The RECORD studies shared a similar design. RECORD 1 and 2 were the hip studies, and RECORDs 3 and 4 the knee studies. These studies were randomized double-blind, enoxaparin controlled international trials. Venograph was used for the efficacy outcome assessment. Follow-up extended for approximately one month after venograph procedure. The major efficacy and safety outcome underwent a centralized adjudication.

Certain considerations are also notable for the enoxaparin comparative dose and the treatment duration in the RECORD studies. RECORD 1, 2 and 4 use the dose of enoxaparin that are approved by the FDA. The RECORD 3

study used the enoxaparin dose 40 milligrams daily, that is not approved for use for patients undergoing knee replacement surgery in the United States, but it is approved for use in other countries. Perhaps more notably, the duration of active drug therapy differed in the RECORD 2 study where rivaroxaben was administered for 35 days while enoxaparin was administered for only 12 days.

The treatment effect of enoxaparin in control groups may have been potentially underestimated in the RECORD 2 and 3 studies.

Approximately 12,700 patients were randomized in the four RECORD studies. About 90 percent of study patients completed studies; however, about one-third of study patients did not have adequate venograph assessment for DVT and were excluded from the primary efficacy analysis, the MITT population. No important imbalances were observed in baseline characteristics between the groups in each study.

The primary end point of total VTE was a composite end point that consisted of any DVT or non-fatal PE or death for any cause. Statistical difference was demonstrated in both hip studies as shown here. In RECORD 1, the primary end point result was 1.1 percent for the rivaroxaben group compared to a rate of 3.7 percent for the enoxaparin group. In RECORD 2, the rivaroxaben rate was 2 percent, compared to a rate of 9.3 percent in the enoxaparin group.

The outcomes may have been related to imbalance in the duration of the study drug administration between the two groups.

As highlighted at the bottom of the table, the treatment effect was mainly due to differences in the venograph detection of proximal and distal DVT.

Statistical difference for total VTE was also demonstrated in both of the knee surgery studies. In RECORD 3, the primary end point result was 9.6 percent for the rivaroxaben group, compared to a rate of 18.9 percent for the enoxaparin group. In RECORD 4, the rivaroxaben rate was 6.9 percent, compared to a rate of 10.1 percent in the enoxaparin group.

Again, the treatment effect in these studies was mainly due to differences in venographic detection of proximal and distal DVT.

This slide summarizes the secondary efficacy end point of symptomatic VTE, which consisted of symptomatic DVT or PE. In all four RECORD studies, the rates for symptomatic VTE was numerically lower for the rivaroxaben group compared to the enoxaparin group. However, statistical difference was demonstrated only in RECORD 2 and 3.

As previously mentioned, in RECORD 2, the active study treatment duration was unbalanced while the RECORD 3 study used a dose of enoxaparin that is not approved for use in the United States.

Next I'm going to present the safety results. I will start with all adverse events in the RECORD studies, followed by a summary of bleeding, hepatic and cardiovascular events. I will close with a mention of certain renal laboratory test abnormalities.

This slide summarizes all adverse events in RECORD studies. Nearly 70 percent of study patients report at least one adverse event in both treatment groups. As is shown in the table, numerically low rates were observed for rivaroxaben group compared to enoxaparin group for occurrence of any adverse event: Death, serious adverse event, and an adverse event resulting in permanent study drug discontinuation.

This slide summarizes the number of deaths that occurred during the treatment and follow-up period in each RECORD studies. In RECORD 1 to 4 studies, the number of deaths was the same between the two treatment groups. In RECORD 2 and 3 studies, less number of deaths was observed with rivaroxaben than with enoxaparin. However, the treatment duration was unbalanced in RECORD 2 study, and the enoxaparin dose was not approved in the United States in the RECORD 3 study.

The RECORD studies identify bleeding as a major risk associated with rivaroxaben treatment. This table summarizes the composite outcome of major bleeding, which consisted of five components as listed in the table. In the RECORD studies, the occurrence of major bleeding was approximately twice for rivaroxaben group compared to enoxaparin group, .4 percent versus .2 percent.

As is shown in the bottom rows, this imbalance in bleeding was evident in most of the components of major bleeding composite.

The only deaths related to bleeding occurred in the rivaroxaben group. One of these deaths occurred prior to receipt of the rivaroxaben,

while the other death occurred in the setting for rivaroxaben use concomitant with use of three non-steroid anti-inflammatory agents. This patient was a 53-year-old man who died after presenting to the emergency room with upper GI bleeding.

This table summarizes the non-major bleeding in the RECORD studies. Overall, the occurrence of any bleeding event was about 7 percent, with a slightly higher number of patients in the rivaroxaben group. The imbalance of more bleeding in the rivaroxaben group was also evident for clinically relevant non-major bleeding as well as other type of non-major bleeding.

This slide begins a brief summary of data regarding the liver toxicity within the RECORD study database. It was noted that a small imbalance in the rate of serious hepatic events and the occurrence of a specific biomarker for liver injury: An ALT more than three times the upper limit of normal, combined with a total bilirubin more than two times the upper limit of normal.

These laboratory abnormalities are components of definition of Hy's law cases as described in the FDA draft guidance on drug-induced liver injury. As described in the guidance, Hy's law case are markers, potentially predictive of liver toxicity. A case definition is shown in this slide. This guidance also notes that finding one Hy's law case in clinical trial is ominous; finding two is highly predictive of a potential for severe drug-induced liver injury.

Overall, 16 patients in the RECORD studies experienced ALT elevations greater than three times the upper limit of normal, concurrent with a total bilirubin level greater than two times the upper limit of normal. Nine of these patients were in the rivaroxaben group and seven were in the enoxaparin group. The patients had their clinical data adjudicated by a liver assessment panel.

For the RECORD studies, the distribution of this panel's assessment is shown at the bottom of the slide where the patient or group accounting for the most relatedness assignment by any adjudicator. As you can see in the highlighted row, a possible association to the study drug was noted for six patients in the rivaroxaben group and only two patients in the enoxaparin group. Both groups had one patient assessed as having liver test abnormalities probably related to the study drug, and no definite associations were made.

This table summarizes occurrence of ALT and total bilirubin test abnormalities in the RECORD studies. In general, the distribution shows the rate of these events were similar between the study groups.

This slide shows the incidence of serious hepatic adverse events that were reported in RECORD studies. Overall, the pooled data showed a slight increase in numerical rate in the rivaroxaben group compared to the enoxaparin group, .5 percent versus .4 percent. This imbalance was predominantly due to serious adverse events reported for the ALT increases.

The rates of other categories for hepatic serious adverse events were similar between the two groups.

In the phase 2 studies, five patients in the rivaroxaben group and two in the enoxaparin group experienced ALT elevations that represent three times the upper limit of normal concurrent with a total bilirubin greater than two times the upper limit of normal. Two out of five rivaroxaben patients subsequently died. Adjudicator reports that both of these patients had comorbidities that is related to the liver abnormalities, although the liver advisory panel also noted that rivaroxaben toxicity could not be excluded in one of the patients.

In ongoing clinical studies, 27 patients have been reported as having ALT more than three times upper limit of normal, with a total bilirubin more than two times the upper limit of normal based on six-month safety update for the NDA.

Of these reported, six were from the unblinded studies, whereas -- three reported came from rivaroxaben group and three from the control group.

In ongoing blinded studies, 21 reports were provided with selective unblinding disclosing that one report was from a patient in the rivaroxaben group and four reports were from patients in the comparator group. Overall, the data from ongoing studies were limited and preliminary.

The next few slides provide a few additional indicators of possible safety concerns.

This table summarizes the overall incidence of cardiovascular events throughout active treatment and the follow-up periods of the studies. Overall, 31 patients in the rivaroxaben group and 39 patients in the enoxaparin group experienced cardiovascular events. With respect to the specific type of event, the distribution of events generally favored rivaroxaben except for the occurrence of ischemic stroke where 12 patients in the rivaroxaben group experienced ischemic stroke, compared to seven in the enoxaparin group. This imbalance was due to ischemic stroke that occurred following discontinuation of study drugs.

Six out of 12 ischemic strokes in the rivaroxaben group and one of seven in the enoxaparin group occurred after the study drug discontinuation.

This table summarizes the time windows for the occurrence of cardiovascular events following discontinuation of study drugs in the RECORD studies. Overall events were reported for 17 patients in the rivaroxaben group and 14 patients in the enoxaparin group.

As highlighted in the table, 11 of the rivaroxaben group events occurred less than ten days following study drug discontinuation compared to three events in the enoxaparin group.

One of the findings in the laboratory data review was a small imbalance in creatinine and BUN abnormalities. As shown in the table, abnormality of more than one times the upper limit of normal creatinine occurred in 12 percent of rivaroxaben group and in 10 percent in the

enoxaparin group. BUN abnormalities of more than one times the upper limit of normal occurred in 9 percent of rivaroxaben group and 8 percent in the enoxaparin group.

As I mentioned initially, we have had four major questions during our review. Here are our major observations. Do the data show efficacy? Yes, we regard the data as support the drug's efficacy based on the primary efficacy analysis of total VTE. Compared to the approved enoxaparin dose regimen with the same treatment duration, rivaroxaben has shown to reduce the total VTE, mainly due to asymptomatic DVT.

Rivaroxaben has not shown to reduce mortality, has not shown reduce symptomatic VTE significantly.

Does rivaroxaben increase bleeding? Yes. The data show that the risks of major and non-major bleeding are increased compared to enoxaparin. The bleeding risk consideration will subsequently also be addressed in a clinical pharmacology presentation.

Does rivaroxaben increase risk for hepatotoxicity? Based on current data available, we cannot exclude rivaroxaben from the hepatotoxicity. Additional liver considerations will be addressed by presentation from the FDA office of surveillance and epidemiology.

Finally, is there an increase of thrombotic cardiovascular risk after rivaroxaben discontinuation? Again, the data do not exclude this possibility.

The ongoing studies may provide clear answers to the last two questions.

Dr. Xu will now provide the statistical considerations regarding the safety and efficacy analysis for the RECORD studies. Thank you.

DR. XU: Good morning. My name is Qing Xu. I'm the primary statistical reviewer for rivaroxaben at FDA.

I will limit my presentation to a brief description of some key elements of the clinical development program of rivaroxaben and a discussion of integrated analysis of the data from this program.

As you have heard, this product is for prophylactic use as a anticoagulant in patients undergoing total hip replacement and total knee replacement surgery. The total hip replacement consisted of two active control randomized, double-blind, multi-center trials called RECORD 1 and RECORD 2. The active control used was enoxaparin.

RECORD 1 study was well-designed with appropriate enoxaparin regimen. However, in RECORD 2 study, shorter duration of enoxaparin was used. This could potentially lead to an underestimation of enoxaparin effect in the trial.

The total knee replacement program paralleled total hip replacement program with two enoxaparin-controlled, randomized, double-blind, multi-center study called RECORD 3 and RECORD 4. In this program, RECORD 4 study was well-designed with appropriate enoxaparin regimen. However, in RECORD 3 study, a

dose of enoxaparin was used that is not approved in the United States. As a result, this study was conducted entirely outside U.S.

Once again, this control regimen could potentially lead to an underestimation of enoxaparin effect in the trial.

For both programs, the primary end points was total VTE. As has been stated, this end point is a composite of clinical events of death and non-fatal PE and a venograph-based end points of proximal and distal DVT.

Statistical superiority of rivaroxaben was achieved in all four studies in terms of total VTE primarily due to its effect on venograph-based end points.

All RECORD study protocols include several secondary efficacy end points. However, the studies' statistical analysis plan, or SAPs, did not include control of false positive rate for confirmatory evidence of benefit based on secondary end point.

Nominal P-value for these secondary end points were less than .05 only in RECORD 2 and RECORD 3 studies which used less than optimal regimen of enoxaparin and a shorter duration of treatment in enoxaparin group.

Based on this result, the review team is in agreement with the sponsor that data from RECORD studies demonstrate efficacy of rivaroxaben for use as prophylactic anticoagulant after total hip replacement or total knee replacement surgery.

Having stated this agreement, I will now turn to the question, what

is extent of prophylactic benefit?

A clinically important end point in this patient population is symptomatic VTE or deaths. However, statistical analysis plan for each RECORD study did not include a planned confirmatory comparison of rivaroxaben with enoxaparin in terms of this end point. Therefore, any comparison of rivaroxaben with enoxaparin for symptomatic VTE or deaths is exploratory and the best hypothesis generating.

Having stated this analytical limitation, we will evaluate the data for this end point further.

Now, let us look at -- observe the data for the components of these composite end points.

This slide summarizes the observed data for symptomatic VTE which consisted of symptomatic DVT or PE. In all four RECORD studies, the rates for symptomatic VTE were numerically lower for the rivaroxaben group compared to enoxaparin group. However, in RECORD 2 or 3, the difference was larger, potentially due to a shorter treatment duration of enoxaparin in RECORD 2 study and unapproved lower enoxaparin dose used in RECORD 3 study.

Similar findings were shown in the component of deaths during the treatment period in RECORD studies. Again, in RECORD 1 and 4 studies, the number of deaths were similar between the two treatment groups. In RECORD 2 and 3 studies, there were fewer deaths with rivaroxaben and with enoxaparin. This is potentially related to a shorter treatment duration of enoxaparin in

RECORD 2 study and unapproved lower dose enoxaparin used in RECORD 3 study.

The sponsor analyzed this data from all four studies in an integrated analysis. The plan for this analysis was put in place while these studies were ongoing.

As per this plan, data from all four studies were combined without weighting, and an analysis was performed as if the data were derived for a single study, therefore, not accounting for between-study variation. This is important that background of controlled rate could be different study by study.

In the sponsor's analysis, important study characteristics, such as type of surgery, dose and duration were ignored. Also, control of false positive rate was not built into the plan for confirmatory analysis. Any analysis with this limitation can yield spurious results.

With that in mind, let us look at the sponsor's result. In all four RECORD studies, the rates for symptomatic VTE or death were numerically lower for rivaroxaben group compared to enoxaparin group. However, nominal P-values were less than .05 only in RECORD 2 and RECORD 3, as highlighted here.

As previously mentioned, these two studies had unique features regarding dose and duration of treatment in enoxaparin group. For the pooled data, the sponsor, based on sample pooling, showed nominal P-value is less than .05, and a 95 percent confidence interval is excluded -- in favor of rivaroxaben.

Leaving aside the issue of lack of control of false positive rate, FDA conducted pooled analysis of data from four RECORD studies using two methods that account for different study characteristics. One is meta analysis. Meta analysis provides ability to control between study variation, and this is important that background or control rates could be different from study to study.

In addition, proportional hazard regression, adjusted for covariates were used after an adjustment for the risk factors such as duration of treatment, study and age and so on.

The comparison of survival times between groups should be less biased and more precise than simple comparison, and also increased model power.

The following slides present the result of this analysis. This slide shows the result of meta analysis for symptomatic VTE or death for pooled study. The overall -- the combined hazard ratio is .65 with 95 percent confidence interval of .03 to 1.4. That includes 1 and it does not provide evidence of significant benefit of rivaroxaben over enoxaparin in terms of symptomatic VTE or death.

In particular, for RECORD 2, when the effect of duration of treatment is considered, rivaroxaben's hazard ratio is 2.13 and the yellow color is on the right side, which is different from RECORD 1, RECORD 2 and RECORD 3 and RECORD 4.

This shows that simple pooling of the data from four studies is not appropriate.

This slide shows the result of proportional hazard regression as adjusted for covariates of study duration and age. The P-value is .07, which is consistent with the result from meta analysis.

Now, let us briefly turn to an assessment of bleeding risk of rivaroxaben in relation to enoxaparin which itself has labeled bleeding risk.

This slide shows observed data on bleeding based on the sponsor's pooled sample. The blue bar stands for percentage of bleeding for rivaroxaben group. And yellow bar stands for the percentage of bleeding for enoxaparin group.

Clearly, we can see that rivaroxaben has numerically higher percentage of bleeding than enoxaparin group for all type of bleeding: Major bleeding event, major bleeding, including surgical site, major or non-major bleeding, clinically relevant bleeding and any bleeding event.

To analyze this data, the sponsor used a proportional hazard model without adjust any covariate. We re-analyzed the data using more appropriate proportional hazard regression and adjust for covariate which clinical relevant as well as meta analysis.

This slide shows the result from sponsor's unadjusted analysis in yellow font and FDA adjusted analysis in white font. The result shows that an adjusted analysis provides stronger evidence increased bleeding associated

with rivaroxaben in all type of bleeding event.

This slide shows meta analysis for major or non-major clinically relevant bleeding. The overall hazard ratio is 1.45 and the P-value is .001 which is consistent with the previous result that rivaroxaben significantly increased bleeding.

This slide attempts to provide a simultaneous look at the analysis of both potential benefit and the potential risk. The meta analysis results for symptomatic VTE or death are shown in the top of panel, and the results for the bleeding risk are shown in the bottom of panel to allow for simultaneous benefit-risk assessment.

As you can see, the combined result for benefit overlaps one. The combined result for risk is to the right one against rivaroxaben.

To summarize, first, the data from four RECORD study provides sufficient evidence to conclude that rivaroxaben is efficacious as an anticoagulant for prophylaxis after total hip replacement and total knee replacement surgery.

Second, exploratory analysis shows no evidence of potential superiority of rivaroxaben compared to enoxaparin in terms of clinical important outcome of symptomatic VTE or death.

All analysis of bleeding provides consistent evidence of significant increased risk of bleeding for rivaroxaben compared to enoxaparin.

These conclusions lend themselves to more evaluation of benefit-risk

profile of rivaroxaben using the data from ongoing long-term studies. Thank you, and I will give the podium to Dr. Gelperin for clinical presentation on hepatotoxicity of rivaroxaben.

DR. GELPERIN: Good morning. My name is Kate Gelperin. I'm a medical officer in the FDA office of surveillance and epidemiology.

During the next 15 minutes, I will be presenting a high-level overview of FDA's ongoing evaluation of a potential signal for severe liver injury with rivaroxaben. I will describe our initial analysis of selected clinical laboratory data from completed and ongoing rivaroxaben clinical trials.

I wish to acknowledge and thank Dr. Ted Guo from the FDA office of biostatistics for his analysis and graphic display of the data sets, as well as Dr. John Senior, an FDA hepatology expert, who developed the analytic concepts.

For this analysis, we focused on clinical laboratory results of ALT and total bilirubin, with a cutoff of ALT greater than three times the upper limit of normal and total bilirubin greater than two times the upper limit of normal to describe severe liver injury. The rationale for this is that ALT is a sensitive test for severe liver injury, but poorly specific.

Evaluating concurrent total bilirubin improves specificity and increases positive predictive value for serious outcomes such as liver failure.

Cases identified as potential severe liver injury using clinical lab data must undergo additional in-depth evaluation and adjudication to determine whether the injury was drug-induced. Relevant to the adjudication process is the concept of Hy's law. Dr. Hy Zimmerman was a hepatologist and author who observed that drug-induced hepatocellular jaundice is a serious lesion, potentially life-threatening.

The explanation is that hepatocellular injury great enough to interfere with bilirubin excretion in the absence of biliary obstruction involves a large fraction of the liver cell mass. The concept of Hy's law has been relevant in FDA experience with several drugs, two of which I'll briefly describe.

Troglitazone is an oral anti-diabetic drug which was found to cause severe hepatotoxicity and liver failure post approval. In clinical trials which led to troglitazone's approval in 1997, there were no cases of liver failure in 2,510 patients comprising the NDA database. About 2 percent of patients receiving troglitazone had ALT elevations greater than three times the upper limit of normal and, of these, five had ALT greater than 30 times the upper limit of normal, two of whom had jaundice and, in retrospect, they represented Hy's law cases.

The drug was withdrawn from the U.S. market in March 2000 after the FDA had received 94 cases of drug-induced liver failure. Of these, 19 were determined to progress to irreversible liver injury within less than a one-

month period, and that cast doubt on the value of monthly monitoring in a setting of rapid drug-induced liver injury.

The second case example I'll discuss is ximelagatran, an oral anticoagulant drug developed for similar indications as rivaroxaben. In long-term atrial fibrillation trials with ximelagatran, there were 37 -- which is 0.5 percent -- patients with severe liver injury as defined by the laboratory cutoffs, compared to five -- that's 0.08 percent -- receiving warfarin, and a relative risk of 6.6.

The expert adjudication process determined a positive causality assessment for 19 of the ximelagatran-treated patients, compared to two of those receiving warfarin, with a relative risk of 8.5.

No signal for severe liver injury was detected in short-term orthopedic trials, but a strong signal was found in the long-term atrial fibrillation trials.

Analysis of the long-term data showed initial signs of liver injury within the first 30 days for six study subjects who went on to develop severe liver injury, of which four cases were adjudicated as causally related to ximelagatran.

An advisory committee voted that the potential benefits of ximelagatran did not outweigh the risks and so the drug was not approved in the U.S., and the sponsor later decided to withdraw the drug from worldwide marketing after an additional case in Europe.

In the next few slides, I'll present an overview of clinical laboratory data from the rivaroxaben clinical program, using the format you see here in this graph, which was previously described in the previous talk, and it shows a distribution of peak values of ALT and total bilirubin for all study subjects -- in this case in a hypothetical trial. Each data point represents an individual patient from the trial. The lab results are displayed as multiples of the upper limit of normal for ALT and total bilirubin on a logarithmic scale.

The graph is divided into four quadrants, separated by the two times the upper limit of normal line for total bilirubin and the three times the upper limit of normal line for ALT.

Data points for study subjects with ALT greater than three times the upper limit of normal are shown in the right lower quadrant. And potential Hy's law cases with concurrent increases in ALT and total bilirubin are shown in the right upper quadrant.

This slide shows peak ALT and total bilirubin laboratory data for all study subjects in the four RECORD trials for the orthopedic surgery indications. In the right upper quadrant, you can see there were, overall, ten potential Hy's law cases in each treatment group, and these were further adjudicated by the sponsor's expert panel.

In the right lower quadrant, it is clear that a substantial proportion of patients in each group experienced transaminase elevations, with

nearly 4 percent of those receiving enoxaparin and 3 percent in the rivaroxaben group developing ALT greater than three times the upper limit of normal.

I want to point out that the current approved labeling for enoxaparin, the comparator drug in all four of the RECORD studies, does describe ALT greater than three times the upper limit of normal to be reported in nearly -- up to 6 percent of patients. And the elevations are generally considered to be reversible.

Increased risk of drug-induced liver failure has not been demonstrated with enoxaparin during 15 years of post-marketing experience.

Potential Hy's law cases from the RECORD trials were adjudicated by the sponsor's liver advisory panel. I acknowledge that Dr. Watkins presented a different causality assessment this morning, and would like to state that the FDA hospitalized not separately adjudicated these cases. However, of nine cases identified by the sponsor with concurrent elevations of ALT and total bilirubin, seven were considered possibly related to rivaroxaben therapy by at least one member of the expert panel.

In contrast, for seven potential Hy's law cases in the enoxaparin group, only three were considered possibly related to drug by the panel.

The sponsor recently provided FDA with fully blinded clinical laboratory data sets for ALT and total bilirubin from the ongoing ROCKET atrial fibrillation trial. Nearly 11,000 subjects have been randomized in

this long-term double-blind trial with current mean treatment duration around 230 days in this data set here.

The comparator in the ROCKET trial is warfarin, which is not known to be hepatotoxic. The trial remains fully blinded, so the clinical importance of the 142 cases of transaminase elevation or the 20 potential Hy's law cases remains to be determined, and these data should be available in the next year or so.

This slide shows clinical laboratory data for peak ALT and total bilirubin from the ongoing open-label EINSTEIN DVT/PE acute treatment studies. The EINSTEIN studies compare rivaroxaben 30 milligrams for three weeks, followed by 20 milligrams, with enoxaparin vitamin K antagonist active control.

To date, there are nearly 1700 patients randomized in each treatment group, with a current mean treatment duration in this laboratory data set of about 155 days. Four potential Hy's law cases have been identified to date, three on rivaroxaben. I will briefly discuss one of these three cases which had a fatal outcome.

This graph shows longitudinal laboratory data for a 63-year-old woman with a history of COPD who was randomized to rivaroxaben for the treatment of pulmonary embolism. The patient received 15 milligrams of double-blind rivaroxaben twice daily for a total of 17 days.

On day 16 she was hospitalized for dyspnea. On day 18 her ALT was

found to be 150 times the upper limit of normal and total bilirubin greater than four times the upper limit of normal.

On day 19, she was admitted to the ICU for a liver transplant discussion. On day 25 she experienced cardiac arrest and died the next day.

Autopsy showed hemorrhagic necrosis of the liver, massive dilatation of the right ventricle and left ventricular hypertrophy. The study site investigator considered the events were possibly related to study drug.

The sponsor's liver advisory panel did not reach a consensus initially, but felt that the case was consistent with ischemic hepatitis. However, one member considered that the diagnosis of drug-induced toxic injury of the liver is more likely.

In summary, OSE concludes that a potential signal for severe liver injury with rivaroxaben has not been fully characterized at this time. We recommend complete assessment, with a full evaluation of safety data from long-term clinical trials should be undertaken.

I'd like to thank colleagues at FDA who contributed to this analysis, and I'd like to introduce Dr. Cristoffer Tornoe who will present clinical pharmacology findings.

DR. TORNOE: Good morning. My name is Chris Tornoe, and I'm the pharmacokinetics reviewer from the FDA. I will summarize the key clinical pharmacology findings for this NDA. Particularly, I will focus on the estimated dose or exposure response relationships for effectiveness and safety

and the special populations at risk for clinically relevant increases in exposure.

The three key questions and answers from the clinical pharmacology review are presented on this slide. First question is whether there is evidence of dose exposure response for effectiveness and safety. We found a shallow dose response was evident for the composite efficacy end point. This means that the dose does not result in significant increases in the effectiveness.

Secondly, we found an increased risk of bleeding with increasing rivaroxaben dose and exposure.

The second key question of the review was whether -- which special populations are at risk for clinically relevant increases in exposure. We found that patients with moderate to severe hepatic impairment were found to have greater than two-fold increases in exposure, as well as patients receiving strong CYP3A4 and P-gp inhibitors.

Mild to moderate renal impaired patients plus moderate CYP3A4 or P-gp inhibitors have not been studied, but are likely to have greater than two-fold increases in exposure.

Finally, the last question is, what are the strategies for addressing increased exposure and bleeding risk in these special populations? We believe, instead of contraindication, the availability of a lower dose is the best option to manage exposure and help manage the risk of major bleeding

and allow a larger patient population to safely receive this treatment option.

This slide summarizes the pharmacokinetic characteristics of rivaroxaben. Rivaroxaben is almost completely absorbed after oral administration of 5-milligram tablet, and linear pKa was observed up to 15-milligram. The elimination half-life is five to nine hours in healthy volunteers. Thus, every 24-hour dosing will not result in significant accumulation of the drug.

Once absorbed, rivaroxaben is eliminated through multiple sites -- routes. Approximately 50 percent of an oral administered dose undergoes metabolic degradation, predominantly by CYP3A4 or 3A5. The remainder is excreted unchanged via active renal secretion and into the feces.

Patients with renal and hepatic dysfunction and, therefore, expected to have increased rivaroxaben exposure compared to patients with normal liver or renal function, and concomitant use of drugs that inhibit the above enzymes will likely -- will increase the systemic exposure of rivaroxaben.

This brings us back to the first key question of the review, whether there's any evidence of dose or exposure response for effectiveness and safety. The dose-response relationship for rivaroxaben was evaluated in the dose ranging phase 2 trial in 852 patients undergoing total hip replacement surgery. The active comparator, enoxaparin, was dosed daily at 40 milligrams, shown in red at the left. And rivaroxaben was dosed at 5 to 40 milligrams once daily for 9 to 11 days.

The composite efficacy end point presented on the Y-axis was defined as the proportion of patients with DVT, PE or any cause of death.

The enoxaparin response rate of 25 percent was substantially higher than the doses of rivaroxaben. A shallow dose-response relationship was observed for rivaroxaben, with no substantial decrease in the proportion of patients with DVT, PE or death when increasing the dose from 5 to 40 milligrams.

Based on these findings, we conclude that the choice of 10-milligram for the general population is acceptable, and increasing the dose beyond 10-milligram does not result in increased effectiveness.

In the same phase 2 dose ranging study, the risk of major bleeding was found to increase with increased dose and exposure. The definition of major bleeding in the phase 2 study included clinical overt bleeding associated with falling hemoglobin, leading to blood transfusion, re-operation or warranting treatment cessation.

A substantial increase in the risk of major bleeding from 0.7 percent to 5.3 percent was observed when doubling the dose from 10 to 20-milligram.

Similarly, the risk of major bleeding was found to increase with increased exposure as shown on the right graph showing the logistic regression analysis result with steady-state AUC or exposure with a P-value less than 0.01.

The exposure observed after 5 to 40-milligram was ranging from zero to 10 microgram hour per liter, and the probability of the risk of major bleeding is shown as a solid line with the confidence around it.

The risk of major bleeding increased from 2.5 percent at the mean AUC following 10-milligram to 3.8 percent at the mean exposure following 20-milligram. Based on these findings, we conclude the 10-milligram dose selection is appropriate from a safety point of view for the general population, and the bleeding risk increases with increasing exposure.

For -- the second key question is whether -- which special populations are at risk for clinically relevant increases in exposure? The key results from the renal and hepatic impairment studies, as well as the drug interaction studies are shown on this slide.

Patients with renal impairment had 1.4 to 1.6-fold increases in exposure relative to normal patients. Patients with mild and moderate hepatic impairment had 1.2 and 2.3-fold increases in exposure. Concomitant administration of strong CYP3A4 or P-gp inhibitors such as ritonavir or ketoconazole resulted in a 2.5-fold increase in exposure relative to normal.

Any combinations of renal and hepatic dysfunction, together with moderate to strong CYP3A4 and/or P-gp inhibitors are likely to have increases in exposure and, therefore, at a higher risk of bleeding.

Finally, to the third key question of the review: What are the strategies to address increased exposure and the risk of major bleeding in

these special populations? This slide represents an illustrative example showing how the availability of a 5-milligram tablet enables managing exposure and the risk of major bleeding in special population patients, such as patients with moderate hepatic impairment shown on this slide.

This is the same graph as shown previously from the dose ranging study where the risk of major bleeding increases with increasing exposure. The X-axis represents the steady-state AUC of rivaroxaben and the Y-axis shows the risk of major bleeding.

The mean AUC in normal patients receiving 10-milligram is 1.3, with a risk of major bleeding of 2.5 percent. A patient with moderate hepatic impairment with have a 2.3-fold increase in exposure, and the risk of major bleeding increases to 4.1 percent.

By administrating a 5-milligram tablet to a moderate hepatic impaired patient, the exposure will be similar, slightly higher than a normal patient, and the risk of major bleeding is reduced to 2.8 percent.

In summary, I hope I've demonstrated to you through the phase 2 dose ranging study that there is a shallow dose-response relationship for the composite efficacy end point with no substantial increase in the effectiveness for the increased rivaroxaben dose.

I also showed that the risk of major bleeding was found to increase with the increased rivaroxaben dose and exposure.

The results from the special population studies indicate that

moderate to severe hepatic impaired patients have a greater than two-fold increase in exposure, as well as patients receiving strong CYP3A4 or P-gp inhibitors.

Mild to moderate renal impaired patients, in combination with moderate to strong CYP3A4 or P-gp inhibitors have not been studied, but will have exposures greater than two-fold higher than normals.

Finally, I've illustrated that the availability of a lower dose is the best option to manage exposure and help manage the risk of major bleeding and allow a larger patient population to safely receive this treatment option. Thank you.

DR. LINCOFF: All right. Now, the schedule now calls for questions for the FDA, but we have a list of panel members who had questions earlier and so, in fairness, I'm going to start with that, although, if you do -- as I call you, if you do have questions that are preferentially for the FDA and can save -- because we'll have time later in the afternoon to, again, go back to both the FDA and the sponsor -- but it's your choice, and we'll go in the order that we had had the questions.

So first for Dr. McGuire.

DR. McGUIRE: Yeah, I have just a couple of points of clarification from Dr. Lu. We've heard many times that in RECORD 3 the enoxaparin strategy was not approved. And if you could clarify, is it not approved in the U.S. because the application has not been submitted or it's been reviewed and not

approved?

DR. LU: I don't believe we have data for the 40-milligram for knee replacement surgery. I think other countries approved it because they only showed efficacy for hip studies, but they gave the broad indication for orthopedic surgery.

DR. McGUIRE: So just to clarify, it has not been submitted formally for review?

DR. LU: We don't have data. I don't see any data shows efficacy for 40-milligram once daily for knee surgery patients. Other countries approved this based on the hip studies for using the 40-milligram, but they gave the broad indication for orthopedic surgery.

DR. McGUIRE: And then the second quick point of clarification, have you had the opportunity to review the drug withdrawal data from the ATLAS trial for cardiovascular events specifically for ischemic stroke?

DR. LU: No.

DR. LINCOFF: Dr. Wolfe?

DR. WOLFE: I have two questions. One is a follow-up of Dr. Kaul's question earlier which is now illuminated by the presentations by the FDA. Since it was valid to pool both the hip and knee studies, RECORDS 1 through 4, and since the question has been raised several times about the problem of adjusting things in 2 and 3 so that there was a more favorable looking result -- I mean, whether it was done with that intention or not is not relevant;

it's just that I think enough question has been raised about the duration of treatment in number 2 and the dose of 40 versus, essentially, 60 in 3 -- has anyone, the FDA or the company, done an analysis that pools 1 and 4?

And the reason I'm interested in is in Dr. Lu's slide 11 -- if we could put that up -- and what is shows is that the hazard ratio is most favorable, obviously, for the drug in 1 and 4 -- in 2 and 3, rather, where there arthroplasty problems with enoxaparin, either the dose or duration, and that -- whereas in those two, the 95 percent confidence intervals don't get up to 1, in the other ones, 1 and 4, the higher bound is 1.5 and 1.3.

So the question is, has someone done a pooled analysis just looking at 1 and 4? Dr. Xu, using a different method which adjusted, as you saw, in a proportional hazard regression for duration, but not for dose, found that when you pooled all four of them, you did not have an upper bound that missed -- it went above 1. So I'm -- is there an analysis just looking at 1 and 4 together, the two studies that don't have problems with enoxaparin dose or duration? Has that been done?

DR. XU: I did pooled analysis for just RECORD 1 and 4. The result seems -- there is no statistically different efficacy benefit in favor of rivaroxaben group.

DR. WOLFE: So you've done a pooled analysis and there is --

DR. XU: Yes. From meta analysis.

DR. PETERS: We have slides that we could show --

DR. LINCOFF: Yes. If you have that, go ahead.

DR. WOLFE: Using the same method that you used --

DR. PETERS: Yes. Yes. Using the same method.

DR. WOLFE: Okay.

DR. PETERS: So here's RECORD 1 and 4 -- slide on.

Just to comment before I go over the data as well, I think the -- it is important to remember that there was a statistical analysis plan for this pooled analysis. It was written while the studies were ongoing but before any study was unblinded, and it did prespecify one primary end point. That's why there's no adjustments for multiplicity.

In the statistical analysis plan for the pooled analysis, there was one primary end point, which was symptomatic VTE or death, and these studies reflect a global program and reflect practice across the United States. So the rationale for pooling all four together is reasonable and is strong.

I think the question is, are you comparing against -- what estimate do you want to get from these analyses? The RECORD 1 to 4 pool I believe is a very reasonable estimate and the best estimate of the overall treatment effect for rivaroxaben versus enoxaparin, as it's commonly used.

If you start picking studies, picking the best or the worst studies, you're going to get different estimates.

And so what you're asking for is kind of the, how does rivaroxaben do versus the strongest, or maybe versus the best enoxaparin regimens? And we

still do very well.

So you can see for the total VTE, which again, wasn't specified to be pooled for the primary efficacy analyses -- we did do it for benefit-risk in subgroups -- you can see very strong results there for the odds ratio: For total VTE, .52, confidence interval well away from no difference; for major VTE, also just to comment in the individual study statistical plans, there was specific ordering for -- the total VTE was the primary end point, major VTE was a prespecified secondary end point with even specific non-inferiority margins for it for the three studies that had non-inferiority testing.

Then there were another list of end points of which symptomatic VTE was one -- and others -- death by itself, PE by itself. And it is true that symptomatic VTE or death was not one of that list of end points in the individual studies, but because we knew that the events would be rare -- and when we were looking for pooling the studies across, we constructed the symptomatic VTE or death and did prespecify that.

So the major VTE results, which again, were prespecified in each individual study -- the hazard ratio for these two studies is .3, well away from no difference, and for the symptomatic VTE or death, looking at just the treatment phase, it is .61. It does just stretch across the no-difference line. Same for treatment in follow-up, .66, stretches across the no-difference line. But, again, the studies weren't individually powered.

And then if we add in the -- just the active therapy phase from

RECORD 2, the hazard ratio becomes .58, and that, again, is statistically different.

And I showed you the results looking at just the day 12 or the full 1 to 4 active control pool earlier as well. So --

DR. WOLFE: Then the answer is that, when you combine them, you do go above 1 because, in the FDA analysis in slide 11, the upper bound was 1.5 on one and 1.3 -- and because you've got more patients --

DR. PETERS: Right. And then --

DR. WOLFE: -- it gets a little bit lower. But it is --

DR. PETERS: And then --

DR. WOLFE: -- above 1, though.

DR. PETERS: And that's for the --

DR. WOLFE: Symptomatic.

DR. PETERS: For symptomatic VTE or death, right --

DR. WOLFE: Right.

DR. PETERS: -- which wasn't planned to be, you know, significantly powered in each individual study. And then I think we should also think about the benefit-risk, which Dr. DiBattiste can show some slides on how that efficacy --

DR. WOLFE: I have a second question, just a quick one. Fine. Thank you.

DR. LINCOFF: I think he's had his question answered.

DR. WOLFE: The second question is for Dr. Senior, because he's been involved in this for a very long time.

The conclusion by Dr. Watkins is, quote, a liver safety signal is not evident in the clinical trials database for rivaroxaben.

The conclusion of Dr. Gelperin is complete assessment fully evaluating -- excuse me -- a potential signal for severe liver injury with rivaroxaben has not been fully characterized at this time.

There is a big difference between these two, and I'd like to ask you, Dr. Senior, based on the fact that if this drug is approved now, even though the approval is limited to prophylaxis for total hip/total knee -- and it is very likely it will wind up being used for longer periods of time -- if you had your druthers, do you think that it is safe to approve this drug now before getting more assessment, particularly from the longer-term trials that are currently going on that will shed light on this very time-related phenomenon?

I mean, one of the things that was alluded to in these case examples is that these cases are starting to occur later, rather than earlier -- for instance, in the trials of the predecessor of this drug -- at 11, 12 days, 15 days nothing showed up.

So, direct question: Do you think it is a good idea to approve this drug now without waiting to see the results of much more data from much longer duration trials?

DR. SENIOR: First of all, Dr. Watkins gave a very thoughtful and I think very clearly expressed summary of his review of the cases that had previously been adjudicated by Drs. Maddrey, Schiff and Horsmans. But he didn't quite reach the same conclusions. That's not unusual.

As we all know, the adjudication of causality -- the attribution of causality -- was it the drug or was it disease or was it some combination or all that that's responsible? And experts differ. In the NIH-sponsored study of drug-induced liver injury for the past five years, conducted in five medical centers around the country -- and that adjudication committee is chaired by Dr. Watkins -- there's considerable difference of opinion about whether it's likely or possible or probably drug-related.

So this is a fine art. It's not a science yet. So I think we have to be careful about the adjudication.

Now, what Paul showed, I think very convincingly, that the six cases where there was possible effect of rivaroxaben on fatal liver disease all had some other explanation.

Now, what we don't know is what is the effect of a drug that occasionally -- rarely, perhaps -- can cause an injury to the liver when you already have another problem, when you've already got congestive heart failure, when you've already got alcoholic hepatitis, when you're 72 years old and you've been through anesthesia and surgery. We don't know those combination effects.

And yes, Sid, I am impressed with the ATLAS data, which I saw for the first time this morning, on -- the long-term six-month data compared to placebo looks good. But I want to see more, in answer to your question. I'd like to see the long-term data.

We should have learned a lesson from ximelagatran. We didn't see the signal in the short-term orthopedic study, which was a two-week study for, I think, knee replacement, but we did begin to see the signal out there beyond five, six weeks and beyond in the atrial fibrillation patients. And I'd like to see those data before I'm convinced that there is no problem with the liver.

DR. WOLFE: So your answer, if I may read between the lines, is that you think that we should wait for more long-term data before making an approval decision?

DR. SENIOR: Unless it can be shown -- I'm not convinced yet. If -- if rivaroxaben is truly reducing the risk of fatal pulmonary emboli -- not just all this combined end point where you throw everything but the kitchen sink in it -- but fatal pulmonary emboli are what we're trying to prevent.

If it can be shown that the drug is saving more lives than it's risking, then I think I would be -- I would think reduction in mortality would trump the risk of liver injury.

So -- but I haven't been convinced that those data are real. I think we need to see that.

DR. WOLFE: Thank you.

DR. LINCOFF: Can I just clarify. So the ATLAS data -- I mean, is there a time frame for that? Because that's a sizable number of patients. That's 2200 patients exposed for six months.

DR. SENIOR: The studies are already underway. They have thousands of patients in the long-term studies. We just haven't seen the data yet.

DR. LINCOFF: No, I understand, but this is still a sizable database that is completed, that does provide six months' data that is within the range of -- similar to the ximelagatran. I realize that was a larger experience -- do you have a comment?

DR. DiBATTISTE: Yes.

DR. SENIOR: Agreed. It's helpful, very helpful. And it's hopeful. I would like to see a drug approved that really saves lives and has more benefit than risk.

DR. DiBATTISTE: Just to confirm, the ATLAS study has been completed. Although the study report has not been finalized, the study was completed months ago, and the data were submitted in pieces, initially in the NDA, and then further in the four-month update. And then the final data that you saw today were submitted in early February, I believe, to FDA. And those data represent, as you point out, results in 3491 patients, 2200 of whom received rivaroxaben.

DR. LINCOFF: And EINSTEIN is also -- because, in total, you end up

-- in your CC-63, you have 4656 patients exposed to rivaroxaben in the total. Are all those data in a form that the FDA could review as rigorously as they've reviewed these others? Because these are long-term data.

DR. DiBATTISTE: Yes. So on this slide the first line includes 824 subjects in phase 2, and all those data are completed and submitted. The ATLAS data we just described.

The EINSTEIN study is ongoing. It is an open-label study, and so those data are available on a rolling fashion.

DR. LINCOFF: Thank you. Dr. Venitz?

DR. VENITZ: Thank you. I wanted to follow up on Dr. Gross' question about the dose response with Dr. DiBattiste. I was intrigued when I saw the package that you provided us with where you actually showed the dose response for both the efficacy, the reduction incidence of VTE, and the increased incidence of bleeding as a safety signal.

I was mostly intrigued by the fact that you actually compared it graphically with the effects of enoxaparin. I'm looking at page 79. That's where the graph is. And I was wondering whether you could maybe put the graph up and discuss a statement that I'm going to make, whether you agree or disagree with it. Because the way I look at it, comparing to enoxaparin, all the doses that you have of your compound show significant, or at least numerically improvement relative to the incidence of total VTEs. On the other hand, they also show increased bleeding risks.

Would you agree or disagree with that statement?

DR. PETERS: Is this the correct figure that you're referring to --

DR. VENITZ: Yes.

DR. PETERS: -- from the briefing book?

DR. VENITZ: Yes, the 11527 study, correct.

DR. PETERS: And just to reframe the question --

DR. VENITZ: If I compare your comparator to your doses that you have from 5 to 40 milligrams per day, that all your doses have increased efficacy relative to the comparator, but they have increased, or at least the same, incidence of bleeding.

DR. PETERS: So the enoxaparin comparator group rate in this study was close to 20 percent, so that is higher than all of the rivaroxaben groups in this one once-daily study. Again, I think, as pointed out earlier, we do need to be a bit careful. There's 100 to 150 people per group, so it's relatively small sample sizes. In a sister study to this one, the enoxaparin was actually lower than that, so the rates may be closer than this appears.

DR. VENITZ: Okay.

DR. PETERS: The rate -- as we looked at all the data -- and we can maybe show the phase 2 table from the briefing book as well -- so this was one study out of four. It was the only study with once-daily dosing in phase 2.

So if you look at the bleeding rate, certainly -- and we showed the numbers on the other graph. There were three at the 5-milligram dose, one,

and then six at the 20. So that 20-milligram dose group does appear to be above the dose response curve, although it's still within the upper bound of the enoxaparin confidence interval.

So we do -- there's no disagreement that bleeding increases with dose. I mean, that is definitely true. And beyond the dose of 10-milligram, I think there's also no disagreement that there's little gain in efficacy.

DR. VENITZ: So would it then be reasonable for me to conclude that if you had used a lower dose of enoxaparin, which you obviously didn't, that you could -- I'm sorry -- a higher dose of enoxaparin, that you could actually improve, potentially, the efficacy and, at the same time, see the same bleeding rates that you see at your 20 and 20-milligram doses? In other words, it's the degree of anticoagulation, really, that drives your efficacy and safety, and your dose is just something that you use to find the right balance, but you could do the same thing for enoxaparin -- forget the fact that it's used at an approved dosing regimen right now.

DR. PETERS: Right. Well, but -- correct, if we used a different dose of enoxaparin, we would get different results, but in all of our programs, both phase 2 and phase 3, except for the RECORD 3 40-milligram once daily, with did use approved enoxaparin regimen. So it's difficult to speculate on what might happen with a different enoxaparin dose.

If we could have the slide on -- this is a very busy slide, but it was in the briefing book, so hopefully you looked at it. I just wanted to

point out some of the bleeding event numbers and also the efficacy event numbers.

So if you look at the bottom row, which is all three of the twice daily studies pooled -- so that's the other three that we did in addition to the one we just looked at -- and you can see the rate of 7.1 percent at 2-1/2 twice daily, which is 5-milligrams total daily dose, 9.4 percent and then 9.9.

So, again, when we looked at all of the data from phase 2, looked at all of the data we had from clinical pharmacology, we actually looked at the range from 5 to 20. 20, as you highlighted, is maybe getting close to, even in the phase 2 studies, the bleeding risk was clearly higher than 10 or 5, and the efficacy gained from going from 10 to 20 did not seem to be there.

And then the 5 -- I showed you the data that we were concerned about loss of efficacy with the 5-milligram dose. So it really kind of homed in to the 10-milligram once-daily dose as the one picked for phase 3.

As we look at the different subgroups and think about a lower dose, or restricting use in certain subpopulations, you know, the bleeding risk, again, is in the 20 to 50 percent range between a 10 and a 20-milligram dose increase on -- absolute bleeding event rates in the 2 to 3 percent range. So we're not talking about huge absolute differences in bleeding events, and we saw substantial reductions in the total VTE end point in the individual studies.

DR. VENITZ: You've already anticipated my next question, because it

was exactly to look at this very table, because it does suggest that if you go from 10 to 20-milligram -- and this is where you pool across all your phase 2 studies, so you have a larger number -- in other words, you have more confidence in the incidence rate -- you're basically doubling the incidence of bleeding, going from 10 to 20.

DR. PETERS: Not from 10 to -- from 10 to 20 twice daily, so -- correct. That's from 20 to 40. So -- right. So look at the 5-milligram BID is the 10-milligram dose, is the 9.4 percent in the bottom row as an example -- goes to 9.9 percent at 20 a day, and then it goes to 18 percent.

So that is why, when I said earlier, we drew the line at a doubling of the dose. So we do agree that we do not want to expose people to more than a two-fold increase in dose because, once we get beyond that 20-milligram dose level, the curve does seem to be steeper.

And that's true if you look up at the major bleeding event as well. It goes from 1.6 to 2.3 between 10 and 20, which is a modest increase. But then it goes from the 2.3 -- it doubles again to 4.6.

So we are agreed. We would like to keep exposures at the 10 twice a day and lower range in our discussions with the agency.

DR. VENITZ: Thank you.

DR. LINCOFF: Dr. Skinner?

DR. SKINNER: Actually, that was just my question that he was dealing with, the BID dosing thing.

DR. LINCOFF: Dr. Kaul?

DR. KAUL: I have a comment/question for the sponsor and then a question for Dr. Xu.

I'm trying to understand the benefit, the driver of benefit. Although the composite end point is recommended by the regulatory agencies to meet licensing requirements, this approach may mislead if the components are of widely differing importance to patients and to practicing clinicians. And the size of effect differs markedly across components.

So the analysis of the composite end point in RECORD 1 is quite instructive in this regard. You have 18 versus 58 events in the primary end point, translating into a 70 percent risk reduction.

85 percent of this benefit was driven by the impact on all DVTs, which is the most prevalent but, arguably, not the most important component.

With respect to non-fatal pulmonary embolism, the point estimates favor the comparator. There are four versus one, translating to a risk ratio of 3.94, and the death was neutral.

So when you look at this and you do a formal analysis of heterogeneity, there is significant heterogeneity across the different components. So it is driven by all DVTs, which are presumably picked up on the basis of venography.

And I would like to ask -- see a show of hands here of the panel members, with the permission of the Chair, how many of us, or you, use

venography to diagnose DVTs in clinical practice routinely?

DR. LINCOFF: I'm not sure that's all that relevant. It's an appropriate end point for a trial. I mean, we've already heard from the FDA that this is an appropriate --

DR. KAUL: Maybe we could come back to that.

DR. LINCOFF: Yeah.

DR. KAUL: All right. So -- that was my comment. The question I have for you is, if we focus on symptomatic VTE and death and focus on trials 1 and 4, you have an upper bound of the hazard ratio of 1.5 and 1.3. The question I have for you is, did it meet the non-inferiority criteria in these two trials?

DR. PETERS: So let me answer the -- so there were not non-inferiority bounds estimated for symptomatic events because, in order to do non-inferiority, we have to have some placebo-controlled data on which to set, you know, how much of the effect we're going to retain.

Previous drugs approved based on venography, there is no basis for really establishing a non-inferiority margin. So that's the answer to the question. I would like just to comment to your comment. You picked the one study where the symptomatic PE went in the wrong direction based on a very small number of events. If you look at all three of the other studies, it is actually all of the symptomatic events -- the symptomatic DVT, the PEs and the deaths -- do favor or are neutral for the death end point I think in RECORD 4,

but they do, in RECORD 2, 3 and 4 consistently favor rivaroxaben which is why, when we pull them together across all four studies, we have a very strong result.

DR. KAUL: I would agree, that is quite correct. In RECORD 4 there is no heterogeneity. So are you suggesting that there are no data for symptomatic VTE for enoxaparin versus placebo comparison?

DR. PETERS: The only data I am aware of is looking at meta analyses of pooled extended low molecular weight heparin versus short-term low molecular weight heparin where, again, in each individual study, based on venography, there were clear reductions in symptomatic events -- and, actually, if we could pull up the slide with the ACCP data for venography events versus symptomatic events.

Where in those symptomatic -- so I'm actually aware of two situations. One is for the total hip replacement, extended therapy versus short-term therapy, where there were six individual studies, all of them, by venography end points, reduced total VTE. When you do a meta analysis for that extended period -- not for the initial period -- there were reductions in symptomatic events. But that doesn't apply directly here.

And similarly fondaparinux, they did an extended treatment after hip fracture and showed in that individual study clear venographic reductions, but also parallel reductions in symptomatic events.

Slide on.

This is actually from a very recent paper in Chest, February of this year. And what you see to the far right -- this is looking at the relative risks of venographic and symptomatic VTE from large -- defined as greater than 500-patient -- trials, comparing pharmacologic agents with placebo. And the far right is venographic deep vein thrombosis, you know, a very large reduction, and pretty tight confidence intervals because of a lot of events.

Next to that, moving to the left, you have symptomatic deep vein thrombosis, which has a very similar median but much wider confidence intervals, because there aren't many events. Then you have any pulmonary embolism and you have any deep vein thrombosis, symptomatic and asymptomatic.

So in the literature, looking across studies -- and our data is very consistent with this when we look at our symptomatic event reductions and we look at the venographic-based reductions, which are mostly asymptomatic DVTs, we see very concordant reductions.

DR. KAUL: So if I'm reading this data right, the upper bound is 20 percent, right? 20 percent risk reduction? 20 to 80 percent risk reduction. Is that correct? .2 to .8.

DR. PETERS: For which column?

DR. KAUL: For the symptomatic deep vein thrombosis.

DR. PETERS: Right. So it looks like the median is about -- so it looks like the median is about .4, right. And it looks like, right, it goes -- the range goes up to about .8. But again, this is not --

DR. KAUL: So -- just bear with me. So 20 percent to 80 percent risk reduction. And if you were to use these data to construct your non-inferiority margin, what would your margin be based on this data?

DR. PETERS: I'm not sure I should try to calculate it here on --

DR. KAUL: 10 percent.

DR. PETERS: -- the spot.

DR. KAUL: Half of 20 percent, which is the lower limit, would be 10 percent, meaning that your hazard ratio should not exceed 1.10. Now, the estimation of non-inferiority margin is not just purely a statistical exercise. It has to be justified on the base of clinical reasoning.

DR. PETERS: Right.

DR. KAUL: I'm willing to concede that this should be around about 25 percent. And if you use that criteria -- mind you, this is all post-hoc -- the non-inferiority criteria would not be met with regard to symptomatic VTE in RECORD 1 and RECORD 4. Would that be a correct statement?

DR. PETERS: As individual studies.

DR. KAUL: Correct.

DR. PETERS: Right. But again, we showed the RECORD 1 and 4 combined if people -- and you were interested in that. And that has a hazard ratio of 1.03 as the upper bound, which would meet either of your criteria.

But, again, I think it's very problematic to try to design non-inferiority margins on very low-frequency events in an individual study that

was not powered to detect differences in those events. I mean, that's just --

DR. KAUL: And the solution for that is what?

DR. PETERS: Do very, very large clinical studies.

DR. KAUL: Or have a placebo arm.

DR. PETERS: But we -- we had, again, agreement with all these study designs through the special protocol assessment procedure with FDA. Each study individually did meet its primary end point, which is clinically meaningful. I mean, there is a relationship between the asymptomatic events and the symptomatic. They move in parallel reductions. So I would actually submit that our estimates for the total VTE events would be a good estimate for our treatment effects on the symptomatic events.

DR. LINCOFF: Just so no one thinks otherwise, placebo control in this setting is unethical. There's no potential for that.

Did you have a related question?

DR. KAUL: No. A question for Dr. Xu.

Slide number 14. Your pooled estimates have an upper boundary of 1.44, and so my question to you is, do you think that this would meet non-inferiority criteria?

DR. ZALKIKAR: From statistical point of view, this analysis was not designed for any confirmatory analysis, whether superiority or non-inferiority. They had .05 type I error, but each of the four RECORD studies which were used for total VTE. And now the prespecified plan, so-called

prespecified plan for the pooled analysis had one end point of symptomatic VTE or death -- if you want to apply .05 to that, then you have to pretend -- that's another -- study number 5, which you cannot do, because it's pooled data.

So there was no confirmatory analysis of any kind of hypothesis from this pooled analysis. This is all exploratory.

DR. KAUL: Are you suggesting that we shouldn't have pooled the data to begin with?

DR. ZALKIKAR: I'm only suggesting that this should be viewed as exploratory analysis which, at best, is hypothesis generating. That's all.

DR. KAUL: I agree with you, but you haven't answered my question. Are you -- do you think that pooling the data is valid?

DR. ZALKIKAR: Pooling the data for exploratory analysis is valid, yes.

DR. PETERS: So, again, just -- if I could comment on this slide and make the statement again that there was a statistical analysis plan for this pooled analysis that specified the end point and the method.

This result for RECORD 2 -- we have not seen these data, and it is very puzzling how we could get a hazard ratio over 2 based on the raw data in that study.

So if we could actually show the Kaplan Meier -- and a hazard ratio of 4 for the bleeding events. If I could actually show the Kaplan Meier for

RECORD 2 which had three events on rivaroxaben, if I remember, and 15 on enoxaparin -- so slide on.

So here's symptomatic VTE or death for the RECORD 2 study. You can see the rivaroxaben group in the solid line at the bottom had one or two events very early and then very flat, and a few vary at the end. And then the dosing, again, was stopped at about day 12. And the Kaplan Meier curve for the enoxaparin in the first 12 days, and then placebo -- there's separation of those curves both in the enoxaparin period and in the placebo-controlled period.

So how you take this raw data and get a hazard ratio of 2 for that study for efficacy is hard for me to understand.

And if I could -- do we have the Kaplan Meier for the major --

DR. LINCOFF: Actually, before you show that, this was one of my questions as well. I'm not sure how -- I mean, that drives much of -- this pooled analysis that the FDA presented was this hazard ratio of 2 for RECORD 2. And I agree, I don't -- I mean, no matter how you censure this, I don't know how you turn this into a worse outcome with rivaroxaben.

So perhaps before you go on to the bleeding, we can find out how that was done. And then, by all means, show your bleeding.

DR. XU: That is based on consider of duration of treatment, age and study. So I adjust this rate covaried, and get that result.

DR. PETERS: And the adjustment must -- okay. I mean, maybe we

should show the bleeding because the same issue probably applies for the adjustments with both.

If we could have the slide for bleeding where the hazard ratio became 4 -- slide on.

And here's the treatment-emergent major or non-major clinically relevant bleeding -- again, the Kaplan Meier. So these are the real event rates as they accrue in time. And you can see, actually, there's very little separation between the curves during the first 12 days, which is active versus active. And then a little bit of separation after the active treatment period, but certainly not a four-fold increase in the rates, which would be off this scale.

So, again, I'm not sure how these adjustments were done.

And, actually, if I could show the symptomatic VTE or death subgroup figure to show that we did have consistent results for the age subgroup and all the other subgroups in this pooled analysis.

And one other comment is that we did stratify the pooled analysis. It is not correct that it wasn't adjusted at all. We did stratify the pooled analysis by study. So -- slide on.

Here's the data for symptomatic VTE or death for the subgroups. We didn't do all the subgroups we did for total VTE because there were smaller numbers of events. But you can see here again for age particularly, which you adjusted by, the confidence intervals there for the highest age group is a

little bit closer to no difference. But certainly consistent effects being directionally favoring rivaroxaben versus enoxaparin in all the age groups.

And, in fact, for the age group less than 65 and -- 65 to 75, the confidence interval excludes no difference on these symptomatic events in those age groups. So this -- the data -- we haven't had a chance to look -- to look at these data. This is the first we've seen it today.

DR. LINCOFF: Okay. We're going to revisit this -- it is getting well into the lunch period, so we're going to stop now.

I now that Dr. Neaton has one question of data that he'd like to see when we come back, and then I know that we're going to be coming back to this issue. And we'll start, though, with Dr. Paganini who has been very patient.

DR. NEATON: I just have one question -- and maybe the sponsor or the FDA has done it -- that we can kind of come back to to look at this so-called pooled analysis. The pooled analysis should not be done just by throwing everything together. If that was done, that's wrong. However, what I'd like to see is a Cox model stratified by study for the symptomatic VTE or death end point -- no other covariates -- stratified by the four studies, and to get that estimate of the hazard ratio that we can look at after lunch.

DR. LINCOFF: All right. With that, we're going to now break for lunch. Maybe we can cut it a little short. We'll reconvene at 1:10. Panel members, please remember there should be no discussion of the meeting during lunch amongst yourselves or with any member of the audience. Thank you.

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

AFTERNOON SESSION

(1:12 p.m.)

DR. LINCOFF: If we could reconvene, please. So just a brief overview for the rest of the day. We're going to start with the open public hearing. Then we'll resume with the questions to the sponsor and the FDA, and then follow up with the questions that are going to be asked of the panel.

Now we're beginning the open public hearing. I have a statement.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes it's 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 relationship at

the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy and respect.

Therefore, please speak only when recognized by the Chair. Thank you for your cooperation.

So if we could have the first...

MR. HENRY: Good aft. My name is David Henry. First, I would be remiss if I didn't thank the committee for the opportunity to speak to you today. We definitely appreciate that.

I am here today with support from the National Alliance for Thrombosis and Thrombophilia. To meet the financial requirements, I can state that while we do receive some funds from pharmaceutical companies, it is for the purpose of setting up outreach, education and website development. In no way are we here to promote any particular pharmaceutical interests. We also receive money from the CDC and others for the furtherance of our education and awareness projects.

The support that we get -- that I get from that is that I am a board

member. I am the impending -- incoming treasurer for the organization. I am a long-term warfarin user as a result of idiopathic DVT and PE events, and I have a very personal interest for that reason.

What I'd like to do very briefly is a little bit of information on that, a little bit of information on why we are of interest -- why we have an interest in the topic, share a very personal experience that occurred to another board member who, unfortunately, could not be here today, and then some results that we're interested in from a personal perspective from our organization.

NATT is a nationwide community-based volunteer health organization. We have a mission to prevent, diagnose and treat thrombosis and thrombophilia through research, education, support and advocacy. We were awarded -- that is our mission. We were awarded two cooperative agreements by the CDC in 2007 through 2009, supporting the topics of patient education, health -- professional education, website development and also the development of the nationwide chapter network for our group.

In September of 2008 the Surgeon General issued a call to action to prevent deep vein thrombosis and pulmonary embolism, spotlighting the public health urgency affecting somewhere between 350 and 600,000 Americans annually who have blood clots, those resulting in approximately 100,000 deaths.

While recent data from Mayo Clinic suggests a higher number of affected Americans and a mortality rate approaching perhaps 300,000 -- while

the numbers may vary, the threat is very real. Whichever data is used, blood clots, many of which can be prevented, represent a leading cause of death in the United States.

Of people that have DVT and PE episodes, 30 percent die within one month of diagnosis. 25 percent of those with PE die suddenly.

DVT and PE survivors face an uncertain future, as one-third have a recurrence within ten years, and one-third with DVT experience other complications, such as post-thrombotic syndrome.

In the call to action, the Surgeon General had specific language the important work that you're here to begin today. In that regard, an entire section was devoted to gaps in application, an awareness evidence-based interventions.

Interestingly enough, considerable documentation exists that discloses evidence-based DVT and PE guidelines are not being followed. One large epidemiological study disclosed that a majority of at-risk patients with ultrasound-confirmed DVT were not prophylaxed despite the risk.

So the CDC recommended encouraging the development of new pharmaceutical agents with faster onset, a wider therapeutic range and fewer food and drug interactions. That was from the call to action. The call to action also recommends conducting research into the best drugs, dosing strategies and anticoagulant treatment regimens for certain patient populations.

The demand for hip and knee replacements is trending upward due to our aging population. Again, the numbers vary greatly. Some numbers that we've seen look like 1.2 million may experience these procedures this year. And in the future, the trends will probably be up. Baby boomers, as a result of their aging and staying active, want these treatments.

The reluctance to follow evidence-based guidelines on the part of orthopedic surgeons who treat these patients is of great concern to us. Obviously, the major concern is bleeding, and it might be said that a clot could be an act of God, whereas bleeding is a surgical error -- we are not sure that we understand why orthopedists don't implement prophylaxis to a greater extent than they do now, other than accepted guidelines.

What I'd like to do at this point is introduce a letter written by Tom Hogan, who is our board secretary. Tom could not be here today, but he experienced recently a hip replacement and had some things that he wanted to share for information for the committee. The letter reads as follows:

My name is Tom Hogan. I'm secretary of NATT and also a recent hip replacement patient. December of 2008 I had a hip replacement surgery to my right hip. Going into this operation, I knew the procedure was considered a high risk for development of blood clots. I also knew that anticoagulant medication needed to be used during my surgery. But what I would like to point out is I knew this not because the orthopedic surgeon told me, but rather through my own research.

You see, back in the early and late '90s I suffered two separate DVTs and a pulmonary embolism and was subsequently diagnosed in 1996 as having Factor V Leiden thrombophilia. As a result, I am on life-long Coumadin therapy. When I discussed my medical past with the orthopedic surgeon, his reply was that I was going to be his first thrombophilia patient. My silent response to him was first that he knew of, given that 5 percent of the population has an underlying thrombophilia.

I asked if a hematologist was assigned to his medical team to manage anticoagulation and his reply was no, I would need to discuss this issue separately with the medical center's hematologist. It was not a normal protocol to have his patient assigned to an anticoagulation manager.

As a result of our conversation, I met with a staff hematologist to ensure anticoagulation prophylaxis was used both pre and post-surgery.

My surgery went well, as did my recovery. During my stay, I had the pleasure of having a roommate who had the same procedure done by -- the same day by the same physician, and we were able to compare notes in regards to our recovery and our symptoms. One glaring discrepancy in our treatment was that I was on anticoagulation medication while he was not, yet we both had pneumatic stockings while in bed; however, guidelines highly recommend anticoagulant medication be used in patients with hip and knee, and it did not seem to be the norm at this hospital. I can't say that every patient who had knee or hip surgery was on aspirin therapy, but I got the impression they

were.

If I wasn't an educated patient who knew risks and wasn't a life-long Coumadin patient, I probably would have only been on the aspirin therapy following my surgery. Anticoagulation medicine not only prevents DVT and possible PE following this type of surgery, but in the long run, may well save a patient's life.

With the Centers for Medicare and Medicaid Services' recent ruling regarding hospital-acquired DVT/PE, I am truly dumbfounded that anticoagulation management wasn't a part of the standard protocol at this prestigious medical center.

Speaking to the local Coumadin clinic at another hospital, apparently the use of anticoagulants during hip and knee replacements is also a problem. Do the protocol suggest use of anticoagulants following surgery? The majority of orthopedic surgeons felt the risk of bleeding was more important than the risk of clotting.

As a patient and a patient advocate, I feel it's essential that orthopedic surgeons follow evidence-based guidelines regarding the use of anticoagulants as part of hip and knee replacement surgeries. While I marvel at my surgeon's skill in replacing my hip, I am profoundly disappointed that it appears I only received proper anticoagulation management because of my history with blood clots and underlying thrombophilia.

Just think of the hundreds of other hip and knee replacement

patients he will see each year who will not be completely protected from DVT and life-threatening PE.

My surgeon is not alone, as I understand many, if not most, orthopedic surgeons are reluctant to use currently available anticoagulants. It's my hope that if your review of the safety and efficacy of rivaroxaben is positive, it will be approved by the FDA as soon as possible because I believe this may help overcome much of the reluctance to prophylaxis by many orthopedic surgeons because of what appears to be a more acceptable management strategy, particularly if taken for four to six weeks after surgery.

More acceptable because of uncomplicated treatment by taking an oral pill versus worrying about injections -- I had 66 injections in my stomach over 33 days -- or the bridging of injections and warfarin following surgery.

At current, low molecular weight heparins and warfarin are the suggested means of treatment. Products like rivaroxaben may well be the wave of the future. I appreciate that, while reviewing this drug, the cardiovascular and renal drugs advisory committee will carefully consider the safety and efficacy of this medication.

Thank you very much for your efforts in safeguarding and expanding therapeutic options for me and millions of Americans at risk for DVT or PE while undergoing hip or knee replacement surgery in the years ahead. Respectfully, Tom Hogan, secretary.

Where this really goes is that we believe patients will benefit from

the acceptance of drugs like this because of no INR monitoring, pill instead of injection, limited or no food interactions, minimal interactions with other drugs and quick on and offset.

Moreover, if the potential benefits are realized, patients will experience close to optimal care, reduced risk for complications, increased acceptance by orthopedic surgeons performing hip and knee replacements, and reduced morbidity and mortality.

As an organization, NATT supports the Surgeon General's call to action, and we appreciate the committee's review of this promising drug. We would like to have a thorough review of safety and efficacy and, if approval is recommended, we urge an expedited FDA consideration so that more than 1 million hip and knee replacement patients annually can reap all of the benefits as soon as possible.

I thank you very much for your time today.

DR. LINCOFF: Thank you very much.

The open public hearing portion of this meeting is now concluded, and we will no longer take comments from the audience.

The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments.

I'd like to continue now with the questions -- we had at the lunch break a question regarding a re-analysis by Dr. Neaton.

Jim, do you want to expand at all -- any more on this, or just allow the sponsor to make their comments?

DR. NEATON: In relation to the -- I don't know whether you want to do it now or later. I have, like, three or four questions that relate to the primary end point analyses.

DR. LINCOFF: Well, perhaps we'll let them present -- address your question, then actually Dr. Gross was first, and then we'll come back to you.

DR. PETERS: So -- slide on. So I believe the -- slide on. All right. Thank you.

So I believe the question was how we adjusted for study. So what this table shows is the Cox proportional hazards analysis of the symptomatic efficacy end points of VTE or death and PE or death in the 1 to 4 pooled analysis. The analysis we actually did as primary is the left column. So the study was included as a covariate, and we did it as a stratified model on the right. And you can see the differences are very, very -- they're essentially identical, both statistically significant.

There was also the question raised earlier about the prevention of the really important events, the PE or death. We did do that composite end point. It was post-hoc, to be very clear. The results were in the briefing book, and you see them again here. But we did have reductions for death or PE of -- and the upper confidence interval does exclude 1, which would suggest that we are reducing those events. Both death and PE were reduced about

equally, and the number of events was 8 versus 16 in the treatment period.

So we would like to have Dr. Friedman -- there's been a lot of discussion around the pooling of all four studies based on differences in the enoxaparin regimens. So if we could have Dr. Friedman just make a very brief comment about the enoxaparin dosing.

DR. LINCOFF: Dr. Neaton, did you have a follow-up on this slide before we do that?

DR. NEATON: Maybe while going up to the microphone -- I just want to -- I think you said this, but the analysis on the left, the top line, the symptomatic VTE or death was prespecified to be a pooled analysis across the four studies before you saw any data?

DR. PETERS: Correct.

DR. FRIEDMAN: Thank you. Let me just speak to the relevance of the RECORD 2 and RECORD 3 study because, in fact, they are extremely clinical important.

The RECORD 2 study looked at extended prophylaxis. We have had a number of papers published in the past, beginning in 1996 with two papers out of Europe, from Planes in France and Bergqvist in Sweden, showing a decrease statistically in the venographic rates after a total hip arthroplasty. Each site had approximately a couple hundred patients.

We did a similar study in the United States and published that in 2001 with 438 patients, and showed the same thing. But each study in and of

itself was empowered to show symptomatic events, so the meta analysis that was shown before does show that, but again, that's been slow to be accepted by orthopedic surgeons. So I would say, in the United States, most physicians do not carry out prophylaxis in total hip patients for four weeks.

The value of this RECORD 2 study is that it was powered to show a significant difference in symptomatic events, which it did show.

There are other reasons why we don't carry prophylaxis out to four weeks for orthopedic patients in total hips. Aside from the lack of symptomatic data, there's also the fact that patients have to be injected daily for four weeks, and there's a cost associated with that.

So I would submit to you, now that we have the symptomatic data available from this study, that may change practice pattern behaviors.

In the RECORD 3 study, it is true that the 40-milligram once a day enoxaparin dose is not approved in the United States. But I can tell you, in the real world, it is used frequently. And why? Well, again, when patients go home on post-op day three or post-op day four, it's very difficult to send a patient home with twice-a-day injections for another ten days or so. There's a cost associated with that, and there's numerous injections twice a day. It's very hard to sell a patient on twice-a-day injections.

You can get them to do once-a-day injections, but twice-a-day is very, very difficult.

So as a result, physicians in the real world will send their

patients home on 40 milligrams once a day for another 10 or 12 days to get that 14-day total. And that's what goes on.

Now, if you have an agent such as rivaroxaben that's oral and once a day, you, in fact, may change off-label behavior and you may promote on-label behavior. And I think from a public health point of view, on-label behavior and practice by everything-based guidelines is something I think we would all like to see.

DR. LINCOFF: All right. Dr. Gross, I think you had a question.

DR. GROSS: Yes, thank you, Michael. I have three questions.

I feel kind of naked without laboratory tests telling me where I am. Is it possible to do factor 10a levels or activity? Any relevance for bleeding tests or INRs? You know, I haven't heard that mentioned one way or the other. And it might help us understanding if there -- if something does eventually become apparent about cardiovascular risk, whether patients become hypercoagulable when you stop the drug.

DR. PETERS: So -- slide on.

Rivaroxaben does affect global coagulation tests. This is data here that's right from the briefing book that shows the factor 10a inhibition in the PT. This was with a very specific PT, the Neoplastin assay. So that slope that you see here is very specific for that assay with a central lab.

So you can see there is a very good correlation between rivaroxaben levels and inhibition of these pharmacodynamics assays.

We used the PT assay in the phase 3 program as a surrogate for pharmacokinetics. We did look at the relationship between the peak PT levels -- slide on -- that's shown here. And so the panel at the left is people with no bleeding -- patients with no bleeding, major bleeding, clinically relevant bleeding, and any bleeding at the far right.

And you can see, for all of those groups, if you look at the no bleeding to get kind of the median in the spread, there is an increase in the prothrombin time level at the day 6 peak, which you would expect -- it does go up. But the people with bleeding did not have any difference in the median levels or the range of levels.

So, again, within a 10-milligram dose, there's a relative limited range of values, and there are lots of reasons that go into why people bleed. So the prothrombin time doesn't seem to be particularly good at predicting who would bleed and who would not bleed.

And I think -- there's a long precedence with the low molecular weight heparins, when they first came out, without assays, to be able to measure their effects. So a little bit were analogous to that situation here.

DR. GROSS: Okay. Thank you. My second question is, did you look to see if recommendations were followed for transfusion? Transfusion is not a benign thing, and if somebody drops their hemoglobin from, let's say, 13 to 10, and they're hemodynamically stable, they may not need a transfusion.

DR. PETERS: Transfusions were managed entirely at the discretion of

the local site. We had nothing in the protocol about -- a lot of these patients will be transfused, and it was balanced between the two groups for both hip and knee. But we did not manage the transfusions at all in the protocol.

DR. GROSS: Okay. And my last question is Dr. Watkins did an intensive analysis of deaths due to rivaroxaben. Has the same kind of analysis been done with enoxaparin in the RECORD studies? Perhaps there is something we need to know about enoxaparin that we don't now.

DR. PETERS: So I'll have Dr. Watkins come up and respond to that question.

DR. WATKINS: There were no deaths at all in the RECORD trials, so the deaths -- the six deaths that I showed were over the entire clinical program, which includes ongoing studies, completed studies, blinded and unblinded. So there were six total deaths. Four were treated with rivaroxaben, one with placebo and one with enoxaparin.

Do you still want to hear any further information? Because the question was, I think, directed towards the RECORD study.

DR. GROSS: Then maybe it wasn't the RECORD study, but there were -- in one of the presentations there were more deaths with enoxaparin than rivaroxaben.

DR. WATKINS: It wouldn't have been deaths. It might have been in some study -- slide on here.

This is the slide that I showed of the only deaths where there was liver injury within 30 days of death defined by these criteria.

DR. GROSS: And not necessarily related to liver injury.

DR. PETERS: Right. So the overall death rate was 13 for rivaroxaben and 25 for enoxaparin. That included treatment and follow-up, all causes of death, bleeding, pulmonary emboli, pneumonia. That was the total across both groups.

DR. GROSS: And were the enoxaparin deaths attributed to enoxaparin or to something else?

DR. PETERS: We have the adjudication by the different committees. If you would like to see -- the VT committee adjudicated deaths into VT-related, not VT-related or unexplained.

Slide on.

So for the 13 and 25, you can see there were fewer confirmed PEs, one versus three -- small numbers. This was a very rigorous -- you know, it had to be really a definite PE. Not VT-related were 7 and 11. And unexplained, which actually included quite a few events that were suspected PEs, but not confirmed, were 5 versus 11.

DR. GROSS: Thank you.

DR. LINCOFF: Unless it's directly -- okay. Go ahead, Dr. Kaul.

DR. KAUL: Can we have the slide back, please?

If I understand correctly, of the 583 total VTEs, only four resulted

in death attributable to VTEs? That would come to a case fatality rate of less than 1 percent, close to about .7 percent.

DR. PETERS: VTE -- again, these were centrally adjudicated with very rigorous criteria. Autopsies often not done. You may not have confirmatory imaging. So one versus three is a low number. There are likely -- with the difficulty of diagnosing pulmonary emboli, there are likely, but we don't know for sure, pulmonary embolism-related deaths in the other two categories shown on this slide.

DR. KAUL: Are you agreeing with my statement that the case fatality rate is .7 percent? Four out of 583?

DR. PETERS: The 583 --

DR. KAUL: Is total VTEs.

DR. PETERS: Then that would be correct, if those are the numbers. I'm not as --

DR. KAUL: Okay. So contrast that with 37 major bleeding and two of them resulted in fatality.

DR. PETERS: Right, but again --

DR. KAUL: So two out of 37 gives you a cast fatality rate of 5.4 percent. I'm just trying to sort of gauge --

DR. PETERS: Right, but those are the --

DR. KAUL: -- the clinical relevance of VTEs and bleeding.

DR. PETERS: Right. So there I think the denominators would need to

be different. You need to look at the safety denominators because there were differing numbers of obviously asymptomatic DVT than major bleeds. And if you look at overall mortality, it's 13 to 25. If you look at overall symptomatic VTE or death, we had much more greater reduction in that than we had increase in major bleeding events, which was 24 versus 13, an absolute difference of 11. And we had a much larger reduction in symptomatic VTE or death, most of those people requiring full-dose anticoagulation for three months, you know, clinically important events, as Dr. DiBattiste showed the clinical impact of those.

So the case -- I'm not sure what point you're trying to make what the case fatality within the thrombotic versus the bleeding end point.

DR. KAUL: Case fatality rate gives me an idea of how clinically relevant an end point is. What are the consequences of an end point? That's it.

DR. DiBATTISTE: We didn't do the case fatality rate analysis that you've described and that I know you had done for the prasugrel analysis as well. We did do a weighted utility analysis, which I think is another way at getting at the same thing. It was described in the briefing book, and we can -- if you'd like, we can discuss that in more detail, if that would maybe be another way of getting to the same question.

DR. KAUL: Okay.

DR. PETERS: The other point to just make -- by intent to treat, it

was two events. But one event occurred intraoperatively. The person never received rivaroxaben. So we have one excess death from bleeding. And even if you take the very strict VTE-related, we had one versus three.

So we were numerically -- those numbers are too small to --

DR. KAUL: Agreed.

DR. LINCOFF: So Dr. Neaton --

DR. NEATON: I'd like to kind of come back to the FDA's presentation, which I think kind of was very helpful, but raised a number of questions. Just to make certain that we have the data straight in our mind when we make the judgment.

Maybe to begin with, in the FDA presentations, there was not much of a comment on the total VTE kind of end point with regard to the missing data. And I just want to come back to the question I raised earlier. I looked at the sensitivity analyses that the sponsor did in their report -- and they commented on it briefly this morning.

I take it you carried out similar analyses and came to the same conclusion based on what you've stated that there seems to be a clear effect when you look at total VTE.

DR. ZALKIKAR: I didn't state my name earlier. My name is Jyoti Zalkikar. I'm from the statistics review team at the FDA.

Yes, we did conduct all those sensitivity analyses, verified them, matched the sponsor's results -- in terms of total VTE, yes, they pan out.

DR. NEATON: Okay. Thank you. So then it comes back to the question I think Dr. Kaul raised earlier -- this is a composite outcome. And if you do a study like this, it makes a lot of sense to throw all-cause mortality and the pulmonary embolism events in there. I mean, you want to include them as part of the composite, but understandably, when you design a trial like this, you know in advance that this is going to be driven by the events on the venography. That's just the way the study was set up and designed per, I guess, guidelines from the FDA.

And so it is important, then, to look at the components and to be confident, I believe, as Dr. Senior said earlier, that we see an effect on those outcomes.

And so I understood -- from what I understood the sponsor did, and showed on the slide earlier, to be kind of an analysis which I think directly addressed that, I guess, in the way I would do it as a pooled analysis. So what they did -- and the sponsor can correct me if I'm wrong -- is that you didn't just throw the data together. You actually carried out a model in which you considered each study separately and took each study into account and pooled the results in a formal way, in this way by using a Cox model.

And so the FDA statisticians used a slightly different approach -- and I'd like to get your insights on why the result seems to be so discrepant.

DR. ZALKIKAR: Well, I want to sort of point out that all the analysis that we see on the pooled data are driven by study 2 and study 3.

When we put study 1 and 4 together, the statistical significance in terms of symptomatic VTE and death is not there, that advantage.

Now, study 2, the duration was different for the two treatments. And so there are several ways to adjust for that duration -- treatment duration. And so the analysis that we conducted was one such analysis that showed a different result from what the company's result was and, to me, that indicates lack of robustness --

DR. NEATON: So how was --

DR. ZALKIKAR: -- in terms of that end point.

DR. NEATON: What was the nature -- I mean, how did you adjust for study duration? Because -- I mean, I'm a little worried about the nature of that type of adjustment. Don't you implicitly adjust for it when you pool the results over the studies, because that was the way the treatment was defined?

DR. ZALKIKAR: There were other study-to-study differences, such as the type of surgery, as well as age. And so we threw in the variable study, as well as the treatment duration, which was particularly different in study 2 between the two arms of the treatment groups.

DR. NEATON: So that what -- operationally, then, what did you do in the analysis with duration? I mean, I don't understand what you did to get such a --

DR. XU: We put the duration in the model, and I found the P-value is less than .001 --

DR. NEATON: The duration -- when you mean [sic] you put duration in the model, you put a number in there for each patient?

DR. XU: The duration of -- yeah.

DR. NEATON: The duration of the period that they were on the treatment?

DR. XU: Yes.

DR. NEATON: Okay. I think I see the difference, then.

DR. XU: For RECORD 2, the duration of rivaroxaben treatment is 35 days.

DR. NEATON: Right.

DR. XU: And for enoxaparin group is 10 to 14 days.

DR. NEATON: So did you only count the events in the control arm through the first 12 days?

DR. XU: It's --

DR. ZALKIKAR: Over the first 12 days -- we didn't count the events just over the first 12 days. We counted all the events that occurred in the control arm as well as the rivaroxaben arm.

All the events pretty much occurred after the treatment has stopped in both arms, many events -- the majority of the events occurred after the treatment has stopped.

DR. NEATON: Right.

DR. ZALKIKAR: So the premise was that the patients should be

anticoagulated enough so that they wouldn't have any --

DR. NEATON: But the problem, I think, is that treatment duration is totally confounded with treatment. So you can't actually include duration of treatment and treatment in the model at the same time for that study because they're kind of one in the same.

DR. XU: We also did pooled analysis for RECORD 1 and RECORD 4 without --

DR. NEATON: Right.

DR. XU: -- the treatment duration, and the medical VTEs still shows no effect. So --

DR. NEATON: No, I can see that, that the findings -- I mean, I want to put aside the issues, because I think other people here may want to speak to those more clearly about 2 and 4 and their relevance here. But if you put together 1 and 4, you don't get the same answer --

DR. XU: Regarding --

DR. NEATON: -- if you put them all together. It looks a little different, but it's much less precise as a consequence of leaving out two studies.

But you adjusted for study and -- I mean, the adjustment for age, I think you would probably agree, can not have had much of an effect because of randomization if you pooled over study. So the real thing here, it seems to me, is kind of when you adjusted for duration, that perhaps that led to this

kind of very big hazard ratio in RECORD 2 because essentially you're overadjusting in that study because you've -- duration is the same as treatment.

I mean, I think that's the reason for the difference in the two results. I mean, if you kind of think that's the case, then I guess I would accept kind of what we saw earlier for the pooled results, and then just offer that the -- the question that Dr. Kaul raised earlier about non-inferiority is not really relevant in my mind because here, at least for this a priori planned pooled analysis on the symptomatic event, the point estimate is .4 which actually it turns out to be about .4 from that quick picture that we saw before lunch.

And so if you ask the question, by putting those together in a very crude way, there would be a substantial reduction in this outcome relative to placebo, maybe an 80 percent reduction because, if I'm understanding that picture correctly, it was a 60 percent reduction relative to placebo, and the point estimate the sponsor came up with was a 60 percent reduction relative to controlled treatment. So it's a big difference.

I think -- my last question is for the sponsor in terms of the bleeding outcomes that you showed, the pooled analysis. That analysis was done in the same way? That analysis was carried out in a stratified model?

DR. PETERS: Yes. Yes.

DR. NEATON: Okay. So I guess, from my point of view, I think that

analysis is an appropriate analysis, and the argument, I think, would be whether or not all four studies should be pooled or whether or not you think studies 2 and 3 are so different because of biasing the way the control group was defined, that only studies 1 and 4 should be pooled. And that's something I'll just defer until I hear more discussion myself.

DR. LINCOFF: We have some others, and then we can come back to that.

Dr. Gage?

DR. GAGE: So first one clarification and then a question. So in terms of commonly used agents, enoxaparin 40 milligrams once a day is used less often in orthopedic patients than warfarin. And what's used very commonly, regardless of antithrombotic therapy, is intermittent pneumatic compression devices. And these pneumatic compression devices now are also portable so that the -- in about the first hour when we heard about the criticism that these are not worn commonly by patients, it is common for me to walk in the room and they're not on a patient. But I think that's going to become less and less common as we have devices now that allow patients to ambulate and, if necessary, to go home.

And the net effect of this on the relative risk reduction may be small, but on the absolute risk reduction it may be profound because intermittent compression devices have a relative risk reduction similar to anticoagulants, about 60 percent. So that's almost as good as the

antithrombotic therapy.

And what that means is had these patients been allowed to have intermittent compression devices, all of the rates would have been reduced in both arms by about 60 percent.

DR. LINCOFF: Dr. Mayor?

DR. MAYOR: I'd like to address the sponsor with a lump of questions related to dosing. Among them is the question of whether, when the PDF that you sent displayed the plasma concentration versus time, the pharmacodynamics of the medication, it suggested that taking the medication with food resulted in a slight moderation of the peak, but an extension of the tail that resulted in more therapeutic agent in the bloodstream when it's taken with food.

DR. PETERS: The effect of food at the 10-milligram dose is that it slightly delays the peak, but the peak is exactly the same with and without food, and the area under the curve is essentially the same with and without food. We can show you that slide if you need to --

DR. MAYOR: But therapeutically it was --

DR. PETERS: So it delays -- so food would delay -- slide on.

Food delays the peak slightly --

DR. MAYOR: Right.

DR. PETERS: -- but does not change the Cmax or the area under the curve.

DR. MAYOR: But it would seem to me desireable to have that level

maintained slightly higher for a little longer. And under that circumstance, would there not be a benefit of taking a 10-milligram tablet, scoring it, splitting it in half, and taking it with food twice a day?

DR. PETERS: Well, the answer to that is we used the 10 milligrams in phase 3 with or without food -- and you see the efficacy results we had -- you can take the slide off.

I mean, we had very good efficacy results in all of the four studies, and we had, you know, a favorable safety profile as well. There is some increased bleeding.

We did look in the phase 2 -- mostly at twice-daily dosing. And splitting the dose, the efficacy and the safety is not very different. You know, cross-study comparisons, so not definitive, but we did not see differences between the twice-daily and the once-daily dosing for the same total daily dose.

And also that's been our experience in the ATLAS ACS setting which we presented at AHA -- we have not seen large differences -- which is a bit counterintuitive because I think we all tend to think of Cmax as being related to bleeding, but we've not been able to show that in either the orthopedic setting or the ACS setting with rivaroxaben.

DR. MAYOR: And another question that may only be worth raising in order to make the issue an item of consciousness: Are there any environmental concerns related to all of this agent going out in the septic systems of the

country or the world?

DR. PETERS: Not that I am aware of, but I'm not sure I'm qualified to comment on that. Not that I'm aware of. I'm not aware of any of the...

DR. LINCOFF: Dr. Kaul?

DR. KAUL: Well, the way I see it, there are two critical elements to the evaluation of benefit. One is whether the VTE that we are capturing is a valid surrogate end point. And the second one is, if it is not, can we pool the symptomatic VTEs and is pooling justified?

And I would like, with your permission, to have Dr. Neaton weigh in on the pooling issue. And I would also like to have the FDA's perspective both on whether it is valid to pool the data together and also whether -- what the FDA's position is on whether VTE is a valid surrogate end point.

DR. NEATON: So kind of given my understanding about the kind of conditions under which studies like this -- what kind of studies you have to do for approval -- which I'm taking to be the venograms are acceptable outcomes in studies like this -- I think what the sponsor did made a lot of sense to me. And so I would definitely want to reach out and address the symptomatic VTE or death outcome and the only way I'm going to be able to do that, given kind of the plan for the two studies on the hip and two studies kind of on the knee is to pool the results across the studies.

And so I'm comforted by the fact that this was a priori planned and that the analysis, as I understand it now and was shown to us -- whether you

considered the studies as covariates or strata, which is a fine point difference there, you get the same answer -- I accept that analysis. And that is exactly probably -- had you asked me, before these studies were unblinded, that's what I would have prespecified to be done.

And so -- it's another issue, I think, about whether or not the control arm in studies 2 and 3 are acceptable -- and I've heard arguments kind of both ways there. And so if I'm interested kind of in getting my best estimate of what this drug is doing relative to the same control, used slightly different across these four studies on this symptomatic end point or death, I think what they did is quite appropriate.

DR. LINCOFF: Dwaine, do you or someone else want to weigh in from the FDA on the suitability of this as a surrogate end point?

DR. RIEVES: Yes. The regulatory precedent has -- it goes back years, if not decades in fact, to accepting the imaging outcomes, specifically venography, as the basis for approval. There's a long history for that.

Now, I say that with some qualifications because it's not yes or no, do you have venography? It's, where are the clots? For example, if the clots are in the distal DVT, as some folks may remember from a few years ago when Exanta was brought to this committee, that presents a different picture because it has a different clinical meaningfulness compared to proximal clots on a venogram, for example.

But, yes, there's a long-standing precedent for the acceptance of

the imaging outcomes in the development of these products. But the technology is changing in the future. Over the last few years -- ultrasound is improving such that maybe it can be standardized for studies, as well as CT in the future. Those things are on the table. But these studies were conceived many years ago.

So it is consistent with our regulatory precedent.

DR. NEATON: If I could make an editorial comment. So I think, given that -- and that was my understanding -- it is an unavoidable fact that we will always be presented with some lack of clarity on rare, serious outcomes, not only the components of the end point, but the liver outcomes, the bleeding -- we're always going to have uncertainty there because these studies have been powered around something that's very different.

And I think we -- this was through no fault of -- I think of what the sponsor did. It seems like the studies were good. My concern was the missing data, but it seems like that's been dealt with in the best way possible. but it's unavoidable, given that -- those requirements, that you're going to end up in this situation.

DR. LINCOFF: Dr. Mayor, did you have a related question?

DR. MAYOR: I did. With regard to the use of the term "VTE" as a surrogate for deep vein thrombosis, I think we may create some confusion because venous thrombosis is not embolization. Those are two separate events. And we talked about how rare significant embolization is, but we talked about

how common thrombosis is. And I think we need to talk about the possibility of not using VTE because of the confusion that it generates in compounding those two together.

DR. LINCOFF: But you wouldn't want to exclude a patient who died, or a patient who had a pulmonary embolus even, if you never got to the point of diagnosing --

DR. MAYOR: Not in the least, but --

DR. LINCOFF: -- the more proximal cause of that --

DR. MAYOR: -- the confusion in my mind is that we're using venography and talking about VTE without the "E" necessarily being real in the issue.

DR. LINCOFF: I believe the end point, though, is a composite of death, pulmonary embolus or --

DR. MAYOR: Right.

DR. LINCOFF: -- demonstrated emboli -- demonstrated clot.

DR. MAYOR: In concur entirely with that point of view, but I'm just concerned about the term that we're using and that confusion may result.

DR. SWENSON: I'd like to have the FDA weigh in on the pooling issue.

DR. FOX: While you're deciding who should answer that -- excuse me -- can I just clarify one bit about the VTE point that was just made? I think -- my understanding of the way these studies are designed and conducted, and

the interpretation and the venography in particular, you can't really distinguish between a clot in situ in a proximal location that may have arisen all by itself in that location versus some embolization of a more distal clot to a more proximal location.

So I think it's a valid label.

DR. LINCOFF: Dr. Swenson, did you --

DR. SWENSON: Just a clarification, too. The VTE designation is probably realistic because all the best studies that have ever looked at this, with very sensitive techniques, is that there's a considerable amount of silent pulmonary embolism that occurs with just the development of venous thrombosis. So some of the best experts in this field think that it is perfectly appropriate to make this a comprehensive term and include embolism as part of the process. Maybe upwards of 50 percent of clots are associated with, in the vast majority, silent pulmonary embolism of small amounts.

DR. LINCOFF: Dr. Black and then Dr. Paganini.

DR. BLACK: I may be out of order, but I'd like to take this conversation in a somewhat different direction.

DR. LINCOFF: I'm happy to do that, but I'd like to close on this --

DR. BLACK: Okay.

DR. LINCOFF: -- and also get Dr. Kaul's -- Dr. Paganini, did you have a related question or do you --

DR. KAUL: No, it's unrelated, so go ahead and --

DR. LINCOFF: Okay. You're actually next on the list after we close this.

DR. KAUL: Thank you.

DR. LINCOFF: Did you want to address the --

DR. RIEVES: Well, off the top, I want us to remember -- regarding the pooling, I was very -- several months ago, when we first got this application, there was a study report from -- integrated this pooled analysis, but it was very impressive. In the final conclusion down there, efficacy conclusions, the answer was none. And that's to emphasize these are exploratory analyses. That was the sponsor's response: There can be no efficacy conclusions for these analyses. They are exploratory.

And so I think it's important that we bear that in mind and not get caught up in the technicalities, if you will, beyond what we should.

DR. LINCOFF: Okay. Dr. Paganini, you're next.

DR. PAGANINI: I'd like to return to the urinal, if I could, and talk about creatinine clearance. Just -- first question would be, was that a calculated or measured creatinine clearance? And then -- and that's how you classified your patients into the three or four groups.

I was impressed with the fact that they have an exposure potential, 1.3 to 1.5, as you pointed out, which seemed -- but in your meta analysis seemed to favor the drug in that specific subgroup. And yet, later on, there was a request that perhaps that subgroup, because of the potential for

increased exposure, should have a lower dose. And so with that as a background, did you do any data looking at drug-drug interactions, and specifically with ESAs, erythropoietin stimulating agents, to see if there was a counterbalance that may be in effect which would sort of counter what you would have expected, given the increased exposure?

DR. PETERS: So the answer specifically about looking at the erythropoietins, we've not done any interactions with those. Your interpretation of the data in the moderate renal impairment is correct. We did actually have, if anything, a more favorable benefit-to-risk there because the bleeding was not increased very much, and there was still good efficacy. But we've not looked at erythropoietin drugs.

DR. LINCOFF: Okay. The order here now is McGuire, Fogel and Black.

Dr. McGuire?

DR. McGUIRE: As a cardiologist, I'm not familiar with this large joint replacement literature. I'm a little surprised by the median age of only 64, 2 percent African-American and 6 percent Hispanic. One of the challenges to the data set is only 15 percent was derived from U.S. participants. Do these really reflect U.S. patient population in the 1 million cases per year? I would assume there would be a higher median age, a much larger representation of ethnic minorities.

DR. PETERS: So maybe if we could show the GLORY registry data for the U.S. versus the non-U.S., for the RECORD program versus what happens in

the GLORY registry for U.S. versus non-U.S. So while that's coming up -- okay. So slide on. And then if we could find the data for the U.S. versus the non-U.S. as well. Okay. Slide on. We'll show both of these. This one first.

So here's just looking at across the whole program. So this is from the registry that Dr. Friedman was part of, And it's looking at hip replacement, knee replacement in the RECORD problem -- so we had almost 7,000 hip patients; GLORY had about 7,000. For knee, we had about 5500; GLORY had a bit more.

And you can look -- as you might expect, on clinical trials, we had a very liberal inclusion criteria. I think we did enroll a representative patient population, but clinical trials never really reflect the total breadth of things in clinical practice.

So you can see in the real world, this was about 110 sites across the various countries. A little bit older, but not dramatically, female gender being about the same, median BMI actually being pretty same -- pretty much the same.

And then if we could show the other slide, showing U.S. versus the other regions.

So here we have, within the hip -- again, this is from the GLORY registry, so it's comparing the U.S. versus the other regions, getting to the applicability of the data --

DR. McGUIRE: Can you remind me of the derivation of the GLORY -- I'm not familiar with the GLORY registry, what is it and how representative.

DR. PETERS: Probably the best person would be Dr. Friedman since he's a participant in that. My understanding is it's about 110 orthopedic sites.

Richard, why don't you give --

DR. FRIEDMAN: This was a registry where data was collected both in the United States and around the world from physicians who had an interest in doing so. And I think it included academic centers, it included private practitioners and community hospitals. I think it's fairly representative of clinical practice today.

And I would agree -- and I think the orthopedic surgeons on the panel would agree -- that we're seeing the age dropping down and down, younger and younger patients. We've also seen a shift. It used to be one hip for one knee. Now it's about two knees per hip. And in addition to that, the weight is also going up.

DR. PETERS: And this just shows some of the data that Dr. Friedman mentioned briefly that, for the U.S. versus non-U.S. -- for example, median length of stay is very different, and the U.S. patients are going to be heavier, on average.

Now, we do have data for the U.S. -- if we could actually put the slide on -- for the efficacy.

So here's, for all four studies pooled -- most of the data was from RECORD 4. There was a short section in appendix 1 on this. So this is all of the U.S. data for the total VTE and the major VTE end point. And you can see that pretty consistent for both end points, the U.S. with the other regions of the world, for efficacy. And we had similar findings for the bleeding.

DR. McGUIRE: And the last -- do you have race-based breakouts?

DR. PETERS: Race --

DR. McGUIRE: And the reason I ask the question -- there were only 2 percent African-Americans, but the five versus five events for efficacy and bleeding looked to go -- it looked like there was a possible differential treatment effect in African-Americans --

DR. PETERS: So --

DR. McGUIRE: -- based on very, very small numbers.

DR. PETERS: All right. So we can pull up the subgroup for total VTE by race -- is probably the most relevant -- and you'll see the Blacks there.

We did -- this was a worldwide program. In -- RECORD 4 actually had a fair percentage of the Black subgroups, which was the study that had the most U.S. participation. But in the global program, and with most of the patients being enrolled in other countries, we do have underrepresentation of Blacks.

Slide on.

So most of the data, as in many studies, is in Caucasians, so that's the first row you see there, with a very tight confidence interval and highly statistically significant.

The Black is right on the line. We do know, from our phase 1 data, that we have identical pharmacokinetics and pharmacodynamics in Black and White and Hispanic subjects. And then you can see the Asians, the Hispanic, where we had a better representation, and "other" which was everything else. Again, no statistical evidence for heterogeneity, or not strong evidence there. The interaction P-value is given. And directionally consistent across all the racial groups for the efficacy.

DR. LINCOFF: Dr. Fogel?

DR. FOGEL: Thank you. I have a question for Dr. Gelperin. In the material that you presented in your slide 14, you presented a fatal case with liver injury and heart failure. I was looking at your data and trying to compare it to the sponsor's data with regard to liver disease, and I don't see a case that matches up to the one that you presented. Is this from a different study that wasn't included in the initial presentation?

DR. GELPERIN: No. It's the same case that Dr. Watkins presented. It's a 63-year-old female from France, and -- it's the same case. I guess we described it differently.

DR. FOGEL: Okay. So --

DR. GELPERIN: What would you like to know about it?

DR. FOGEL: Well, as you were presenting it -- I was listening to it; I thought that it was ischemic hepatitis or congestive hepatitis. How did the discussion come about that you adjudicated it to be possible drug-related?

DR. GELPERIN: All right. Actually, I did not adjudicate the case, so the point that I made -- and, in fact, Dr. Watkins also mentioned that there's no documented occurrence of hypotension in this patient. He didn't mention, but in fact she did not have a prior history of heart failure, and in fact she had some normal tests regarding her heart function prior to the occurrence of this event.

So the thing that I think is striking about this case, it's her duration of exposure to rivaroxaben was only 17 days. So the possible relevance to a short-term duration of therapy is questionable.

And they also -- one of the sponsor's pathologists on the expert panel considered that this was drug-related. Also, the study site investigator in France considered that the events were drug-related -- I'm sorry, possibly related, or of unknown relationship to drug.

So I think the best way I could describe the FDA's position on this case is that its relevance to the safety profile of rivaroxaben remains to be determined.

DR. LINCOFF: I see that the sponsor would like to make a response to that, and before you do that, or maybe while you're doing that, I had been waiting to make this comment until it was in context, but I think it's

striking that you had a liver panel and you never presented any of the data from the liver panel. So I was wondering if you could queue up whatever slides and clarify -- because clearly there's some degree of disagreement -- I mean, so there's the FDA, there's your liver panel, and the presentation that we had. And I understand the subjectivity, but it would be nice to see all these results.

DR. DiBATTISTE: Well, actually, I wanted to invite Dr. Watkins up to address that also, and to clarify some of the panel's findings over time as more data came in. So -- Dr. Watkins.

DR. WATKINS: That case that was shown from the EINSTEIN trial was the French patient that I presented, so one of the three patients. The patient had COPD and had pulmonary emboli -- that's why they were enrolled in the trial -- had a respiratory arrest and, at autopsy, had, you know, a dilated heart.

And the only -- to my knowledge, the only issue that was brought up that would question the diagnosis of shock liver was the fact there was no hypotension documented. Let me just review that for a second.

That graph you just saw of the ALT coming down, the ALT is coming down with a half-life of 48 hours. That is the half-life of serum ALT, if you look at that. So there was a sudden something that happened to the liver. No blood went to it. Liver cells died. Then blood was resumed, and it washed out the ALT.

And on biopsy, at autopsy, there was peri-central necrosis. That's characteristic for ischemic liver injury. So the only issue is the absence of hypotension, as I say. It's been well-described in the medical literature that you can have ischemic liver disease -- ischemic liver, especially when you get right-sided heart failure and hypoxia, that combination.

And I don't -- as I said, it was only one pathologist. When that pathologist got together with experts to discuss the case and was presented this medical literature information, he agreed, and the consensus was the patient had ischemic liver.

And then there was a statement, there is a possibility, albeit distant, that rivaroxaben could have somehow, you know, contributed to the initiation or the progression of the event. And that was the statement that was made.

DR. FOGEL: Actually, could I ask another liver question while Dr. Watkins is up there? What were the liver synthetic functions? What was the albumin? What were the pro-times in the patients that were entered into the study? Because you said you had some Child's A and Child's B. I'm just curious as to --

DR. WATKINS: That's a better question for the sponsor.

DR. PETERS: As you saw, the exclusion criteria for the trial were clinically significant liver disease. We actually did prothrombin times as part of our pharmacodynamics for entry. So we didn't actually have any Child-

Pugh B that I'm aware of that were enrolled in the trial. We did a phase 1 study in people with Child-Pugh A and B compared with normals. So -- but not in the RECORD clinical trial program.

DR. LINCOFF: Dr. Black, you've been waiting patiently.

DR. BLACK: I was going to also shift back to the liver and what I view as the potential for this agent, if approved for this indication, being used for other things. It may well be something that's so much more convenient than Coumadin is right now, that it will be taken up -- we are a cardio-renal board, after all, and it would be nice to have something to do other than Coumadin.

So I'd like more discussion of the risk of liver disease in particular. We have a great group of people here, and they can't seem to tell me how much I should worry about this, and I wish they would comment on it.

DR. PETERS: Hearing Dr. Senior, you know, clarified something to me. So the concern with the liver with this drug was in a phase 2 clinical trial there was a catastrophic liver event, and the patient died jaundiced. And initially the pathology said they didn't think this was hepatitis B, although the patient was surface antigen positive, because there weren't inflammatory cells.

And as I explained to you, experts in viral hepatitis have looked at this case many times over -- we have Dr. Schiff here who could talk about it more -- and, really, the unanimous opinion is that this was a hepatitis B

case.

Nonetheless, that occurred I think a little bit with the legacy of ximelagatran, which is not data-based, as they went into phase 3 trials.

At the end of my assessment of the liver safety of rivaroxaben, I told the company that I thought this issue would become less and less the closer we got to the advisory committee as everyone had a chance to look at the data. But what I didn't realize is that Dr. Senior did not have an opportunity to look at the ATLAS trial data, which I've put a lot of faith into. Here's 2,000 people treated on drug -- actually, more than 2,000; about 1800 treated for six months, and half that many treated with placebo. And I guess -- slide on.

This is showing the incidence of ALT elevations greater than three times. Dr. Senior has not had the opportunity I have to think of any conceivable reason of why you would not detect an ALT signal with this drug.

So I think that's the difference right there. And someone else could say, is six months enough and is 2,000 treated with drug enough? And obviously more data is always better; however, I am unaware of any precedent of any drug that is recognized to have a serious liability that didn't demonstrate ALT everything greater than placebo in a six-month trial.

And I think there really is actually no discrepancy data for data, but obviously a major relevant piece of data was not reviewed in this case.

DR. LINCOFF: Dr. Rieves, I know you have a point to make in that

regard.

DR. RIEVES: Yes, it is, and I think it's very important, because the charge to the committee today is to try to offer some advice to us based predominantly on the RECORD studies and the studies that preceded RECORD.

I think it's important that that is the agreement and the charge to the Food and Drug Administration. We've got to make that decision within just a few weeks. We are not ramping up our review. As the sponsor mentioned, they submitted some data, what, a month ago, and it's not the final study report. Rest assured, on this -- we have a question coming up here, number 2 -- our second question asks about the ongoing studies.

ATLAS, from our perspective, is substantively an ongoing study. We do not have final study data there. That is over a 3,000-subject study. Our decisions here, the critical thinking, should be based upon the RECORD study results and the studies that preceded that.

Now, ATLAS -- it sounds as if this is a very important study, but we all need the opportunity to review those data. They should not be coming in piecemeal shortly before our decision time. And I think that's important to bear that in mind. The agreement was to focus on the RECORD studies and the studies that preceded RECORD.

DR. LINCOFF: Can I clarify, then? If -- this may be getting a little ahead of ourselves, but if in the end, when we get to the questions, this committee decides that more long-term data is required, can that study

ultimately serve as that?

DR. RIEVES: Yes, it can. Yes, it can. It becomes more of a logistical matter because, as you know, at the FDA we're often on time clocks, and we have to reach a decision based on the application as it was submitted, not as it was modified during its review cycle because, obviously, that would continue perhaps infinitum until we took an action -- a favorable action, and we can't work that way.

We can review the data once it's ready to be reviewed and submitted to the agency. We just have to work out the logistics involved in that.

DR. PAGANINI: Michael. Point of clarification, if I can, please. Dwaine, this committee is to look at the short-term effect, not the long-term. I think, when you came up in your presentation, you said please look at the immediate, not the long-term; is that correct?

DR. RIEVES: That's correct. These are short-term. The focus is on short-term --

DR. PAGANINI: Therefore, while long-term may have some issue, that's not for us to grapple with for decisions on the short-term use in immediate post-operative care; is that correct?

DR. RIEVES: The question comes up -- the perspective may be that we need that long-term data, and that would be a conclusion essentially saying that we cannot come to a definitive conclusion at this time in the absence of the long-term.

But we should not reach a risk-benefit decision upon the assumption that we have some of the long-term data, because we don't. We don't.

DR. LINCOFF: Dr. Krenzelok is next.

DR. KRENZELOK: Thank you very much. This is sort of off the path of what we've been talking about, but as I reviewed the briefing materials, I'd like to make a comment on the overdose section since that's sort of the area where I have some expertise, and suggest maybe a significant revision in the management of these patients.

It clearly states that there aren't any antidotes, so we know there aren't reversal agents to treat this. But it does suggest that activated charcoal should be used to help reduce absorption if within eight hours.

Well, the international position statements on activated charcoal suggest that it's efficacious within one to two hours and that it will adsorb compounds with a molecular weight range of, say, 100 to 1,000. So rivaroxaben has a molecular weight of about 450, so it fits within that profile.

However, the only indication for using charcoal beyond two hours might be if there's enteroenteric recirculation or enteroenteric secretion. And at least from the pharmacokinetic data that I've looked at, it appears that that's not the case. It appears that there's some inactive metabolites that are eliminated the feces and biliary secretion, but not active metabolites.

So it would appear to me that this -- you should consider revision

of this and say that charcoal would be efficacious if used within the first one to two hours, but beyond that, there would, in my opinion, not be any efficaciousness.

DR. LINCOFF: Does the sponsor want to comment?

DR. PETERS: That would be fine, and we're more than happy to discuss that with the agency. The eight hours was based on the animal data, the rat data, and just -- we do know how long absorption occurs in the gastrointestinal tract because we've looked at different extended release formulations.

But we're more than willing to consider a shorter interval.

DR. MAYOR: Just another very brief question -- probably best answered by the agency. I want to make sure, in my own mind, that I understand the indications for this agent would be applied to both primary and revision hip and knee replacement; is that correct?

DR. RIEVES: In general, hip and knee replacement. We're not going to elaborate beyond that. So it gets into some of -- physician discretion there. Hip or knee replacement and, in all likelihood, yes, it would apply to revisions.

DR. LINCOFF: I may have cut off the sponsor's response. Did you have more comment on that?

DR. DiBATTISTE: I actually wanted to provide some update on three points. First of all, there was a curve that was put up that didn't have

labels on the curve, and I just wanted to clarify that the lower arm of that curve was the rivaroxaben data, and the higher arm with the higher rates was the placebo data.

I also just wanted to make two follow-up comments -- you can put the slide on. Now we have the curve with the labels. Slide on -- just so that it's clear for the record.

Two other comments. The report referenced by Dr. Rieves where there was no conclusion was the technical component of the report from the statisticians. I think our position on the value of those data and the conclusions that can be drawn has been expressed, so I just wanted to make that point.

And the other point, while we certainly acknowledge that the ATLAS study report has not been submitted, prior to submitting the NDA, we had discussions with the agency regarding submitting updates to the safety database at the four and six-month updates, which is how these data were supplied.

So there were some data from the ATLAS study that were provided with the NDA submission -- those were moderately incomplete. At the four-month data [sic], those were near complete, and at the six-month update, which, admittedly, was just -- I'm guessing about six weeks ago; I don't know the exact date -- that's where the absolute, all 3491 patients were included.

DR. LINCOFF: Dr. Krantz?

DR. KRANTZ: I just had a surgical question. I was looking at slide CC-45 and looking at the incidence of bleeding requiring re-operation, and I guess I had a more broad question for the orthopedic surgeons and maybe for the sponsor.

What was the aggregate rate of re-operation, period, for any reason, whether it was bleeding or wound dehiscence? Do you have that kind of data? Because certainly, you know, post-phlebitic syndrome is a minor issue, but having to go in as a surgeon and re-operate is a big deal. So I wonder if you have that data.

DR. PETERS: I don't be we have that data for total re-operations. It was specifically collected relating to the bleeding because it was a criterion for a major bleed, but I don't believe -- we can check.

DR. KRANTZ: Just when we looked at your documents, you had information about wound drainage, weeping --

DR. PETERS: Right. Right.

DR. KRANTZ: -- all these other --

DR. PETERS: That we collected as adverse events, so I was going to say the only information we would have about re-operation other than related directly to bleeding would be as adverse event reports or as re-hospitalizations. But I don't believe we've analyzed that specifically.

I mean, we did look at wound complications, adverse event reports and grouped them into infectious and non-infectious. That we do have.

DR. KRANTZ: Can you show -- what's the aggregate for that?

DR. PETERS: Slide on.

So this is the pooled studies, treatment and follow-up, so it would be all of the events. Any surgical wound complication was about 1 percent higher, 6 versus 5. Infectious, very balanced. And the non-infectious, accounting for about the 1 percent higher -- and if you look at individual terms, that is most commonly due to an increase in wound secretion, which probably is consistent with some increase in the non-major clinically relevant bleeds as well, I would suspect.

DR. KRANTZ: Thank you.

DR. LINCOFF: Dr. McGuire?

DR. McGUIRE: On the same bleeding theme, the available chemoprophylaxis agents approved have box labeling for epidural and spinal hematoma, and I have seen your proposed product label; you also have chosen to include that. Do you have data in that regard in the RECORD studies as a component of that major bleeding, spinal or epidural hematoma?

DR. PETERS: We had the one spinal bleed, which occurred before drug. Because we dosed post-operatively, the person never received rivaroxaben. The warning is there because with any anticoagulant there could be that risk. So particularly I think if you were thinking about doing, you know, prolonged epidural catheters, we will follow the same path as the low molecular weight heparins -- would discourage that. But if you're going to

use those, you should pull them at troughs and be careful.

DR. LINCOFF: Well, sort of in that vein I have a question myself. I'm struck by, both in the open public hearing as well as throughout the discussions here, that a number of people have talked about the lack -- the relative lack of compliance in orthopedic -- among orthopedic surgeons in terms of this prophylaxis.

I recognize there are differences between guidelines by the orthopedic bodies and American College of Chest Physicians, et cetera, but nevertheless, it does seem like it's underutilized -- but the question that I wonder is, what are the major reasons for that?

If it's issues such as bleeding or concern about bleeding into the joint, that may not [sic] be something addressable by a more convenient anticoagulant. But if it's issues regarding the difficulties with compliance with low molecular weight heparin or warfarin, then certainly from a public health standpoint an easier drug to give might be more useful.

So I don't know if Dr. Friedman or if the orthopedic members of our committee would care to comment, but I would be very interested.

DR. FRIEDMAN: I would agree that there are a percentage of orthopedic surgeons who have a fear of bleeding, period, and so they will be very, very concerned about that. But I think most of the issues that come up are due to factors that I mentioned at the beginning in terms of the available agents that we do have having particular drawbacks that limit their use either

at all or in the best optimal way for the correct duration of time, so I think that's probably the big issue.

And I think from a public heath point of view, having an oral agent once a day I think would promote on-label use, and I think would improve compliance and, therefore, improve patient care. And I would be interested to hear what the orthopedic members of the panel have to say as well. Thank you.

DR. SKINNER: Well, I will speak to that. I agree with Dr. Friedman on that. I think that our open speaker -- our open session speaker alluded to it to some extent, and I think that affects some orthopedic surgeons. When mama has a stroke after her total hip or she has an MI, it's an act of God. And when there's a wound drainage and there's an infection subsequent to that, or a re-operation, that's a surgeon's problem. And that's really a concern to the surgeons.

DR. LINCOFF: Any other comments from members -- yes, sir.

DR. MAYOR: I can certainly suggest that, when I had my knee replaced, I was on prophylaxis, but I wasn't reluctant to give myself my own injections. So I was in a different population. There is no doubt that it's difficult to get patients to subscribe to an injectable anticoagulant on a long-term basis, even though putting them on Coumadin requires frequent phlebotomy, but that's a different issue in terms of how they perceive it.

So I think it would be a significant advantage to the population at risk to have a more convenient technique to bring to bear.

DR. LINCOFF: Dr. Gage?

DR. GAGE: I would agree with that, but it's interesting. You look at the AAOS guidelines by the orthopedic surgeons, which we've largely adopted, and you'll notice the target INR is less than or equal to 2.0. So they disagree completely with the chest guidelines that say target INR 2 to 3. So, you know, that's pretty clear that a primary reservation from orthopedists is fear of hemorrhage. And to the degree that that's true, then, having an alternative agent doesn't directly address that.

DR. LINCOFF: I'm actually in the unexpected position of no names on my list. Do we have any -- oh, I'm sorry. Dr. Paganini.

DR. PAGANINI: Michael, one of the things that sort of impressed me was the lack of any comparator to Coumadin. Is that not a drug that can be taken orally and used in this type of situation? And if it is, was there any comparator done to that besides the point of it being very difficult to establish an adequate level early on with frequent -- is it because they come into the hospital and leave within two or three days that you don't have enough time to transfer over to that? Or is Coumadin not just as effective orally as your drug? Any comparative data?

DR. PETERS: I guess that's a question for me for why we chose enoxaparin and not Coumadin. There certainly have been studies done in the past versus warfarin in this setting. So it can be done. It is more challenging to do the blinding, for sure.

We chose enoxaparin because it is, on a worldwide basis, the most widely used agent. That may not be true for the United States. May be an exception. But certainly worldwide it's very widely used, the most frequently used agent for chemoprophylaxis.

And also, because of that, it is very well documented in clinical studies. We had to establish non-inferiority margins for studies 1, 3 and 4. So there was a lot more data with enoxaparin to base establishing those non-inferiority margins than there is with warfarin.

And also it is highly effective and it has a favorable safety profile. So we considered it the most appropriate comparator to use across the program, with the variations in the regimens to fit some of specific questions and specific studies.

And the data from the literature would suggest that enoxaparin is more effective than warfarin, so indirect comparisons would certainly suggest we have more efficacy, but also there would probably be more bleeding, which would go along with that as well.

DR. LINCOFF: Dr. Skinner, you had a comment in that regard?

DR. SKINNER: Yes. Let me preface my remark by saying I use Arixtra or pentasaccharide and low molecular weight heparin, enoxaparin. But I think that one of the advantages that an orthopedic surgeon sees with Coumadin is that if you give the patient 10 milligrams the night of surgery, it doesn't do anything until the day after that. So they've sort of protected themselves

from that bleeding episode until the risk of bleeding is decreased.

So this drug, or something similar, would be a big advantage in helping those initial clots that form.

DR. PETERS: And if -- there was one question way earlier about if we had looked at ATLAS data for strokes. So if you're winding down on the questions, I could address that, if you would like.

DR. LINCOFF: Dr. Neaton had a question.

DR. NEATON: I just wanted to come back to something you said this morning, I believe, that I don't think I've seen data on, and that is the -- in the RECORD studies, what -- were there any patient characteristics that you looked at that predicted bleeding? You looked at subgroups by bleeding, but I don't have a sense for -- are there high risk individuals for bleeding in these populations?

DR. PETERS: We've -- we started with the prespecified subgroups. We have gone further than that in --

DR. NEATON: It's not so much the subgroups I'm interested in.

DR. PETERS: Right.

DR. NEATON: I'm interested in kind of within the treatment arm, are there baseline characteristics of patients that you've looked at that have a high probability of bleeding?

DR. PETERS: Right. Those analyses are in process. I can verbally give you some preliminary results, but we're not prepared to present them here

at the meeting.

We have started those analyses probably late in the process. Gender is actually the strongest predictor, which we see in the subgroups, with males being higher than females by about double the rate. That's actually true in the rivaroxaben -- for both rivaroxaben and enoxaparin: Males have higher bleeding rates than females.

We also see for rivaroxaben, which is a little bit apparent in the subgroups, that the higher weight and BMI may be a bit higher risk. We've also looked at the benefit in those groups -- the benefit versus risk in those groups, and it does still appear to be favorable.

DR. NEATON: I mean, this seems something, given the conversation I've been listening to for the last half hour on this, to be pretty important for you to generate to help maybe provide some patient management guidelines that would be more relevant in terms of observation and monitoring.

DR. PETERS: Right. And certainly we're starting that and would be very interested in, you know, sharing that with the agency as we move forward after the meeting. But we literally did just start it a few weeks ago, and it's very complicated, multi-variable analyses.

DR. LINCOFF: Dr. Kaul?

DR. KAUL: I just want to follow up on Dr. Paganini's question and respond to your comment. There was a meta analysis published I think several years back, looking at the oral vitamin K antagonists versus enoxaparin. And

for the all-DVT outcome, venography-determined, there was clearly an advantage for enoxaparin. But when you looked at symptomatic DVTs and pulmonary embolism, the results were neutral.

Similarly, in the Pentathlon study, when you looked at venography-determined all DVTs, fondaparinux did better, but when you looked at symptomatic DVTs, clinical DVTs, then enoxaparin did better.

So when you get these disparate results, they make me question the validity of these venography-determined DVTs.

DR. PETERS: All right. So I can comment on that. In the fondaparinux program -- and maybe we can pull up some of those slides -- fondaparinux did a four-study program, one hip fracture study and three studies in joint replacement. They did do -- actually, slide on.

So here are the four studies. You mentioned one of the four. They did do bilateral venography between days 5 to 11. They had a 75 percent availability rate. They did a preplanned meta analysis similar to what we're discussing here for our events.

Next slide shows the efficacy results, which is what you're referring to. So they saw very robust reductions in total VTE and proximal VTE, but did not see reductions in the symptomatic events.

This is the exception, if I could say it, to the -- I mean, this data would be in the ACCP data that I showed earlier that pools all trials. So this is an exception. So why would that be?

This was much shorter dosing, perhaps. I mean, we're looking at long -- this was five to nine days; even in knee, we're going out to 12 days. It is a different drug. It's an indirect inhibitor. So I don't know that I can speculate much.

We have our data. Our data is consistent in that we reduced the venographic outcomes; we reduced the symptomatic outcomes proportionally the same. That fits with when you add the fondaparinux data into all the other studies in the literature, you also see that proportional reduction.

So I don't know why, in this program, which was actually smaller than ours -- I don't know why, in this program, there does seem to be a disparity between the symptomatic -- again, you're dealing with very small numbers of symptomatic events, even for these four studies. They were about 1,000 patients each, so you're looking at about -- approximately 4,000 patients in each of the treatment groups.

DR. KAUL: I gave you an additional example of the meta analysis between Coumadin and enoxaparin, 2004. And you're probably right; the explanation is they're so rare, infrequent events, and it's quite possible that's why you get these discordant events.

DR. PETERS: Right. I can't comment on the meta analysis, but I have looked -- there was a larger -- large-ish clinical outcome study with warfarin versus enoxaparin done a number of years ago which actually did show, in the early period, when you would expect enoxaparin, after hip surgery -- it

was short-term dosing, and it did show, in the dosing period, actually no venographic outcome, reduced symptomatic events for enoxaparin compared to warfarin.

But then, in the follow-up period, the difference went away. So that would also support that maybe some of the differences may be with duration of therapy and really protecting for the full period at risk because, as you saw from Richard's slide, after hip, the risk really goes out through at least a month.

So you might, even with fondaparinux, might have had an advantage early, and then lose it.

DR. LINCOFF: Are there other questions?

You mentioned that you had some stroke data that was --

DR. PETERS: If we could --

DR. LINCOFF: Before we do -- Dr. Rieves, is it appropriate for us to present this data from outside trials? There had been a question, did we have stroke data for --

DR. RIEVES: I'm not aware of a reason not to.

DR. LINCOFF: All right.

DR. PETERS: So -- slide on.

So we have looked, because we've been concerned as well about rebound thrombotic events. So this if from the ATLAS ACS study. It's looking at the hard end points, the death, MI and stroke. And these are the patients,

as they completed treatment. So it's as they completed treatment. That could have been early, if they discontinued early, or for the full six months, if they did the full six months.

And what you can see -- and on the left panel is the first ten days, which would be the period of time when you'd be most worried about rebound hypercoagulability -- and you can see the curves for the composite are very superimposable.

And then if we can show -- the next slide shows the table, the breakdown by the components. Again, unbalanced randomization, so it's 23 versus 9 total events, but twice as many patients.

And if you go down to the stroke row, it was two versus zero, but one of those was hemorrhagic. So only one ischemic stroke out of over 2,000 patients with rivaroxaben, zero with placebo with half the number of patients. So there doesn't appear to be an excess of strokes in this setting.

DR. RIEVES: You know, it raises the issue of how do we handle interim safety data in the review process because, as you can imagine, a database that's coming in with over 12,000 patients in the confirmatory clinical studies -- that's a formidable task to complete that within the several months' assignment that we have.

In general, with respect to the safety data, the interim safety data that come in, it's almost viewed as snapshots, if you will, because we very, very rarely get data sets, if you will. These safety updates are coming

generally towards the end of the review. They're intended to provide a snapshot that allows us to see whether the effects -- there is consistency with the effects that we detect in the initial submitted data, or whether there are important deviations. They're not necessarily intended to resolve critical problems that are evidenced in the original submission because we do not vet these safety updates, if you will, to the same extent that we do the original submissions.

So while they're interesting and provocative and, hopefully, reassuring, if the original data review raises important questions that need critical review of subsequent data, we need to critically review those subsequent data in an appropriate time span.

This review cycle is focused on the RECORD studies and the studies that preceded them.

DR. PETERS: This data -- just for clarity, the data was included in the six-month safety update, so it is there if you want to look at it.

DR. LINCOFF: All right. Are there any more questions for the FDA or for the sponsor?

Well, we had planned a break at 3:30 and then to go on to the questions, but I think since we're here early at this point, why don't we take the break now and then we'll go on and do the questions in an uninterrupted fashion. So we'll take a short break. Panel members, please remember that there should be no discussion of the meeting during the break amongst

yourselves or with any member of the audience. We'll resume at 3:05.

(A recess was taken from 2:44 p.m. until 3:06 p.m.)

DR. LINCOFF: I'd like to get started please.

All right. I want to take a last chance, before we get to the questions, for any comments, and I know that Dr. Pazdur would like to make a comment.

DR. PAZDUR: I just wanted to touch bases with the committee on this issues of data that has been submitted to the FDA and we haven't reviewed it, the Coumadin trial, Coumadin control trial.

One of the issues here -- a lot of discussion from Dwaine has centered on timelines, and I want to really emphasize to you that what we're really interested in is doing the right thing. And if, in your discussions and in your deliberations, you feel that we really do need to really review this data, we want to hear from you on that.

So it's not a black or a white yes or no today. If you really think that to make an accurate characterization to approve this drug, even for a short-time use, a limited use, we need to see this additional data, we want to hear from you in the discussion on that, as well as when you vote on the risk-benefit decision on this drug.

There's regulatory ways of handling it. Again, it's not an issue of a deadline or a timeline. It's doing the right thing. And if we need more time in reviewing this data that has just been submitted, or even the

completion of the entire trial, we want to hear your opinion of it.

At the end of the day, you have to feel comfortable in a risk-benefit decision regarding this drug.

The second point I wanted to talk about is this issue of convenience. The food and drug law states safety and efficacy. Nowhere in it does it say the word "convenience." It's not less safe and more convenient anywhere in the drug regulations. Okay?

In making regulatory decisions, you have to first make up in your mind, do you have a safe and effective drug here? And then you could answer the question -- and then the consideration of convenience should come into play, but if and only if you are able to make that decision in your mind that this is a safe and effective drug.

If we start down the pathway of just approving more convenient drugs with an uncertainty regarding safety and efficacy, we could, over the generations of drug approvals in a specific indication, be just simply approving more convenient toxic placebos.

So the issue here is -- it's safety and efficacy first. You have to answer that question. Then you could get into any discussion of convenience.

So I hope I made these two points very clear. First of all, you have to feel certain in your mind that this drug is safe and effective for the indication, even though it is a limited indication. If you feel that you cannot make that decision at this point and you need more data from these

Coumadin control trials, we want to hear from you on this. It's not about meeting a deadline here. It's not about a PDUFA deadline.

Number two, it's not about convenience; it's about safety and efficacy. That has to be demonstrated first; then a discussion of convenience can be entertained.

DR. LINCOFF: Are there any last questions or -- before we get -- Dr. Gage, did you have a point that you wanted to make?

DR. GAGE: I think it would be useful, in terms of the safety and efficacy, to hear either from one of the FDA biostatisticians or the sponsor in terms of number needed to treat.

DR. DiBATTISTE: As I mentioned, we had analyzed the benefit-risk in a number of different ways. So we presented the excess numbers of events, but we also did number needed to treat. So -- slide on.

So these are the same kinds of analyses that I had presented to review benefit-risk comparing the end points that we discussed earlier, so whichever your preference, if you look at total VTE versus clinically relevant or major versus major or symptomatic versus major.

What you'll note is that both the excess number of events and the NNT are based on the absolute risk difference and, in fact, if you multiply this number by that one, you get 10,000 because, again, they're both based on the absolute risk difference.

But if you go down the right-hand column, you see the numbers needed

to treat range from 20, to prevent one total VTE, to 132, to prevent one symptomatic VTE or death. And in the flip side, on the far right column, the numbers needed to harm range from 157 to 560.

DR. GAGE: So if what I'm interested in is major bleed or clinically relevant bleed and symptomatic VTE or death, then the relevant numbers for me to compare would be the 64, which is in blue, and the 76 in green. Is that right?

DR. DiBATTISTE: For numbers needed to treat, you would be out here. So 132 to prevent one symptomatic VTE or death and 560 to cause one excess major bleeding event.

DR. GAGE: Just to clarify, but that calculation is only major bleeds, not -- it does not include the clinically relevant bleeds, then?

DR. DiBATTISTE: Right. The clinically relevant -- the major plus non-major clinically relevant is illustrated in the top bar. So you're right. 64 is the excess number and the NNT that corresponds with it is 157.

DR. GAGE: Okay. Yes So the -- in other words, these are approximately equal if what we're interested in is symptomatic VTE or death and we're interested in major bleed or clinically relevant bleed. Those -- number needed to treat, number needed to harm for those events, which I think most clinicians would say are relevant, is about the same; is that right?

DR. DiBATTISTE: Well, the 132 versus 157, yes. A difference of 25.

DR. LINCOFF: Well, can you show the -- do you have a slide that

shows the definition of a non-major clinically relevant bleeding event? Because my recollection was that, although relevant perhaps, certainly not of the same magnitude as a symptomatic VTE.

DR. PETERS: Yes. Can I have a slide with the definitions -- the bleeding definitions. So -- slide on.

So the non-major clinically relevant bleeds are those that did not qualify as meeting one of the major bleeding criteria, but did require a medical intervention or an unscheduled contact or temporary cessation of treatment. It could include something like a nosebleed going to the ER, for example.

So -- slide on. These were the examples of the medical importance that were on the CRFs that we collected that the adjudication looked at. So you can see this ranged from, you know, just having a hematoma above a certain size to nosebleeds of certain durations.

So it was -- I would have difficulty personally equating these with a symptomatic DVT or a PE -- certainly a PE. But all of those symptomatic events were clinical events. The vast majority of those people got three months of full-dose anticoagulation with all the, you know, potential consequences from that as well.

DR. LINCOFF: Dr. Kaul, you had a comment?

DR. KAUL: Well, by my estimate, if you focus your analysis to major bleeding plus surgical bleeding, and symptomatic VTE, the numbers needed to

treat in RECORD 1 is 454, numbers needed to harm is 303.

And there's another way you can do this where you adjust the NNT for the harm, so the adjusted NNT is 678 in RECORD 1. In RECORD 4, the numbers needed to treat is 213, numbers needed to harm is 141, and the adjusted NNT is 784.

DR. DiBATTISTE: So if I can have the slide on.

We did look at surgical site bleeding as well -- and this is in the entire pool, again, representing probably the most precise estimate across all studies. And for that comparison you see here. But I certainly won't argue that, in different studies, you would get different numbers.

DR. KAUL: But we just heard from Dr. Rieves that even in the judgment of the sponsor's statistician, pooling was not considered to be appropriate.

DR. DiBATTISTE: No, I don't think that's the correct interpretation. The statistician was saying that they are not offering a medical interpretation. That's what the no interpretation -- that's what was in the report, which we can share if you'd like.

DR. PETERS: Right. So the integrated analyses that are done, all of the data, it follows the statistical analysis plan. The statistical analysis plan was developed, signed, locked before that was done, prespecified end points. And then the report is done by the statistical group. So it comes out with a very brief just methodology -- essentially methodology and

what's contained in the thousands of pages -- and says that it has to defer to medical judgment to make any interpretation.

It doesn't address or negate that they were prespecified analyses. Clearly, as we presented them in the NDA, we presented them as very important analyses, and we actually included the symptomatic events in our proposed label, to make that information available to physicians.

DR. KAUL: What is clear to me is that whether to pool or not to pool is controversial, and we're not going to be able to resolve that. So what I would like to do is focus on the non-controversial studies, which is RECORD 1 and RECORD 4. And I've already provided you with the numbers needed to treat and numbers needed to harm. It's a wash.

DR. LINCOFF: Yeah, but Sanjay, you point out it's controversial whether or not it's appropriate to treat, so -- to pool, so by focusing on two studies, you're essentially discounting the other studies. So for -- you know, I'd be very interested in -- we've already heard from Dr. Neaton, I think, who, certainly from the statistical point of view, believes it was proper.

As a clinician, I would weigh in that I think it was appropriate, that you're looking at a range of clinically relevant treatment regimens, and that you would not be able to expect this infrequent event, this infrequent symptomatic event, to ever be discernable in any single study, and that you needed the power of the four studies.

Given that there's regulatory precedent and appropriateness to use the imaging, quote, surrogate -- if we want to call it that -- but the imaging end point as a criteria for approval, I think I -- from my standpoint -- and I would welcome input from the other panel members, because we won't have, actually, explicitly a point in the questions to discuss it -- but from my standpoint, I think it is appropriate to pool and that, in fact, you can't look at the symptomatic end point in any other way, that any other point estimate is so unstable because of the small sample size.

Again, I would welcome any other...

DR. FOX: I guess just a point to emphasize what I think I heard Dr. Rieves say earlier that the regulatory standard for registration has been established for a long time. The sponsor followed the guidance of the agency with respect to those requirements. I think the statistical analysis plan, as described, was done in a logical way and locked and sent to the agency ahead of the program completion. And I think to try and criticize it post-hoc at this point is -- and to pick and choose which studies you want to look at and which ones you don't want to look at is a bit disingenuous.

DR. LINCOFF: Are there any other comments before we go on to the voting?

Okay. So I'll read the introduction to the questions first. We have two questions for discussion that we don't vote on formally, but are another opportunity to have opinions of the panel members, and they focus on

the hepatotoxicity, and then two questions that will be formal voting, and I'll outline the voting procedures before those.

Rivaroxaben was studied in four phase 3 clinical studies, RECORD studies, that examined its ability to prevent venous thromboembolism, VTE, among patients undergoing hip or knee replacement surgery. Clinical studies are currently ongoing to assess the drug's effects in multiple other settings.

The primary end point in the RECORD studies was a comparison of the occurrence of a composite end point that consisted of venographic evidence of DVT, non-fatal PE or death. Statistical success upon this end point was demonstrated in all four RECORD studies.

The main safety finding in the RECORD studies was increased bleeding among patients who received rivaroxaben compared to patients who received enoxaparin. Major bleeding had occurred at a rate of 0.4 percent within the rivaroxaben group and 0.2 percent within the enoxaparin group.

The only bleeding-related death occurred in a patient who received rivaroxaben.

Safety findings also noted a numeric increase in the occurrence of serious alamine aminotransferase, ALT, elevations among patients receiving rivaroxaben, 0.3 percent, versus 0.2 percent, as well as the occurrence of a composite liver marker, ALT greater than three times the upper limit of normal with total bilirubin greater than two times the upper limit of normal, 0.15 percent versus 0.11 percent.

So question 1, if we could put on the screen.

This, again, is a discussion question. Do the available data preclude approval of rivaroxaben at this time for the prophylaxis of VTE among patients undergoing hip or knee replacement surgery due to the potential risk of severe hepatotoxicity?

And I'll just preview that there will be an opportunity, with the next question, to discuss whether or not -- what additional data from long-term may be required. Do we have any comments?

DR. WOLFE: I was relieved to hear a couple of minutes ago from the FDA that despite PDUFA and whatever, we should try and do the right thing. I think we all want to do that.

And part of the answer to this question -- my brief answer to the question is that there has certainly been a suggesting by Dr. Gelperin this morning that you -- we haven't been able to fully characterize the potential signal for several liver injury. I realize that's part of the next question, so I guess my answer to this question is that, particularly in light of the statement by Dr. Xu, the statistician, this morning that when you look at symptomatic VTE or death, there is not a statistically significant superiority of rivaroxaben, that my answer would be we should not rush into this; we should wait until we get more data.

I mean, as you remember from the literature and elsewhere, one out of 2,000 patients with a Hy's law hepatotoxic death is worrisome -- and we're

talking about a sort of intermediate length study, the ACCESS study of 2,000 patients, that might or might not include some patient like that. And we're also talking about longer studies, including atrial fibrillation and others, that are going to yield far more data on more patients for longer periods of time.

So I guess my answer is there aren't enough available data on the question -- the signal of hepatotoxicity.

DR. LINCOFF: Dr. Fogel?

DR. FOGEL: With regard to the way the question is worded, I do not believe that the available data preclude the approval of rivaroxaben. The points in favor of the use of the drug are, one, the animal studies that did not show any hepatotoxicity, and, two, the lack of cases in the RECORD study that were identified as being definitive causes of hepatotoxicity.

However, I have reservations about whether the drug should be approved, and for the following reasons. The first reason is that there's one probable case of hepatotoxicity, which is worrisome. Looking at the graph, there are six cases in the left upper quadrant that meet Hy's law criteria, and I think that does represent a signal that we need to look at.

My third reason is I have safety concerns should the drug be approved. Patients are only going to be in the hospital for two to three days, and then they're either going to go home or they're going to go to nursing homes for rehab, and I have concerns about the adequacy with which

they're going to be both dosed as well as observed.

And my fourth concern is whether the study sample is representative of the larger population. We never really got at the underlying liver disease in these people, their use of alcohol -- we don't have the characteristics of the study population, and that represents a major focus of concern for me.

DR. LINCOFF: Dr. Rieves?

DR. RIEVES: Yes. I just want to emphasize again our wording is preclude approval at this time. It's not necessarily preclude approval at any time, but it's at --

DR. FOGEL: Okay. I don't think it precludes approval at this time, but I think that there are issues that need to be addressed before it's approved at this time.

DR. LINCOFF: Dr. Paganini?

DR. PAGANINI: Tough act to follow. That Hy's area -- also in that same area says that you can't find alternate explanations, and I think there were alternate explanations for most of those cases, with that one exception.

So it puts it in there -- sort of a concern, but not an absolute onus. This is a short-term area and short-term use. I think that the data that was presented for that particular use is adequate to allow for this to be approved for that particular use at this time.

DR. LINCOFF: Dr. Gross?

DR. GROSS: Yeah. I think we have enough evidence to -- for safety

and efficacy to approve short-term use, with a caveat that we have to warn the prescriber to not use it for other conditions, and certainly not use it for long-term at this particular time, until more data is available.

DR. LINCOFF: Mr. Dubbs?

MR. DUBBS: I may be missing something in terms of the big picture, but I don't see why we should preclude approval. But I don't see the statistical significance of a difference between .4 and .2 when you have two choices, either the study drug or the other drug, in terms of bleeding. I mean, if you didn't give the study drug, you'd give the other drug, and you'd have a .2 percent incidence, as I understand it, in bleeding.

And from the liver standpoint, you have .3 percent versus .2 percent, and if you didn't have the study drug, you'd give the other drug, and you'd still have a .2 percent. So I'm not being able to put this all together and say there's a statistical problem with the study drug.

DR. LINCOFF: Dr. Skinner?

DR. SKINNER: I agree with the concept that the data do not preclude the approval of this medication. I don't think the evidence shows that, for short-term use, it's dangerous from a liver viewpoint. I think it's fairly safe from a bleeding viewpoint. And I think that some of the worries that we hear around the table are from the thought that there's a group of doctors that are going to use it long-term, and I don't think we should be swayed by the worry that some doctors are going to use it off-label.

DR. LINCOFF: Dr. Venitz?

DR. VENITZ: I believe the data, as they exist, do not preclude approval based on concerns about liver toxicity.

DR. LINCOFF: If I could -- from my standpoint, I agree that the -- I don't believe the data preclude. I do -- I do wonder how much responsibility we have, though, to protect against what is likely to be off-label use. I think that the impetus to use this drug, if it's available, for many of the indications of warfarin considerably longer than its label -- I think there's going to be a lot of impetus for that. And I'm not, you know, real sure what the sort of regulatory responsibility -- but I think it's a reality.

You know, I think that the presentation that Dr. Watkins presented, showing the very plausible reasons why many of these Hy's law right upper quadrant cases were, in fact, not likely to be due to drug was very compelling, but nevertheless a liver panel that was blinded, and may have been flawed but nevertheless, as has been pointed out, there is a great deal of subjectivity, did suggest that there were more likely or probable or likely related cases in the rivaroxaben group than in the control group.

So I think it raises the question that there may be a question, and it would be nice to be able to resolve that. And I think the impending availability of longer-term data is reassuring, but as has been pointed out, this data has not been subject to the rigorous that all the other data that

we're looking at is.

So I don't think it precludes, but I think that there's a bit of caution.

MR. DUBBS: So I'm not sure -- your comment was we can't not consider -- or not concern ourselves with the longer-term use off-label that some physicians may allow this drug to be used in place of long-term warfarin. Is that our responsibility now? I mean, does the FDA want us, as a -- I mean, the sponsor is asking only for a specific indication. So should this panel be overly concerned with off-label use that the sponsor has specifically said they're not seeking approval for?

DR. LINCOFF: Perhaps we can get the FDA's response. It's my understand, of course, that --

DR. PAZDUR: It's the indication that they're looking at here, and here again, I think it's important -- perhaps they want to address this -- well, we're past that period of time, but during their presentation they did point out areas that they were considering to minimize any risk -- that includes blister packages, patient education. So I think they were aware of this issue, and there have been attempts to address this.

Let's face it. With every drug that anyone approves, there is always a risk of off-label use, of misuse. We try to minimize this and mitigate those risks. The naming of drugs, for example. If they have similar names, we look at that. So, you know, this is a process that is there with

all drugs.

DR. LINCOFF: Yes, Dr. Gross.

DR. GROSS: Let's not assume that Coumadin is a totally safe drug the way it's used. People are often not carefully for their INRs, come in with major hemorrhagic complications, and sometimes come in under-anticoagulated and get thromboses. So until a side-by-side comparison is made with Coumadin, I don't think we can conclude that Coumadin is safer than rivaroxaben.

DR. LINCOFF: Dr. Krenzelok?

DR. KRENZELOK: Thank you. Just very briefly. I certainly support the approval of this drug for short-term use. I'm not convinced that what we're seeing from a hepatotoxicity standpoint might not just be background noise rather than something that's valid.

But I think, in light of that, we would be prudent to recommend long-term toxico-surveillance on the drug for the future, just to make sure that this isn't background noise.

DR. LINCOFF: Dr. Wolfe?

DR. WOLFE: Just responding to these comments about probable, or I would say certain off-label use, I mean, we've heard in several presentations that this is, A, the first oral anticoagulation in 40-some years and, B, you don't have to do INRs on it. It sort of has two things about it, and if that is not a guarantee for long-term use, I don't know what is. I mean, even

though technically the approval that's being considered is relatively short-term for total hip/total knee, this has been exciting people for enough of a time that, if it's approved for that, I will bet large amounts of money that within a few months it will be used massively off-label for durations of time for which we don't have data on hepatotoxicity.

DR. LINCOFF: Dr. Black?

DR. BLACK: I've been very much on the fence, as I imagine many of us have. I expressed a concern about off-label use -- it seemed to be about three days ago, and it's curious that Hy's law is in the right upper quadrant. I think that's very indicative of what we're dealing with when it comes to the liver.

But I think the way you've cleverly worded the question -- I think it's much easier for us to address. I think -- though certainly longer-term data is very critical here, and I think we'll have it. It's on the way, and we certainly should ask for more.

I'm agree -- I think I would vote to approve it now, but I wasn't so sure 20 minutes ago.

DR. LINCOFF: Dr. Krantz?

DR. KRANTZ: I think this is a very good discussion. I think what's sort of reassuring to me is -- we had the meeting yesterday and we saw discordant data in terms of death, and I think overall there was twice as many deaths in the enoxaparin group, if I recall, in the safety database. So small

trials -- you know, 6,000 or so folks in the RECORD trial, but I think that's a little bit reassuring.

I do think still, despite that, there's a strong interest for all of us to follow this long-term in terms of a -- safety regarding the liver because I think troglitazone and certainly ximelagatran are in our minds.

DR. LINCOFF: Dr. Neaton?

DR. NEATON: I'll just offer that I think it's been challenging enough to deal with the short-term data, and that's what we should stick with, and not speculate. I personally don't think six months is long-term, and so that -- you know, we're going to be reassured perhaps when the FDA reviews the entire ATLAS package about six-month data, but we know later more data is going to come down the line.

We can always speculate about how this is going to be used, but I think we should deal with the indication and the data we have in front of us.

DR. LINCOFF: Dr. Skinner?

DR. SKINNER: One thing that I think will mitigate the use of this as a long-term medication is that, first of all, the band-aid people will price it very highly. Secondly, the health insurance companies will try to get everything they can to keep us from using it. And the pharmacists will prevent us at every turn.

So I think long-term use is less of a problem than you think.

DR. LINCOFF: Mr. Dubbs?

MR. DUBBS: Well, part of my comment and question earlier was, what does the FDA think we should do in viewing it -- off-label use long-term in the considerations we're having today for the approval for short-term use after the knee and hip surgery?

DR. LINCOFF: Does the FDA have any more comments on this topic, either about that or in general?

DR. PAZDUR: I think we made our point real clear. You know, to address Dr. Wolfe's comments, we've had these same conversations internally, believe me, and then we have to bring ourselves back to the issue of -- the issue that you brought up, you know, what is the indication that they're seeking here? Because we can speculate here as much as we want, and there are other mitigating factors, such as price, that we don't look at, that may influence prescribing behavior. There are programs that try to mitigate the risk of long-term use, the packaging of the drug.

But here again, at the end of the day, you have an indication, a database, and if you take a look at how we asked the question for approval, it's a risk-benefit decision that ultimately comes us, and that's what we want you to focus on the existing data.

DR. DAL PAN: We've looked at this with other drugs labeled for short-term use for which there's been a concern about long-term use. Bromfenac is an example of that, where it was labeled for a certain period, but we had data to show that, despite the labeling, it was used for a long-

term period. We looked at that for metoclopramide and have published that as well.

So I think -- it gets back to what I think a number of you are saying, that there is likely to be long-term use if there's a rationale for that, despite what the label says, and we've studied that in at least two drugs.

DR. LINCOFF: Dr. Mayor, did you have a comment?

DR. MAYOR: Yeah, just to make sure that my point of view is represented in the discussion on this topic, I would not want to be counted as one who would discount the dreadful consequences of drug-induced liver injury, but my sense would be that to conclude non-approvabiltity of this application would be to throw the baby out with the bath water.

DR. LINCOFF: Yes, Dr. Swenson?

DR. SWENSON: I wonder if I could ask the agency -- maybe you can't answer this, but if we do approve it for just the indication as it's stated, you're going to be monitoring the outcome here. If a significant liver signal becomes evident, would you then go back and disallow this indication on the fears and possible data suggesting that the drug is being disseminated beyond this indication?

DR. PAZDUR: That's a very hypothetical question. We generally don't answer hypothetical questions, but obviously if there's a significant liver toxicity, yes.

DR. LINCOFF: All right. Then we can move on to the next very closely related question.

The proposed rivaroxaben dose regimen is for a maximum of 14, for knee surgery, or 35, for hip surgery, days. Are the data from the ongoing "long-term" clinical studies essential to assess rivaroxaben safety prior to its approval for the prophylaxis of VTE among patients undergoing hip or knee replacement surgery?

Any comments? Yes, Dr. Mayor.

DR. MAYOR: Prior to its approval? No. The important issue is that the ongoing surveillance of experience with the drug is absolutely undiminished, but I don't consider it essential to stand in the way of a decision about approvability.

DR. LINCOFF: Dr. McGuire?

DR. McGUIRE: I'm not sure how relevant the long-term studies are going to be. They are very different patient populations and the relative safety effect or safety signal may well be different, but may not influence the perioperative period we're studying this drug in afib and medically ill patients and acute coronary syndrome, so I don't know that those will be relevant, so I don't think this is relevant here.

DR. LINCOFF: Dr. Paganini?

DR. PAGANINI: I'm still super-amazed at how the CKD patients are somewhat protected by this when, in fact, you would have normally thought them

to be more exposed and having a little bit more of a complication with them. So while they're not one of the listed folks -- they're not livers, but with liver and CKD -- that's a problem.

I wouldn't stop it from being approved for short-term, but boy, I would really watch it and hawk it for those subgroups of patients that may have an increased risk during the post-approval period. So I would strongly suggest that those subgroups be clearly identified and followed very closely so that perhaps the early indications, especially in the CKD patient population, that seems to be so different than what one would have expected, isn't just a factor of just small groups and small numbers.

DR. LINCOFF: We can also address this issue in question 4, so -- any other comments on this? This is pretty much the last chance for free-form comments before we get to voting.

Yes, Dr. Neaton?

DR. NEATON: I just was going to say that I guess the slide that we saw this morning with the other studies that are ongoing was reassuring to me, and I'd much rather be able to assess the long-term safety of this drug from carefully controlled randomized trials than some observational study that might be done to look at safety afterwards.

So I think we'll have a lot better data based on what's being done already than what might have been done under other circumstances.

DR. LINCOFF: But the FDA is saying you can't -- if you needed to be

reassured, then you can't really do it from that data. I mean, that's summary data. I mean, all the other data that we've seen has been data that they've seen on a patient-level basis, so --

DR. NEATON: I'm not arguing for the data being in hand right now. I'm happy that there is a, quote, post-approval kind of randomized trials that we will see the results of down the line.

DR. LINCOFF: Would you feel the same way -- because I feel the same way. I thought it was reassuring, but that may be improper. If you hadn't seen the data, if you knew the trial was being done but you hadn't seen the data, would you feel as sanguine about it?

DR. NEATON: I would, because I think we ought to view this based upon how this drug is proposed to be used in this population, and not speculate on how it's going to be used long-term off-label.

DR. LINCOFF: Yes, Dr. Gage?

DR. GAGE: So if I hadn't seen the longer-term data, I think I personally would be very comfortable prescribing this for up to 14 days with knee replacement, but not necessarily up to 35 days for hip replacement.

DR. LINCOFF: Can you expand on that because we -- I mean, that's what they tested, right?

DR. GAGE: Yeah. So my point being that when somebody is undergoing knee replacement, we often prescribe anticoagulant therapy for 14 days, and knowing that we have data going to 35 days, and some that we saw even longer

that we tend to discount here gives me a great deal of confidence that my patients undergoing knee replacement would do well and would be at low risk for liver toxicity.

But my patients undergoing hip replacement, I guess I have a little more reservation because they will sometimes get more than 35 days, and we don't have much long-term data. And so for them I think the question is not so clear in my mind.

DR. LINCOFF: Dr. Venitz, I believe you had a comment.

DR. VENITZ: Yeah. I would say that the data from those long-term studies are not essential -- they are helpful. So I don't think they should preclude -- or the absence of those data, vetted as they should be, should be precluding approval.

I think we are looking at an anticoagulant, major toxicity is related to its pharmacological effect, somewhat predictable. I think we've just resolved -- or at least some of us have resolved the liver toxicity issue. My concern that I have that kind of tempers my enthusiasm a little bit is this idea of rebound hypercoagulability that seems to pop up in the -- at least FDA analysis of the existing data.

So that's something that to me would be very helpful to look at the long-term data in terms of resolving that. But I don't think the data is essential for approval.

DR. LINCOFF: Dr. Black?

DR. BLACK: Just kind of philosophical comment I think is, there is off-label and there is off-label. There are things that get approved for one indication that people do studies on -- there's something that might make sense -- and years or months later it becomes adopted for that, and then gets the label changed.

And then there's something like this which, as it becomes to be discussed, it looks a little scary to use it any way but we have data on. So it may not be as much of a problem as it might be in some other ways.

DR. LINCOFF: Last chance for comments before we go the voting.

Okay. We will be using the new electronic voting system for this meeting. Each of you have three voting buttons on your microphone: Yes, no and abstain. Once we begin the vote, please press the button that corresponds to your vote. After everyone has completed their vote, the vote will be locked in. I'm going to add to this. The lights stay on. That doesn't mean it didn't record your vote. Don't worry.

The vote will then be displayed on the screen. I will read the vote from the screen into the record.

Next, we will go around the room and each individual who voted will state their name and their vote into the record, as well as the reason why they voted as they did.

So the third question, and the first voting question is as follows: Do the available clinical data demonstrate a favorable risk-benefit profile

for rivaroxaben in the prophylaxis of VTE in patients undergoing hip or knee replacement surgery?

Wait till these light up. Okay. Please vote.

Everyone has voted. The vote is now complete and locked in. I will read the record from the screen -- I will read from the screen into the record. Yes, 15 votes; no, two votes; abstain, zero.

Now the vote is complete. We will go around the table and have everyone who voted state their name, vote and the reason they voted as they did into the record.

So if we can start, I believe -- Dr. Fox, you're not voting, so Dr. Paganini, if you could start, please.

DR. PAGANINI: I voted yes for this. I believe that the data that was -- demonstrated effectiveness and safety for this particular use, and that is for the short-term use in post-knees and post-hips.

DR. LINCOFF: Also, if your comments are -- I mean, it's fair to say that your thoughts have already been summarized, it's fine.

DR. BLACK: Henry Black. I voted yes, and my thoughts have definitely been summarized.

DR. VENITZ: I would only add that -- I voted yes. My name is Venitz. And I would agree with what you've already heard, but I would also point out that, in my mind, the analysis strategy of using a, quote, surrogate end point and pooling across studies is legitimate, so I believe they have

demonstrated benefit adequately.

DR. SWENSON: Erik Swenson. I voted yes in a qualified sense. There will -- I think we've said this, but there has to be careful assessment of this longer-term liver toxicity issue, and coupled with how much the drug use will diffuse away from the proposed indication, and that things be reassessed on the basis of what we know down the road.

DR. McGUIRE: Darren McGuire. I voted yes. I think the efficacy and safety profile has been adequately demonstrated. I will go on record. I don't think venography is an acceptable end point henceforth for this indication. I think we have a number of available therapies presently available. And so my vote is largely driven by the aggregate pooled data with all of its limitations.

DR. FOGEL: Ron Fogel. I voted yes based on the demonstration of efficacy. I do have a reservation regarding liver toxicity. I think that that does need to be watched carefully. But the data that was presented was not strong enough to say that there's a definite liver signal.

DR. KRENZELOK: Ed Krenzelok. I voted yes for the reasons that are previously stated, and I'd also like to mention that I think this -- because as Dr. Pazdur said, once it's safe and efficacious we could talk about other things as well. I do think it offers the patient perhaps a more convenient way to dose themselves rather than daily injections and may enhance compliance and diminish the number of events that occur.

DR. NEATON: Jim Neaton. I voted yes, and I think the risk-benefit profile that was laid out this morning with the sponsor was very helpful in my -- making my vote.

DR. MAYOR: Michael Mayor. I voted yes, given the short-term therapeutic-intense data in the application.

DR. WOLFE: Sid Wolfe. I voted no, partly because of the statistical analysis that was presented this morning were -- in terms of symptomatic VTE or death, it was stated there isn't any evidence of superiority -- went over the bound of 1. Secondly, I am concerned about the bleeding, particularly in the wake of that. And third, as I've said several times, I am very uncomfortable about the certainty of long-term use and the absence of long-term safety data on hepatotoxicity.

DR. LINCOFF: Michael Lincoff. I voted yes. I think the efficacy data is actually compelling. The, quote, surrogate and the harder end points line up with a similar degree consistency. I think the safety -- the bleeding is -- the net clinical benefit, including the bleeding, is still favorable.

I think the liver issue is not completely resolved, but I believe that the signal of liver injury is very weak and warrants continued surveillance in both upcoming clinical trials as well as clinical practice, but does not preclude approval of the drug. And I would encourage aggressive efforts to keep patients using this drug on-label rather than off-label use.

DR. GAGE: Brian Gage. I voted yes, and I'll second that last point

that -- I would be uncomfortable if this drug was used in patients with possible liver disease or in patients that have excessively high risk of bleeding.

DR. SKINNER: Harry Skinner. I agree with Dr. Lincoff, Dr. Gage, and I'd like to add that, in regards to convenience that we discussed earlier, one of the aspects of convenience is compliance, and compliance can contribute significantly to the safety and efficacy.

DR. KRANTZ: Mori Krantz. I voted yes. I had some trepidation, but I think the trial design was excellent, and I think the safety was favorable. I do think certainly there should be a lot of prudence surrounding future liver injury and certainly -- I'm not a hundred percent clear about the need for re-operation and the higher bleeding risk, but I think overall it was a favorable product.

DR. McCORMICK: My name is Paul McCormick. I voted yes for the reasons previously articulated. I think the risk-benefit profile for the stated indications are very favorable. As a neurosurgeon, however, because of the bleeding issues, I would not consider this medication in a neurosurgical population.

DR. KAUL: Sanjay Kaul. I voted no. In -- trials that use clinically important outcomes to assess both efficacy and safety would yield more definitive results that are easier to interpret and more relevant to clinical practice.

Most asymptomatic deep vein thromboses do not progress to cause symptoms, and the proportion that do, I expect it to differ between populations, knee surgery versus hip surgery.

By contrast, most confirmed episodes of bleeding that are reported in clinical trials are associated with symptoms and are clinically important.

I had issues with regards to the choice of end points, and I completely concur with Dr. McGuire: Henceforth, I think the FDA ought to really visit this and provide us with some updated guidance, whether venography-determined end points are a valid surrogate for clinical practice.

I had issues with regarding to pooling. I still haven't heard a convincing argument whether 2 and 3 should be pooled, with apologies to Dr. Fox. And I did not see any signal that would exclude the possibility of hepatotoxicity, cardiotoxicity, with the upper bound of the cardiovascular events being 1.28. Granted, the point estimate was .80, was based on a total number of 70 -- and issues with regarding to bleeding.

What I saw there, the risk-benefit, if you focus only on symptomatic VTE as well, and major bleeding with surgical bleeding sites, I saw a risk-benefit which was a wash. The benefit did not seem to outweigh the risk, and so that's why I voted no.

MR. DUBBS: Bob Dubbs. I voted yes. And I felt that the evidence presented for the short-term use and the risk-benefit profile was compelling. And I agree that the need for long-term studies and monitoring is important.

But I have to say, as a chronic Coumadin user, I am excited by the possibility of not having to have my blood drawn every two weeks.

DR. LINCOFF: A great way to make us all uncomfortable about our votes.

(Laughter.)

DR. LINCOFF: Now, this next question, I've gotten a little clearance from Elaine here to -- I'd like to engage in a little bit of discussion, if we choose to do so on this, because we actually never really spent much time talking about this. So if we could have question 4 -- I'm not going to read the question yet -- can I read it and then not vote?

MS. FERGUSON: No, just -- we're going to have discussion --

DR. LINCOFF: All right. We're going to have discussion regarding -- because this question regards whether or not there should be a lower dose available, and concerns about whether one dose fits all.

In your discussions, if you choose to do so, please try not to say, I'm going to vote such and such, because that's kind of missing the point of -- once we vote, we've voted, and there won't be subsequent votes. So I think the -- if anybody would like to bring up points regarding your comfort or discomfort with a single dose rather -- a one-size-fits-all strategy, then this might be the time because, to my recollection, we hardly brought this up at all.

DR. VENITZ: A couple of things that I'd like to point out. First

of all, the sponsor themselves told us that they're still in the process of identifying populations at risk. So I don't think we have seen the entire picture, even with everything that was presented today and the material that was presented to us.

Also, from my perspective as a clinical pharmacologist, I am worried about drug-drug interactions. There's a table in the FDA background that suggests that there's a seven-fold increase in bleeding incidence in the presence of P-gp and metabolic inhibitor. The current proposed label only would contraindicate the presence of strong inhibitors; it doesn't specifically mention moderate inhibitors, diltiazem, verapamil, things like that, which are pretty prevalent in the population that is studied.

I think there is some concern that I share with the FDA about the impact that chronic renal failure might have, exposure-related increase in bleeding incidence. And I really haven't seen any reason other than the sponsor didn't engage, apparently, in not using a dosage form that would allow down titration.

So without giving my vote away, I think there are plenty of reasons to believe that a dose recommendation -- dose reduction would be useful.

DR. LINCOFF: Dr. Wolfe?

DR. WOLFE: This is really a question for the FDA and possibly, if they can't answer, for the company. In the briefing materials, as just mentioned, there's clearly a suggestion by the FDA that the company do this,

and in one of the pieces of material -- I forget whose it was -- the company said they refused. What was the reason the company told you they didn't want to do this? And then, if they didn't give you one, I'd like to hear from the company what their reason was.

DR. TORNOE: I think the belief is that there is not substantial increase in bleeds in different renal subgroups, which they showed. And then the concomitant medication -- I think they believe there's not that much -- people won't be getting these drugs. But we did find increasing exposure leads to increasing risk of bleeding. And as Dr. Venitz was pointing out, there will be a substantial number of patients on these CYP3A4 moderate or P-gp inhibitors that will cause up to doubling of the exposure.

DR. PETERS: I could address this in several minutes. We didn't get, really, time to delve into the --

DR. LINCOFF: Well, fortunately, we have a little bit of time, so if we stay on the -- I think it's an important topic.

DR. PETERS: So, actually, if I could break this into two parts. One part are populations where we have data, for example, age -- so if we could show the bleeding by the age subgroups -- I think this is very instructive, and it's similar to the moderate renal impairment. And then also if we could show the efficacy and the age by subgroups.

So there are groups, which I mentioned in the talk, like the older than age 75, that we know do have increased exposures. We know that from the

phase 1 -- it's about 40 to 50 percent increase in area under the curve. We know that -- slide -- actually, just the age, the Forrest plot for the age.

And we know that from the phase 3 with the PT measurements. If we look at the PT measurements in those over the age of 75, they are about two seconds more prolonged than the under the age 65, which actually corresponds to about a 40 percent increase in Cmax. So -- slide on.

What you see here, similar to the non-renal -- to the renal data, is that, for enoxaparin, the lowest bleeding rate is in the younger people. The bleeding rate more than doubles as you go up to over age 75, a very expected pattern with enoxaparin. We know its exposures go up.

If we look at the rivaroxaben group, which is now 900 on rivaroxaben in the oldest age group, and 900 on enoxaparin, you can see the bleeding rates really don't change much, even though we know the exposures are becoming higher, as you go to the older age individuals. So the risk relative to enoxaparin actually appears to decrease a bit. I wouldn't say it's less; I think it's consistent with the overall increase still.

So if we could have the next slide.

This shows the corresponding efficacy data for total VTE. Again, if you look at the enoxaparin group, the event rate, despite increasing enoxaparin exposures, goes from a rate of about 7 percent, and about doubles in those over the age of 75. So older age, renal impairment are high risk groups for total VTE events.

In the rivaroxaben group, you see the rate also increases, despite increasing rivaroxaben levels.

So I think some of these subgroups where we have data -- age, moderate renal impairment, fragile -- we need to make the decisions for doses based on the data we have. And the 10-milligram dose looks very favorable from an efficacy to a bleeding risk in these subgroups.

Where we don't have much information -- next slide on -- is -- and we're not -- I should make it clear, we haven't refused to do a lower dose strength, and we're -- we will pursue this with the agency, and we're very happy to have discussions and continue the discussions.

Here's the other component. Where we don't have much data is where you now start combining different degrees of renal function, going from left to right. Normal renal function by Cocroft-Gault, to severe renal impairment across horizontally. And going vertically down from no CYP inhibition to strong CYP3A4 inhibition.

And if you can -- and what you can see, using the upper left as the reference area under the curve of 1, going to the far right, which is severe renal impairment with strong CYP inhibition which, for example, is ketoconazole which had a 2-1/2-fold increase in exposures, we would predict -- those people we are saying already we really don't think we want to expose people to more than two-fold increase in levels.

So the question becomes, how frequent are these groups? We have

very little clinical data -- next slide on.

Looking at the RECORD program, elective orthopedic surgery -- as we heard, people in their mid-60s -- the upper left quadrant, with no CYP inhibition and normal renal function is 50 percent of the population. And if you go just to the mild renal impairment, is another 32 percent. So 80 percent of the people fall in the normal or mild renal function and no CYP inhibitor category.

And then if you go down to the far right, the ones that are shaded are the ones that we project, based on modeling, would be over a two-fold increase in exposure where we actually agree with the agency, we think they should not be exposed to those rivaroxaben levels. It's -- in this estimation, you know, less than 1 percent of the population.

So it's not that we aren't concerned about bleeding risk with various clinical pharmacology issues in terms of CYP inhibition and renal or other combinations with moderate impairment. We think that it applies to a very small percent of this patient population and that it would be better to deal with that with instructions in the labeling -- for example, not recommending concomitant use with ketoconazole, not recommending people that have moderate hepatic impairment, if they were going for joint surgery, that they would not be candidates for rivaroxaben -- that seems to us a simpler and more appropriate approach than having another dose strength where there is the concern that people that should get the 10-milligram might get the 5.

The concern here is if we don't have a lower dose strength, is the concern of people would get the 10 when they shouldn't get the 10.

So we're very willing to discuss both options still, but our position is that we favor the 10 milligrams that we studied in the program where we have a large amount of data in some patient populations.

So I hope that is helpful.

DR. LINCOFF: Dr. McGuire is next.

DR. McGUIRE: My comments are directly along those lines. I think, as we know, in all cardiovascular disease, when we use antithrombotic therapies, we always sacrifice efficacy and safety -- they track in parallel. And so I think if we have an alternative at a lower dose, given the comments from the orthopedists earlier where surgeons are reticent to use antithrombotic therapies for bleeding complications, I think a surgeon would very commonly choose the 5-milligram dose because of that reason. And we may be jeopardizing patient efficacy in that context.

So to -- I think the issue needs to be explored, but I don't think we should, using the available data and the PK data, jeopardize the clinical -- surrogate and clinical outcomes data for PK data.

DR. LINCOFF: I think Dr. Tornoe is next.

DR. TORNOE: So the table the sponsor showed of the different levels of CYP inhibition are likely to underpredict the increased fold in exposures since they showed, with normal renal function and 90 inhibition they saw a

1.3-fold increase in exposure even though the ketoconazole data suggested a 2.5-fold in normal patients.

So -- and then these are mean values. So with the variability of the PK, you will have subjects with greater than 2-fold even though you show 1.5, 1.6-fold increasing exposure. A substantial number of patients will have greater than 2-fold increase in exposure, those different levels of moderate to strong CYP inhibitors or different levels of renal function -- and combinations, which are not tested, but tried to model --

DR. PETERS: Right. So I think the overall point is that -- you know, ketoconazole is a strong inhibitor of CYP3A4. It's also a strong inhibitor of P-gp. So ketoconazole is actually a model of blocking the renal secretion -- so it would make someone be under the severe renal dysfunction category because we're blocking the renal elimination, and in the 90 CYP inhibition.

These are average, but again, our dose response curve, which we started with earlier today, it does -- and we're still willing to discuss with the agency the steepness of the dose response curve. On -- the exposure response and the dose response are also average responses going from 10 to 20 milligrams.

So on average -- these are average exposures. There are people with ketoconazole that would be higher than 2-1/2-fold, obviously, and others that are lower.

But our database -- and we didn't restrict for cytochrome P450 inhibitors other than HIV protease inhibitors, which we knew were strong inhibitors, and we added ketoconazole as a restriction for just RECORD 4.

So our program -- the numbers there for the percentages for CYP inhibitors I do believe reflect what would be used in clinical practice.

For the severe renal impairment, it is an underestimate, because we did exclude those people, but I don't believe there would be a lot of people with severe renal impairment that would be going for the elective surgical procedure.

DR. LINCOFF: Dr. Venitz I think was next.

DR. VENITZ: Two issues. One, I would reaffirm what Dr. Tornoe already talked about, and that is, in your simulations, you are having point estimates; you are predicting means. So you have to account for the fact that you might have somebody who is showing more exposure changes than you predict.

The second comment. I did notice in your ongoing studies, the ROCKET study, for example, you actually reduced the dose for patients that have moderate renal impairment. So you already, in ongoing studies, do what I think you ought to discuss in more detail with the FDA because it reads here that you're giving 20 milligrams and 15 milligrams to patients that are moderately impaired. What's the rationale?

DR. PETERS: It's actually to deal a little bit with the average versus the range of distributions. If we could see the simulation for the

mild renal impairment with CYP inhibition -- I think it would be a good example.

So this brings up a good point. This indication, just to set the context, is short-term use, 14 days or 35 days. It is a prophylactic dose. So in this indication -- and there is precedent with enoxaparin at least for -- until you get to severe renal impairment has one dose, either the 40 milligrams or the 30 twice daily, no dose adjustment. Fondaparinux has one dose, 2-1/2 milligrams a day until it's contraindicated in severe renal impairment.

So in that setting, we're not very different than those.

In the chronic indications, atrial fibrillation for example, we're doing double the dose, 20 milligrams, and it's life-long therapy. So there we have taken the approach that it's probably prudent, in those longer-term dosing settings, to have two doses available, and perhaps to adjust the dose for people with more renal impairment.

So -- slide on.

What this shows, to get a little bit of the range, it shows -- on the left-hand panel is -- actually, if we could have the one for the mild renal impairment is better. Mild renal impairment with CYP inhibition. So this is moderate renal impairment, so -- this is good. Okay. You're right. So -- slide on. So I'm -- it's getting to be late.

So creatinine clearance 50 to 79, which is the mild renal impairment

group, in the blue -- okay. If we could have the one without the dose adjustment. I'd like to show the 10-milligram dose. We'll get this right. Because I think this will be helpful for the concern. Right. Okay. So -- slide on.

So what this is is simulation data based on our understanding of the pharmacokinetics in people with the mild renal impairment, creatinine clearance 50 to 79. And so on the left panel you see the blue is the normal renal function, and so the blue -- the solid line in the middle of that, the black line, is the average, and the blue covers the 90 percent confidence interval.

You can see, when you go to mild renal impairment -- we know from the phase 1 study that there was about a 40 percent increase in the area under the curve.

So you see when you add mild renal impairment in the people we dosed with 10 milligrams, which were the bulk of the people in the RECORD studies, you see that distribution of range of blood levels.

And then the upper right panel is what happens -- sorry -- if you add in a moderate CYP inhibitor. And the bottom panel on the right is what happens if you add in a strong inhibitor.

So the scales are a little bit different, but there's really not a dramatic shift in those curves.

And if you went to the same slide for the 5-milligram dose

adjustment -- slide on.

Actually, if you adjust the dose for these groups, the red shows the adjusted dose, which actually gives you lower exposures than what we studied in the phase 3 programs with the 10 milligrams in the normal people for both the mild -- for the moderate inhibitors at the top and the strong inhibitors at the bottom.

So I think this is for more discussion. To be honest, FDA has not seen this data. I just saw it a few days before this meeting. So we are, again, very committed to -- happy to share this data and discuss it further with the agency.

And for the groups where we have strong data, like the age subgroups, the moderate renal impairment, I think we're coming to agreement with the agency, based on the efficacy and safety data we can see. For these groups where, admittedly, we don't have a lot of data, we prefer, again, not -- to use the 10-milligram dose in those we think it's appropriate, and then ask for physicians not to use the 10-milligram dose in people we think it's not appropriate.

The agency is proposing a 5-milligram dose for some of those groups of individuals.

And either of those strategies have their advantages and disadvantages.

DR. LINCOFF: Dr. Neaton?

DR. NEATON: I guess I have a little bit of a problem with the way this question was worded, and -- I don't recall -- it's been a long day -- seeing any data that's really very definitive on the efficacy of the 5-milligram dose. And so I would hate to see a dose kind of launched kind of just based on the PK simulations.

I think what we want to see is put it to test -- if you're going to have to study the 5-milligram dose, study it and understand the risk-benefit, like we say the 10-milligram.

DR. LINCOFF: Dr. Gage?

DR. GAGE: Yeah. I want to argue in favor of having a scored 10-milligram tablet. I understand the risks of having a separate tablet of 5 milligrams. You don't want somebody to take that if they're supposed to be taking 10.

On the other hand, we know that participants enrolled in RECORD, on average, are going to be younger and healthier than the typical patients we take care of. And, you know, we have made this mistake with pretty much every antithrombotic therapy. If you look at aspirin, we used to give 1300 milligrams per day. Look at warfarin. We used to use the equivalent of an INR well above 3. Look at heparin. We used to bolus for a PTT, you know, greater than 150.

So I'm just concerned that history might repeat itself, and if we don't have that available as an option in patients who do tend to be older,

sicker or more petite than trial participants, we may regret that later.

DR. LINCOFF: I just want to counter-point that and ask you a question. So you saw data that they showed for age. The bleeding rates went up in both groups, but their efficacy was sustained and, if anything, the efficacy was better preserved. So, I mean, we can see the bleeding, but we can't see the clots we're preventing.

So how do you reconcile the idea that, if you make an empiric decision to change a dose, based upon a perceived fragility of a patient, you may be losing efficacy?

DR. GAGE: Right. So there's clearly a trade-off. But what was clear from the four RECORD studies is that the risk of hemorrhage is already about 60 percent increase as compared to the average dose of enoxaparin given. So we're already pushing the limit on the hemorrhage side. And that tends to be the rate-limiting step from the perspective of the physicians caring for the patient.

Knowing that, I would like to have available, as a clinician who takes care of these patients, the ability to break a 10-milligram tablet in half, if I'm taking care of a patient that is, you know, very elderly or end-stage renal disease or very petite so that I don't cause harm.

DR. LINCOFF: Dr. Paganini is next.

DR. PAGANINI: Well, back to my concern. The stage 4/stage 5 were excluded from the studies here, so that was -- and then some of them, quote,

squeaked through, unquote, so that's why you have some people up there. But the low GFR population with a drug-drug interaction -- specifically drugs that are on with liver dysfunction or liver -- especially the antihypertensives, the antiarrythmics that many, many of these people are on because there's an increase in cardio-renal issues worry me a bit.

So the question -- as the question says, should a lower dose be available to treat this population -- I think the availability of a lower dose --

DR. LINCOFF: Don't give us your vote --

DR. PAGANINI: I'm sorry?

DR. LINCOFF: Don't give us your vote yet.

DR. PAGANINI: I'm not. I'm just saying that I think -- I'm paraphrasing what I may want to vote later on.

(Laughter.)

DR. PAGANINI: Unless you want to convince me otherwise, but the -- should -- a lower dose availability would seem to be a nice thing to have in those patients.

DR. LINCOFF: Next we have Dr. Tornoe.

DR. TORNOE: So just to comment to Dr. McGuire and Dr. Neaton about giving a 5-milligram dose to these patients, a 5-milligram dose in these patients will not be a 5-milligram dose as you saw in the dose ranging studies. The exposure will be that of a 10-milligram and, therefore, you

would expect to have similar efficacy and safety.

If it is slightly lower, we also showed there's a shallow dose response. You're not likely to lose much efficacy by going by a lower dose.

To the point of the exclusion of the strong ketoconazole or ritonavir P-gp inhibitors is that adding the components of different degrees of renal impairment together with not as strong CYP3A4 P-gp inhibitors, such as verapamil, amiodarones, which many patients will be on -- those are unknown increase in exposure, but are likely to be greater than the two-fold increases on the mean. And then with variability on top of that.

DR. LINCOFF: Dr. McGuire?

DR. McGUIRE: Just a quick response to that. I agree completely with Dr. Neaton. If we want to consider 5 milligrams, let's study it. And I would like to also counter the scored tablet. I think a scored tablet would actually be worse than a 5-milligram tablet availability. This is going to be a fairly expensive medication, predictably, and giving the physicians an opportunity to cut the tablet in half and save the patient half the money -- that's commonly done in clinical practice.

The other concern I would have is that may take a blister pack of 35 tablets and allow people to use it for 70 days, and also may encourage a lower dose, may encourage -- getting back to Henry's comment earlier, is that we're a little bit scared of causing bleeds, so I think most of us aren't going to race to use this drug long-term, but if giving me half a dose -- and I'm led

to believe that that's going to reduce the bleeding to a reasonable level, I might be more tempted to use it off-label.

DR. LINCOFF: Dr. Black?

DR. BLACK: Yeah. I also wanted to second -- or third -- what's been said about -- what Dr. Neaton said. I mean, it's very wise advice. If we think we should use this, it's really got to be studied. We've been very careful to demand data, and I think we should demand it on that dose as well.

DR. LINCOFF: Dr. Neaton?

DR. NEATON: Back to the question. Can we just change this question, I mean, basically to say -- instead of indicate, we hypothesized based on the data and we should study the 5-milligram dose? Because I think that's where we are.

DR. LINCOFF: We can certainly ask the FDA, but I'd suspect that they may want this question answered. I mean, just as a matter of general principle, we don't always test every dose -- in fact, I think we've discussed this at other meetings -- in the same large-scale format once we establish efficacy. We try to draw from exposure data and pharmacodynamics data and et cetera that -- you know, a reasonable strategy in some vulnerable patients.

That having been said, I think there's a fair amount of disagreement -- my personal look on this is that there's -- it's unclear what proportion of patients and exactly who would have this greater exposure with existing dose, given the potential to undertreat in a range we don't know. I think that a

strategy of just not treatment those with this drug whom you are concerned about, rather than trying to alter the dose, and the risk of dose alteration being extended where it shouldn't is a more important issue. That's my personal opinion on that.

Does the FDA want to comment on whether the question should be used as is or --

DR. PAZDUR: Used as is.

DR. TORNOE: We have several examples -- as you stated, we don't go and test in every population. We have several examples where doses are adjusted based on exposure to prevent certain safety events. So it's not uncommon.

DR. LINCOFF: Yes, Dr. Fogel.

DR. FOGEL: Just -- actually, a comment and then a question. The comment is this is a new category of drug, and I think we have to recognize that there are a lot of things we don't know about this new category of drug. And there are risks associated with extrapolating from what we do know to things that we think we know.

But the question is, can you give me a description of the population that you think would benefit from a 5-milligram dose? Who are we talking about?

DR. TORNOE: So I think considering that about 15 percent of these patients who are greater than 75 years of age, you would expect patients with

different degrees of renal impairment -- a lot of these patients will be afib or CHF patients, so you will be -- there will be concomitant use of some of these drugs, such as verapamil, amiodarone, which, taken together, will have substantial increases in exposure. But the number -- I don't know, but I think these drugs are commonly used in this patient population.

DR. LINCOFF: I think that's actually been a great discussion. So I think we'll move on to the vote on.

We'll begin the voting process. Again, I'm going to read the question, and then we'll vote on our pads.

Rivaroxaben clinical pharmacology data indicate that, based on systemic exposure, a lower dose would optimize the benefit-risk in patients with renal and/or hepatic dysfunction and/or on CYP3A4 or P-gp inhibitors. In addition to the proposed 10-milligram dose of rivaroxaben, should a lower dose be available to treat this population?

Please vote.

Okay. Everyone has voted. The vote is now complete and locked in. And the result to be read into the record is, yes, 5 votes; no, 9 votes; abstain, 3 votes.

Now that the vote is complete, we will go around the table and have everyone who voted state their name, vote, and reason they voted as they did into the record. I think we can start on this side, just to be symmetric. Mr. Dubbs.

MR. DUBBS: I voted no, and the reason I did was although it may be a good thing, I don't think we have enough data at the present time to say it should be approved.

DR. KAUL: Sanjay Kaul. I abstained because I didn't know how to answer this question. If, in my judgment, the risk-benefit is not optimal -- so what do we do with that next? So, technically, I was forced to abstain.

DR. McCORMICK: Paul McCormick. I voted no. I think the disadvantages of having the separate 5-milligram tablet, or the scored tablet, on a broad level outweigh the benefits of being able to titrate down. I think if the patient is perceived as having increased risk of hemorrhage, then the drug probably just shouldn't be used.

DR. KRANTZ: Mori Krantz. I voted no. I think, at the end of the day, the efficacy and the cardiovascular outcomes really is the most important driver, and I think certainly we were presented data that there really wasn't a huge loss of efficacy or worsening of safety in the subpopulations.

DR. SKINNER: Harry Skinner. I voted yes, and I voted yes on practical reasons. I think that the way Lovenox or Arixtra are used now is that the patient gets a dose the next morning, and I think that this is going to be dosed the next morning, unlike what the recommendation are, I think four to six hours after surgery. So I think there's a chance that it might be dosed four to six hours after surgery, which is a 5-milligram tablet.

I don't think any orthopedic surgeon is going to give a full dose

six hours after surgery.

DR. GAGE: Brian Gage. I abstained because I felt that a scored tablet would allow the option of the 5-milligram dose in patients who are at elevated risk for hemorrhage.

DR. LINCOFF: Michael Lincoff. I voted no for the reasons that have been summarized by Drs. Krantz and McCormick.

DR. WOLFE: Sid Wolfe. I toyed with voting abstain, as Sanjay did, but I voted yes, even though I don't think this drug should be approved, because I think this is a pharmacologically sensible risk mitigation strategy for these people who in some cases may have -- if they have kind of combination of factors two or three times higher blood levels, and so that's the basis of my voting yes.

DR. MAYOR: I voted yes because of my perception that adult patients and practitioners are being judged guilty until proven innocent. If 5-milligram doses are appropriate for some patients, I believe a 10-milligram tablet could be produced that can be accurately divided in half, and that that would seem to be a practical arrangement to make a 5-milligram dose available.

DR. NEATON: Jim Neaton. I voted no for actually the same reasons Mr. Dobbs stated, and I guess I'm not persuaded by a precedent being made for other drugs. That weighed into it.

DR. KRENZELOK: Ed Krenzelok. I voted no. I don't think the first issue has been vetted properly or adequately at all, and, number two, the

second part, with regard to the 10-milligram dose, I don't think the agency presented us with any evidence at all to support that position.

DR. FOGEL: Ron Fogel. I abstained. I'm not sure that we saw -- I don't think that we saw enough evidence to say that a lower dose would optimize benefit-risk. I just think we did not see the data. I think that if we had data, we could then make a more intelligent response to the question.

DR. McGUIRE: Darren McGuire. I voted no. While I acknowledge we may reduce bleeding risk, I think we would also jeopardize efficacy and, in the context of the available data where -- in the high risk populations, we don't see a interaction signal.

DR. SWENSON: Erik Swenson. I voted no for most of the reasons that have been stated, and I think that for those with the increased risk of bleeding, there are alternatives available.

DR. VENITZ: I voted yes, and I reiterate there is evidence to suggest that the increase -- that there is an increased incidence of bleeding in the presence of metabolic inhibitors, so there are drug-drug interactions that could be managed by having a smaller dosage form available.

DR. BLACK: Henry Black. I voted no. I'm a little concerned that we may lose some of the efficacy, and I'm not persuaded that we get that much more risk. I would like more data, and I would like this specifically studied, but we've said that already.

DR. PAGANINI: And for those of you that were wondering what I'm

going to vote -- this is Paganini -- I voted yes, and I voted because there seems to be an increase in efficacy in this subpopulation, which was surprising, probably due to increased exposure, and therefore the population that we're looking at is probably underrepresented in these studies. Therefore, the safety signal may not be there, and so, therefore, I think safety is more important than efficacy and 5 is probably better in this population for a safer drug rather than a more efficacious drug with potential safety problems.

DR. LINCOFF: Okay. Well, with that, we're complete. Are there any final comments from the FDA?

I want to thank everybody on the panel, thank the sponsors for a very complete presentation.

(Whereupon, the proceedings at 4:29 p.m. were concluded.)