AT DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE

DAY ONE - AFTERNOON SESSION

Wednesday, September 6, 2006

1:00 p.m.

Hilton Silver Spring
Silver Spring, Maryland

PARTICIPANTS

Maha H.A. Hussain, M.D., FACP, Acting Chair
Johanna M. Clifford, M.Sc., RN Executive Secretary

MEMBERS:

Ronald M. Bukowski, M.D.
James H. Doroshow, M.D.
S. Gail Eckhardt, M.D.
Michael C. Perry, M.D.
Maria Rodriguez, M.D.
David Harrington, Ph.D.

CONSUMER REPRESENTATIVE:

Pamela J. Haylock, RN

NON-VOTING INDUSTRY REPRESENTATIVE

Antonio J. Grillo-Lopez, M.D.

CONSULTANTS (VOTING) FOR FRAGMIN:

William Hiatt, M.D.
Stephen George, Ph.D.

PATIENT REPRESENTATIVE (VOTING):

Karl Schwartz

FDA STAFF:

Richard Pazdur, M.D.
Rafel Rieves, M.D.
Andrew Dmytrijuk, M.D.
Jyoti Zalkikar, Ph.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order and Introduction of Committee

DR. HUSSAIN: My name is Maha Hussain, from the University of Michigan. I want to welcome you to this afternoon's session. WI am going e have a presentation by Pfizer.

Before we proceed to the different presentations, I am going to begin on my left with Dr. Pazdur for introducing the members of the committee who are attending.

DR. PAZDUR: Richard Pazdur, Office Director, FDA.

DR. RIEVES: Hi, Dwayne Rieves, from the Division of Medical Imaging and Hematology.

DR. DMYFRIJUK: Andy Dmyfrijuk, hematology medical officer.

DR. ZALKIKAR: Jyoti Zalkikar, statistics team leader, Hematology Imaging.

MR. SCHWARTZ: Karl Schwartz, patient representative.

DR. HUSSAIN: We have Dr. Hiatt on the phone.

DR. HIATT: Yes, I am Dr. William Hiatt, and I apologize for not being there. I got ill the last couple of days and couldn't travel. But my participation is based more on a cardiovascular background. I am the current chair of the Cardiorenal Division for the FDA. But I will participate by phone. So, thank you for your consideration.

DR. HUSSAIN: Thank you.

DR. GEORGE: Stephen George, Duke University.

MS. HAYLOCK: Pamela Haylock, oncology nurse, University of Texas Medical Branch in Galveston, and I am the consumer representative.

DR. LYMAN: Gary Lyman, consultant and medical oncologist from the University of Rochester.

DR. HUSSAIN: Maha Hussain, University of Michigan, medical oncology.

MS. CLIFFORD: Johanna Clifford, designated federal official to the ODAC, FDA.

DR. HARRINGTON: David Harrington,

statistician, Dana-Farber Cancer Institute.

DR. LEVINE: Alexandra Levine, hematologic oncology, University of Southern California, Norris Cancer Center.

DR. LINK: Michael Link, pediatric hematology/oncology, from Stanford.

DR. BUKOWSKI: Ron Bukowski, medical oncologist, Cleveland Clinic.

DR. PERRY: Michael Perry, medical oncology/hematology, University of Missouri, Ellis Fischel Cancer Center.

DR. GRILLO-LOPEZ: Antonio Grillo-Lopez, hematologist/oncologist and the industry representative on this panel. I do not receive any compensation whatsoever from industry for my participation in these meetings.

DR. HUSSAIN: Thank you. The statement of conflict of interest will be read by Johanna Clifford.

Statement of Interest Statement

MS. CLIFFORD: The following announcement addresses the issue of conflict of interest and is

made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest, with the following exceptions:

In accordance with 18 USC 208(b)3, full waivers have been granted to the following participants: Dr. Ronald Bukowski, for unrelated consulting for a sponsor and two competitors for which he receives less than $5,001 per year per firm; Dr. Stephen George, for unrelated consulting for two competitors for which he receives less than $10,001 per year per firm; Dr. William Harrington, for his employer's research contract with a competitor. His employer receives less than $100,000 per year. Dr. William Hiatt, for his unrelated speaker's bureau activities for two competitors for which he receives between $10,001

t0 $50,001 per year per total.

Dr. Maha Hussain has been granted waivers in accordance with 18 USC 208(b)3 and 21 USC 355(n)4 for her spouse's ownership of stock with the sponsor and two competitors. Two are worth between $5,001 to $25,000 per firm. The other is worth between $50,001 to $100,000.

In addition, in accordance with 21 USC 355(n)4, waivers have been grated to the following participants: Pamela Haylock, for her ownership of stock with the sponsor worth less than $5,001. Because this stock interest falls below the de minimis exception allowed under 5CFR 2640.202(a)2, a waiver under 18 USC 208 is not required.

Dr. Michael Perry, for his ownership of stock with the sponsor worth less than $5,001. Because this stock interest falls below the de minimis exception allowed under 5CFR 2610.202(a)2, a waiver under 18 USC 208 is not required.

Mr. Karl Schwartz, for his and his spouse's ownership of stock in two mutual funds. One is worth less than $5,001, the other is worth

between $5,001 and $25,000. Because these stock interests fall below the de minimis exception allowed under 5CFR 2640.201(b)2, a waiver under 18 USC 208 is not required.

Waiver documents are available at the FDA's dockets web page. Specific instructions as to how to access the web page are available outside today's meeting room at the FDA information table. In addition, copies of all waivers can be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

We would also like to note that Dr. Antonio Grillo-Lopez has been invited to participate in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Grillo-Lopez' role is to represent industry interests in general and not any one particular company. Dr. Grillo-Lopez is a retired employee of the Neoplastic Autoimmune Disease Research Institute.

In the event that the discussions involve

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

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

DR. HUSSAIN: On the agenda, it appears that Dr. Pazdur was supposed to have comments. But you have no comments? Thank you. So, we will proceed with the sponsor's presentation. I want to invite Dr. Connie Newman to start.

Sponsor Presentation

Introduction

DR. NEWMAN: Good afternoon.

[Slide]

I am Dr. Connie Newman and I work at Pfizer, in the Department of Worldwide Regulatory Affairs.

[Slide]

I would like to remind the committee that Pfizer has a number of oncology products but today we are here to discuss a supportive care product for patients with cancer, dalteparin, or Fragmin.

[Slide]

The risk of venous thromboembolism is higher in patients with cancer than the general population, and current medical therapies are not adequate to treat this condition. We are, therefore, pleased to present to you today clinical trial data which support the use of dalteparin for the extended treatment of symptomatic venous thromboembolism to reduce the recurrence of venous thromboembolism in patients with cancer.

This proposed indication is based upon a randomized trial known as the CLOT study.

[Slide]

Our presentation today is outlined here. I will briefly summarize the regulatory history for dalteparin and the supplemental application. Dr. Craig Eagle, of Pfizer, will then provide

background on venous thromboembolism in patients with cancer, highlighting the medical need for safe, effective and clinically manageable therapies. Dr. Agnes Lee, a principal investigator of the CLOT trial, will then present the CLOT trial design and results. Dr. Eagle will then follow with a discussion of the CLOT trial data and our conclusions regarding the study and the use of dalteparin in patients with cancer.

[Slide]

We are pleased to have available to the committee a number of consultants in hematology, oncology and biostatistics: Dr. Agnes Lee, associate professor of medicine, McMaster University, Hamilton, Ontario; Dr. Mark Levine, professor in the Departments of Clinical Epidemiology and Biostatistics and Medicine, from McMaster University in Hamilton, Ontario; Dr. Steven Piantadosi professor of oncology and director of biostatistics, from the Johns Hopkins Oncology Center, in Baltimore, Maryland; and Dr. Frederick Rickles, professor of medicine,

pediatrics and pharmacology and physiology, from the George Washington University.

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Dalteparin is a low molecular weight heparin that was first approved more than 20 years ago, in 1985, in Germany for anticoagulation during hemodialysis and hemofiltration. To date, dalteparin is approved in more than 80 countries, including 19 countries with an indication for the extended treatment of symptomatic venous thromboembolism to reduce the recurrence of venous thromboembolism in cancer patients. Dalteparin was first approved in the United States in December, 1994 for prophylaxis of deep vein thrombosis in patients undergoing abdominal surgery.

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Since 1994 a number of additional indications have been approved for dalteparin in the United States, including indications for prophylaxis of deep vein thrombosis in patients undergoing hip replacement surgery, and for patients with severely restricted mobility because

of medical illness. In addition, dalteparin is indicated to reduce ischemic complications in patients with unstable angina and non-Q-wave acute myocardial infarction when given with aspirin.

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The supplemental application under discussion today was submitted to the FDA in March, 2004. In January, 2005 the FDA advised Pfizer of the approvable status of the sNDA. Pfizer then amended the application and was informed last March that the application was not approvable for a number of reasons that will be addressed here today.

In the past few months we have had several discussions with the FDA and, in June we were informed that the CLOT trial would be the topic of today's Oncologic Drugs Advisory Committee meeting.

[Slide]

Now I would like to turn the presentation over to Dr. Craig Eagle, from Pfizer, who will provide an overview of venous thromboembolic disease in patients with cancer.

Background on VTE and Cancer

DR. EAGLE: Thank you, Connie.

[Slide]

My name is Craig Eagle, and I am head of the Worldwide Medical Oncology Group at Pfizer and what I would like to do now is just briefly share with the committee some of the background behind VTE in cancer.

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The association between VTE and cancer was first noted approximately 150 years ago. Subsequent to that, it has been noted in data that there is a 4our- to seven-fold increase in the risk of venous thromboembolism in cancer patients compared to non-cancer patients, with the estimated annual incidence of one in 200 cancer patients having VTE. VTE causes symptoms through venous obstruction, inflammation around the thrombosis and also embolization of the pulmonary vasculature.

[Slide]

Here as some of the examples of the sorts of things patients with VTE develop. This is a

patient with a swollen left leg that is edematous, often painful and limiting mobility. As has been said before, this can move to the vasculature.

[Slide]

On the left is ventilation perfusion scan, showing full ventilation of lungs but blood flow on the perfusion side, where the arrows are, is missing. On the right is a pulmonary angiogram showing absence of blood vessels in the upper half of the chest. These sort of patients can present with chest pain, shortness of breath, and limitation in mobility as well.

[Slide]

As most people are aware, ultimately this type of embolism can be fatal. This is an example of a patient on a CT scan with an embolus across pulmonary vasculature, and the autopsy sample with the arrows pointing to thrombus in the vasculature.

[Slide]

What is the treatment for venous thromboembolism? This is the current treatment for patients with VTE, particularly without cancer but

also in the past with cancer. There is initial treatment with diagnosis with a low molecular weight heparin or unfractionated heparin. This is continued for approximately five to seven days. Concurrently, a vitamin K antagonist or oral anticoagulant, commonly Warfarin, is commenced at the same time. This is only for a target INR between 2 and 3. This treatment is often continued for 3 months or out beyond that up to 6 months. Particularly for cancer patients prolonged treatment is often indicated.

[Slide]

However, when we look at the data we can see here that in patients treated with this type of therapy there is a difference between the response or occurrence of VTE in patients with cancer versus patients without cancer. As you can see, after a 12-month period the occurrence rate is approximately 20 percent.

Importantly, I would like to draw the committee's attention that most of the rate of occurrence occurs within the first 3 months of ths

study. So, the relative risk is 3.2.

[Slide]

So, if we recognize that Warfarin is pretty much the standard of therapy for long-term management, there are various problems that people are familiar with. Low molecular weight heparin can provide certain advantages in this situation, particularly relevant in patients with cancer who are often sick, have complicated therapies and often undergo procedures.

We know that Warfarin works through reducing the function of coagulation factors including prothrombin which is central to the coagulation cascade. Compare that to low molecular weight heparin which inhibits the activated clotting cascade. We also know that with Warfarin it is difficult to maintain therapeutic control. Patients with cancer particularly have nausea, vomiting, dietary changes and difficulty swallowing. Low molecular weight heparins are more predictable in the dosing and, because they are given parenterally or subcutaneously, they avoid

some of the GI problems.

We also know that these patients undergo procedures and reversal of Warfarin or oral anticoagulant therapy can be challenging. It can takes days to wean off the dose of Warfarin, days to restart it and so it can be a very difficult and tricky period. If the patient is thrombocytopenic, it is the same problem. With low molecular weight heparin, you can interrupt that morning, have the procedure and restart that evening or the next day and the patient has minimal interruptions of the anticoagulation therapy.

INRs are needed for Warfarin therapy, resulting in venous access, the blood testing. Low molecular weight heparin don't require the monitoring in most cases. And, there are multiple drug interactions and also dietary interactions with Warfarin and there are very few, if any, with low molecular weight heparin, suggesting that low molecular weight heparin can provide an advantage in patients who have cancer and are very complicated medically.

[Slide]

Here I just want to summarize for the committee the evidence of treatment of VTE. I would like to draw to the committee's attention that the duration of these studies is very short, 5-10 days. Several studies are aggregated into groups. Here I have highlighted that when dalteparin is compared to heparin OAC, at a dose in the yellow, of 200 IU/kg/day it provided equivalence to heparin unfractionated and oral anticoagulant therapy.

Importantly, this is the largest group of patients that was studied at this dose, therefore, this was the dose that was focused on in the CLOT study.

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So, what I would like to say in conclusion is that cancer patients with VTE are at increased risk of recurrent VTE compared to non-cancer patients. We also know that there is no currently FDA approved medication for prevention of recurrence of VTE in cancer patients.

Low molecular weight heparin has the potential to confer clinical benefit in management of these difficult patients with cancer. Dalteparin also has been shown to be effective for the initial treatment of VTE and this led to the design of the CLOT study.

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On that note, I would like to introduce Associate Professor Agnes Lee, who is the principal investigator of the CLOT study, and she can walk the committee through the results of the CLOT trial.

CLOT Study Design and ITT Results

DR. LEE: Thank you, Dr. Eagle.

[Slide]

Good afternoon, ladies and gentlemen. I am going to change accents on you and, for the next 20 minutes or so, I am going to present the study design and results of the CLOT study.

[Slide]

As you have heard from Dr. Eagle already, the CLOT study was designed to address a very

important clinical problem, and that is how to reduce recurrent venous thrombosis in patients with cancer. Specifically, the study question was is long-term therapy with low molecular weight heparin, dalteparin, more effective than oral anticoagulant therapy in preventing recurrent VTE in patients with cancer?

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The CLOT study was a multi-national, multicenter, randomized, open-label study in which cancer patients with proximal DVT and/or PE were randomized to one of two anticoagulant regimens. The control group received standard therapy, starting with dalteparin followed by oral anticoagulant therapy, and the experimental group received dalteparin only. The treatment period was 6 months, and during this time the patients were contacted by telephone every 2 weeks. They were also seen in clinic at the end of 1 week, 1 month, 3 months and 6 months. In addition, the patients were followed for up to 12 months after randomization for survival.

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This slide shows you the study treatments in more detail. As you can see, the patients in the control group received therapeutic doses of dalteparin at 200 IU/kg subcutaneously once daily. They also received an oral anticoagulant, and the dose was adjusted to achieve the therapeutic INR between 203. Dalteparin was stopped after minimum 5 days and when the INR is therapeutic, after that, the oral anticoagulant is continued alone and, again, the INR was monitored and was checked at least every 2 weeks to ensure that it remained in a therapeutic range.

The patients in the experimental group received dalteparin only. They also received the full therapeutic dose for the first week, just like the control patients, but this group continued with this full therapeutic dose for the first month. After that the dose was reduced by approximately 75 percent of the full dose to continue from month 2 to month 6.

As you can see, this regimen is certainly

simpler than the standard therapy and it does not require laboratory monitoring. But, more importantly, this regimen addresses the clinical need of the patient in that it suppresses the high risk of recurrent thrombosis during the first month and tries to reduce the risk of major bleeding over extended therapy with anticoagulants.

[Slide]

The primary endpoint of the study was objectively documented, symptomatic recurrence of DVT, PE or both. When the original protocol was written we had a co-primary endpoint of recurrent VTE and major bleeding. But this was refined and redefined in March, 1999, prior to the enrollment of the first patient.

There were three secondary endpoints. There was a composite endpoint of symptomatic recurrent thrombosis, including central venous thrombosis of the upper limbs, neck or chest. Bleeding and death were the other secondary sf endpoints.

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To accurately follow these patients for recurrent thrombosis, the patients were contacted every two weeks to ascertain symptoms of recurrent thrombosis. But, because recurrent thrombosis is a medical emergency, patients were also instructed to report urgently any symptoms of recurrent thrombosis to the investigators. When such symptoms were reported the patients were brought in for objective diagnostic testing following pre-specified diagnostic algorithms, using standard tests such as ultrasound and spiral CT scans. The patients were diagnosed and managed locally by the investigators, but all the details of these events were sent to a blinded central adjudication committee for confirmation of the event.

[Slide]

The patients were also followed very closely for bleeding and death. Bleeding events had to be clinically overt in order to meet that secondary endpoint. These events were also reviewed by a blinded central adjudication committee and they were categorized as being major

or minor according to standard definitions using thrombosis trials for evaluating anticoagulant.

We also followed these patients for death up to 6 months and 12 months. The cause of death was determined by the central adjudication committee in a blinded fashion during the first months, and after that the cause of death was determine by the local investigators.

[Slide]

This slide shows you the main statistical analyses that were done, and these are standard for clinical trials looking at efficacy and safety, particularly looking at thrombotic agents and other therapies. This is very important for randomized, controlled studies that have an open-label design in order to reduce bias.

[Slide]

The efficacy data was based on looking at recurrent thrombosis. It was done based on intention-to-treat principle including all patients that were randomized. We included all events that were adjudicated centrally and these were events

that occurred up to six months after randomization that were included. The analysis was based on a time to first recurrent thrombosis, and compared using the two-sided log-rank test.

Safety analysis looked at bleeding and overall survival. For bleeding we looked at the as treated population and this included only patients who received at least one dose of the study drug. We included bleeding events that occurred up to 40 hours after the permanent discontinuation of study drug. We also analyzed the data in terms of time to the first bleeding event and compared it with the two-sided log-rank test.

Finally, for overall survival we looked at the intention-to-treat population. We included all deaths over the 6- and 12-month period and again compared it with the two-sided log-rank test.

[Slide]

Here now are the study results for the CLOT study.

[Slide]

The first patient was enrolled in May,

1999 and the last patient was enrolled in October, 2001. The last follow-up was completed in April, 2002 and the results were first presented at the American Society of Hematology meeting in December, 2002. The results were published in The New England Journal of Medicine in July, 2003.

[Slide]

A total of 677 patients were randomized. This was based on an a priori sample size calculation that required 70 events for us to achieve a statistical power of 85 percent. One of the patients who was randomized did not provide written informed consent and, therefore, was excluded from the analyses.

As you can see, 338 patients were randomized to each of the arms and they formed the efficacy or intention-to-treat population. However three subjects did not receive oral anticoagulant therapy and, therefore, there were only 335 patients in this group who were included in the safety analysis. Finally, there were 180 patients who completed the dalteparin regimen out to six

months, and there were 163 patients who completed the oral anticoagulant regimen out to six months.

[Slide]

This slide shows you some of the baseline characteristics of the treatment groups. As you can see, the two groups are very comparable in terms of their gender, median age, smoking history, previous history of thrombosis, as well as their qualifying episode of thrombosis.

[Slide]

They were also quite balanced in terms of the ECG performance status and their solid tumor extent as well. You can see that the majority of the patients had solid tumors and, in fact, the vast majority of these patients had metastatic disease at the time of randomization. There was a small number of patients with hematological malignancies included in this study.

[Slide]

This slide shows you the frequency of follow-up in the two groups. As you can see, the frequency of follow-ups were entirely comparable in

terms of scheduled visits, telephone contacts and unplanned visits. So, there was no differential of management of follow-up with these patients at all.

[Slide]

Now let's look at the efficacy endpoints for the primary outcome of symptomatic recurrent thrombosis and the secondary outcome of symptomatic recurrent thrombosis, including central venous thrombosis of the upper limb, neck and chest.

[Slide]

This Kaplan-Meier curve shows you the efficacy outcome. As you can see, over the six-month treatment period dalteparin was able to reduce the risk of symptomatic recurrent thrombosis by 52 percent, and this is highly statistically significant with a p value of 0.0017.

You can also see on this slide that the regimen given to the dalteparin patients was able to suppress that high risk of recurrent thrombosis during the early part of treatment and this effect was maintained throughout the six-month period.

[Slide]

To look at the robustness of the results we also performed a Cox model analysis to adjust for the influence of potential prognostic factors on treatment efficacy. As you can see, this also favored dalteparin and the risk reduction was 0.51.

We also looked at the various tumor groups, and you can see here that for patients with solid tumors the effect or benefit with dalteparin was consistent for various tumor types. The potential exception is a group with hematological malignancy but, again, you can see that with the very wide confidence interval this really reflects a small number of events and the small number of patients that were enrolled in this study.

The results were also consistent for patients with metastatic disease, as well as patients who did not have metastatic disease at the time of randomization.

[Slide]

This slide shows you the Kaplan-Meier curve for the composite or the secondary efficacy outcome, including central venous thrombosis. As

you can see, these curves are virtually identical to the primary efficacy outcome, favoring low molecular weight heparin, dalteparin, in reducing recurrent venous thrombosis.

[Slide]

Now for the safety endpoints of bleeding, death and adverse events.

[Slide]

As you can see here, there were 31 patients who experienced a major bleeding event during the study period, 19 in the dalteparin arm and 12 in the oral anticoagulant arm. This difference was not statistically significant.

When we break this down into the various categories that satisfy the definition of major bleeding, you can see that the major difference lies in the category where patients received transfusions of 2 or more units of packed cells or simply had dropped their hemoglobin of at least 2 g/dL.

When you look at the overall bleeding or any bleeding, there were, in fact, more patients

who experienced bleeding while they were receiving oral anticoagulants, and this achieved borderline significance with a p value of 0.05.

[Slide]

This Kaplan-Meier curve shows you the time to event for first major bleeding event, and you can say that the difference was not statistically significant.

[Slide]

This curve shows you the Kaplan-Meier estimates for any bleeding over the six months treatment period. As you can see, the curves diverge after about three months and this achieved borderline significance with a p value of 0.05.

[Slide]

This was actually very well reflected if we look at the reasons for discontinuation of study medication. So, on this table you can see that I have highlighted that, in fact, there were almost twice as many patients who stopped oral anticoagulant therapy because of bleeding in the oral anticoagulant arm compared to patients

receiving dalteparin. On this slide you can also see other differences for reasons why patients stopped study drug.

Another obvious difference, of course, is in recurrent thrombosis. Clearly, more patients stopped because they were on oral anticoagulant therapy because there were more recurrences.

But the other difference that piqued a lot of interest and initially raised some concern was the difference in the deaths. As you can see here, there were 56 patients who died while taking dalteparin compared to 24 patients while receiving oral anticoagulant therapy. As I said, this initially raised some concern but when you really think about the study population of cancer patients who have advanced disease, it became very clear to us that the reason for this is because patients are unable to continue oral anticoagulants when they are dying. They are simply unable to swallow. They might be comatose. Moreover, they cannot undergo laboratory monitoring which is necessary for the safe administration of oral anticoagulants.

In contrast, you can give dalteparin until virtually the day the patient dies because it does not require laboratory monitoring and it is a simple subcutaneous injection once a day.

Dr. Eagle will explain this in greater detail later in the presentation so I won't belabor this more, but what I want to do is bring you back to death again and really what is the true risk of death in these patients in the study.

[Slide]

On this Kaplan-Meier curve you will see the true risk of death over the study treatment periods. As you can see, 40 percent of the patients were dead by six months and about 60 percent of the patients were dead by 12 months. Over this entire one-year period there was absolutely no difference in the risk of dying in these two patient groups.

[Slide]

Not surprisingly because many of these patients had events, the major cause of death or the most frequent cause of death was progressive

cancer. There were a few patients who also died of fatal PE and fatal bleeding as well.

[Slide]

When we looked at adverse events, on this slide are summarized the drug-related adverse events that were reported in more than three percent of the study population. As you can see, there are some differences between the two treatment groups. Not surprisingly, there were more patients who complained of an injection site reaction in the dalteparin arm compared to the oral anticoagulant arm because they self-injected for six months compared to the oral anticoagulant arm who just self-injected for a week.

There were some differences in thrombocytopenia as well, and also in elevation of liver enzymes. But all of these frequencies or these percentages are certainly expected and consistent with what is known about both of the drugs.

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So, in conclusion, in cancer patients with

acute VTE long-term dalteparin therapy substantially reduced the risk of symptomatic, recurrent venous thrombosis by 52 percent compared to oral anticoagulant therapy.

The risk of bleeding is similar between the two groups and there was absolutely no difference in overall mortality between dalteparin and oral anticoagulants.

[Side]

Thank you for your attention, and I am going to turn the presentation back to Dr. Eagle now.

DR. HIATT: Is it possible to ask some design questions at this stage?

DR. HUSSAIN: The questions will be done at the end, doctor. Thank you.

CLOT Study Further Analyses

DR. EAGLE: Thank you, Dr. Lee.

[Slide]

What I would like to do now is move the discussion into areas that have been brought up around the CLOT study and these results.

[Slide]

I want to focus the discussion on really four main areas. The first one is about key characteristics of the CLOT trial design. The second one is on-treatment mortality analysis. Then move through robustness of the data and finally finish on the risk/benefit question.

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So, first in terms of the key characteristics of the CLOT trial design, some areas for the committee to consider include the open-label study design; the initial treatment regimen in the control arm; the dalteparin dosing in the experimental arm; and the rationale behind the six-month treatment duration for this study.

[Slide]

Open-label studies in cancer patients are not a new thing. We know that comparing oral therapies to a parenteral therapy has its limitations. But particularly in this study, when you are dealing with Warfarin the question is how safe is it to blindly manage Warfarin therapy, and

particularly in patients who have surgical procedures, invasive procedures and thrombocytopenia. It would not be uncommon for a doctor to easily unblind a patient who is on Warfarin. They could do an INR and know whether a patient is taking Warfarin or not.

But, more importantly, if we were to develop some sort of INR sham process to try and keep it blind we would have to match the clinical situation. If a patient was coming up for a procedure and the doctor actually stopped the Warfarin and the sham INR didn't reflect that and we report it as remaining elevated, it may impact the patients management and decisions by the clinician. Therefore, it is difficult to sham INRs to mimic reality. Of course, ultimately there is always the question about undesirable testing on patients that don't need it, doing sham INR blood work when patients don't need it and also the undesirable and impractical rationale for giving patients placebo subcutaneous injections. So, for these reasons the open-label study design was felt

to be most appropriate and practical.

[Slide]

However, recognizing that this produces biases potentially, I the study there were safeguards to try to minimize that bias. There was an a priori definition of VTE recurrence based on objective investigations. As Dr. Lee mentioned, telephone checks were every two weeks on follow-up in both groups. Diagnostic algorithms were set up for recurrent VTE. Importantly, an independent, blinded central adjudication committee reviewed and adjudicated all primary and secondary outcome measures.

[Slide]

What I would like to do now is focus on the initial treatment in the control arm. The use of dalteparin in both arms for initial treatment was adopted after careful discussion within the steering committee of the CLOT study. At that time no low molecular weight heparin was approved for use in cancer patients. The feeling was to use dalteparin in both arms because this would limit

the number of variables and enable better comparison across the two arms. Also, at that time dalteparin had documented evidence that it could treat VTE in the initial setting.

[Slide]

Now moving to the experimental arm and the dalteparin dosing rationale, as I have shown previously, efficacy of dalteparin in the initial setting at 200 IU/kg once a day has been shown in acute VTE treatment. So, the decision was made in the first month, because of that increased risk of recurrent VTE, to continue the initial treatment dose of 200 IU/kg/day.

However, recognizing that there was reduced risk of recurrence of VTE after the first month in particular, the dose was reduced down to a 75 percent reduction of approximately 150 IU/kg/day, aiming to minimize the risk of bleeding but continuing to maintain the benefit the patients need in the longer-term therapy.

[Slide]

Why six months? The potential advantage

of dalteparin versus OAC in long-term use in cancer patients needed to be explored. We know that the standard of therapy for anticoagulation in VTE is around about six months in cancer patients. The decision was made that six months would be the appropriate cutoff to enable a more accurate comparison across the two arms rather than doing anything shorter or longer, particularly given that these patients have cancer and, therefore, are at high risk of mortality during the study.

It is also recognized that patients without cancer need to also have a minimum of three to six months so, again, this was considered acceptable standard therapy and duration.

[Slide]

Moving on to the second area of discussion, that is, the on-treatment mortality analysis. As we move through this section it is important to remember, as Dr. Lee has shown, that the overall mortality from randomization in this cancer population was not different in the two arms. The question arises is VTE in combination

with mortality an appropriate way to try and manage this? Is it appropriate to analyze this as on-treatment, which was not a priori?

[Slide]

So, as we look at this and we look at this data, we need to consider the definition of on-treatment. The definition that was commonly used in this study was a one-day definition. That is Kaplan-Meier curve shown on the left. This is defining patients as basically having treatment plus one day and then seeing if they lived or died.

However, if you extend this definition to 14 days there is no difference. Of course, there is debate about what is the appropriate time to analyze any safety event, one day, 14 days, 28 days or 30 days.

But in this analysis here you can see that there must be some events that are happening, particularly in the patients with OAC, because the curves rapidly drop down to equal just within a 13-day difference before they die from their cancer. So, when we do the on-treatment analysis

with the one-day definition we are effectively censoring potential events in the 13 days, two weeks before the patient dies from the cancer.

So, what I have displayed here is the sort of scenario that will help explain why some of these differences are here. As Dr. Lee mentioned and many people who treat cancer patients, in that period before somebody dies there are various issues that you medically need to consider. Can a patient swallow? Is the patient at the right institution to monitor therapy, particularly Warfarin which needs monitoring? Is the patient able to take an injection subcutaneously? These are the decisions that investigators make around that 13-day period before a patient with cancer will die.

[Slide]

So, what I have shown on this slide, on this slide is a schematic diagram of patients within the CLOT study. I would draw the committee's attention that what I am using here is the on-treatment one-day definition. These are the

actual numbers of mortality within the CLOT trial based on those events.

You can see here that the top patient continued therapy right up until the time the patient died. Ergo, they would be counted in both on-treatment and intent-to-treat analysis. Of course, patients could continue therapy and stop for VTE. They could continue treatment and stop for other reasons due to clinical management. Or, they could continue and discontinue for other reasons that were felt to be relevant to the patient or management of the patient. If they die within one day of those events, they are also counted in the on-treatment analysis.

It is important to note here that what we can see is that more patients continued treatment after one day compared to OAC, oral anticoagulant therapy. However, when you look at the intent-to-treat analysis it is the same number. If patients had any of these events more than one day before they died, recognizing as Dr. Lee had shown, all patients die at the same time, overall survival

is no different. So, if patients had an event that precluded them from continuing up to the point of dying, they were excluded from the on-treatment analysis, hence all the zeroes.

Not surprising, patients with OAC, the majority, fall in that category compared to the majority that fitted into this top category. As a result, when you do the intent-to-treat analysis you end up with the death rates with no difference. But if I do an on-treatment analysis with the one-day definition I end up showing this number. So, certainly as we look at the on-treatment analysis we need to consider these sort of events and that 13-day difference very carefully.

[Slide]

So, certainly from our point of view the conclusion of the on-treatment mortality analysis is that it is biased due to informative censoring. We certainly support that the appropriate analysis to assess mortality is the intent-to-treat principle, the standard principle for a mortality analysis, which clearly shows no difference in the

entire 12-month study period.

[Slide]

What I would like to do now is to focus on the robustness of the CLOT study, a very large study that has been well conducted, and we can look at the data and careful analysis.

[Slide]

The robustness of the data I want to consider in three groups. One is the magnitude of the benefit; the consistency of the subgroups; and the competing risk of mortality that is also being questioned, about whether this interferes with the true measure of the relative benefit of dalteparin.

[Slide]

As Dr. Lee has shown, the primary endpoint of recurrent VTE was highly statistically significant, 0.0017 with a 52 percent risk reduction over the entire study period.

[Slide]

We also know that if we look at the Cox model, taking into account various prognostic factors, it also remains positive with a relative

risk of 0.51.

If we look at solid tumors as a group, individual solid tumors, albeit smaller groups so the confidence intervals get wider, the point estimate continually favors dalteparin. If we look at the extent of the malignancy, metastatic or non-metastatic, it favors dalteparin.

As Dr. Lee also commented, the hematological malignancies have the widest confidence interval. They are the smallest subgroup. And, the committee needs to remember that these are hematological cancers. It is lumping together lymphomas, myelomas, leukemias within the same group, and this is an appropriate way to analyze such a small group and it is based on four events.

Also as part of the analysis, if we look at some of these subgroups, there have been some analyses that combined hematology and put in the metastatic, and some of the analyses combine it with non-metastatic. Again, I think one of the discussions that needs to be considered is are

non-metastatic malignant tumors, solid tumors as I have shown here, appropriate to combine on a clinical basis with effects in hematological? Is hematological appropriate to combine with solid metastatic tumors in these sort of analyses? Because one could imagine, that by combining different groups and deciding where they fall, I can get these point estimates to be coming across the hematological ones.

[Slide]

Certainly from a single trial, there have been discussions about what is a compelling p value. There have been discussions in other areas that one could define a compelling p value. A two-sided p value of less than 0.0025 provides the strength of evidence of two independent trials with a p value less than 0.05. For the CLOT study the value is 0.0017 so it makes these criteria. I have also shown you that there is consistency across the subgroups. We also know from other evidence that dalteparin has been proven to be effective for the primary prophylaxis of venous thromboembolism in

various clinical settings.

[Slide]

Finally I would like to move now the discussion now to competing risk.

[Slide]

Some of the discussion is focused on mortality in cancer studies as competing risk with VTE. We can clearly combine these endpoints to produce a combined endpoint but this really assumes that every patient that died was going to have a VTE. Is that appropriate, particularly as the mortality in this study was reviewed by a blinded committee and over 90 percent were diagnosed as dying from their cancer? We also need to recall that competing risk is really talking about measuring the relative benefit of dalteparin versus OAC.

So, the question we need to ask ourselves as we consider mortality and recurrence of VTE is could mortality account for the significant dalteparin benefit compared to oral anticoagulant therapy? The only way this could happen is two

possible scenarios that we can see.

The first scenario would be that the mortality rate would have to be different between the two treatment groups so that one group is having a higher mortality rate than the other.

The second scenario would be that if mortality is censoring the chance of a VTE where the VTE would have been different in the two groups but mortality intervenes.

So, what I would like to do is just briefly walk through each of these scenarios to see how they fit in with the CLOT study.

[Slide]

Scenario one, the mortality rates are different between the two treatment groups. As I have demonstrated, the cumulative mortality at all times within the six-month observation period was almost identical in the two treatment groups. Therefore, the degree of mortality censoring is not informative with regard to relative risk between OAC and dalteparin.

[Slide]

Scenario two, the mortality censoring would have to affect the chance of VTE differentially in the two treatment groups so that mortality is covering these up. As I have already mentioned also, the blinded adjudication committee reviewed all deaths and over 90 percent were considered due to underlying cancer. Therefore, it is unlikely that the probability of VTE for the subjects who died relative to the observed probability would have been different.

Another way to look at this if we are still concerned about mortality is to look at the risk of mortality in a time interval on this study. Most of the patients died after the first month. So, if we look at the first month, does dalteparin in that first month, when mortality is low, show benefit over OAC to try to minimize any concern about mortality?

So, when we look at the first 30 months, as displayed here, as expected, the mortality rate in the first 30 days is approximately 7 percent and

no different. Please note that the VTE events are already statistically significant, with a p value of 0.001 and a relative risk of 0.35 in that first month. So, the time in this study when mortality was low the benefit of dalteparin had already been established.

[Slide]

In conclusion, when we think about competing risk and death in this cancer population, we need to recognize that in the CLOT study the benefit of dalteparin relative to Warfarin or oral anticoagulant therapy has been estimated accurately despite the high cancer mortality.

[Slide]

Finally, I would like to share with the committee some of the discussion around risk/benefit.

[Slide]

Here, on this slide I have shown a breakout of the primary endpoints and secondary endpoints, VTE and major bleed as defined in the protocol. I have split over various time intervals

when the doses where changed in either treatment arm. Also, they are standardized to reflect the incidence per 30 days exposure.

As one can see, when you look across the efficacy side, not surprising when we look at the literature, there are significant benefits in the first 30 days. However, there are numerical differences that persist beyond that to the advantage of dalteparin.

When we compare the risk benefit with major bleed, we can see here that effectively most of the difference occurs in that first month. This is also the time period when you get maximum benefit from being on dalteparin. Similarly, beyond one month there again appears to be a numerical low level with dalteparin compared to OAC.

[Slide]

Perhaps another way to look at this is to look at events together. Again, as defined in the protocol for the primary endpoint and secondary endpoint, we can see here that VTE events were 27

versus 53 and major bleeds were 19 versus 12. If we equate one event to one event, we can say that the overall benefit for dalteparin is a reduced number of total events. However, there is always discussion is a bleed equal to VTE.

Perhaps another way to look at the data is to look at those patients that died from the underlying disease or from major bleeds. Interestingly, in this study the majority of patients are still dying, a total of 14, from VTE.

The other thing to remember about the risk/benefit is that these results are applicable to clinical practice. In this study different tumor types were included. Different extent of tumor was included. Self-injection was shown to be feasible and acceptable, and treatment was well tolerated over the extended six-month period, provided flexibility and could be continued up to the end of life. The control arm results were also consistent with other studies that have been done in cancer patients.

Summary/Conclusions

[Slide]

I would just like to close our presentation with a few concluding comments.

[Slide]

As we have shown you, in patients with cancer VTE recurrence is more common compared to patients with non-cancer. VTE complicates the management of cancer and currently there is no FDA approved medication for the extended use in reducing recurrence of VTE without concomitant warfarin which required blood monitoring.

Oral anticoagulant therapy or warfarin is difficult to maintain and manage, particularly in patients with cancer. Dalteparin has established efficacy and safety in prophylaxis of VTE in non-cancer patients, has predictable dosing and reduced need for monitoring.

[Slide]

The CLOT study, as Dr. Lee showed, was highly significant for the reduction of recurrence of 52 percent. There is a compelling p value of 0.0017. The results are consistent across study

subsets and there is a favorable risk/benefit profile. This builds on previous clinical trial experience with dalteparin in the management of thrombosis.

[Slide]

Finally in conclusion, dalteparin provides cancer patients with VTE an effective treatment, a favorable treatment in terms of risk/benefit, and certainly a more manageable therapeutic option in patients with cancer.

Thank you and I will be happy to take questions if it is appropriate now.

DR. HUSSAIN: We will do the questions at the end, after the FDA presentation. Thank you, Dr. Eagle. The FDA presentation will be made by Dr. Andrew Dmytrijuk.

FDA Presentation

FDA Review of Clinical Data: Fragmin for Treatment of VTE in Cancer Patients

DR. DMYTRIJUK: Good afternoon.

[Slide]

My name is Andrew Dmytrijuk and I am the

lead medical officer for the Fragmin application. This afternoon I am going to provide a summary of FDA perspectives regarding a supplemental NDA for the use of Fragmin in the treatment of venous thromboembolism, or VTE, among cancer patients.

[Slide]

My discussion consists of three major parts. First, I will provide a brief overview of the regulatory background pertaining to drugs used in the treatment and prophylaxis of VTE. Secondly, I will highlight certain items that FDA regards as special considerations in the review of the CLOT study, the clinical study submitted as definitive evidence of safety and efficacy. Finally, I will introduce the major topics for our questions to the committee.

[Slide]

As denoted by the two major bullets on this slide, anticoagulant drugs used for the management of VTE are broadly divided into two major types of indications. Firstly, an anticoagulant drug may have an indication specific

for the prophylaxis of VTE. That is, the drug is administered to patients in order to prevent the occurrence of VTE. This form of prophylaxis may also be referred to as primary prevention of VTE. Clinical experience has shown that prophylaxis of VTE may generally be accomplished with relatively low anticoagulant drug dosages.

The second major bullet highlights the other major indication for anticoagulation in VTE, which is the use of the drug in the treatment of an established VTE. That is, the anticoagulant drug is administered in order to halt extension of the clot or recurrence of the clot. Treatment of an established VTE is also sometimes referred to as a form of secondary prevention of VTE and, as indicated here, generally necessitates a higher anticoagulant drug dose than that used for VTE prophylaxis.

As noted at the bottom of the slide, these two types of indications have unique risk/benefit considerations since the dose regimens and clinical considerations importantly differ. Hence, some

prophylactic dose regimens, while safe, have failed to provide acceptable VTE treatment efficacy. Similarly, some VTE treatment dose regimens have shown efficacy but have also been associated with unacceptable risk for bleeding. Hence, FDA generally regards these two indications, prophylaxis and treatment, as unique even though the underlying conditions somewhat overlap in pathophysiology.

[Slide]

Listed here are drugs approved for VTE prophylaxis and drugs approved for VTE treatment. Three of these drugs, heparin, Lovenox and Arixtra are approved for both VTE treatment and prophylaxis, while the other drugs, Fragmin, warfarin and Innohep are approved for only one of the two major VTE indications. This variation in indication underscores the unique risk/benefit considerations for anticoagulant drugs, including considerations of each drug's unique dose regimen properties.

[Slide]

Certain notable regulatory precedents are summarized on this slide. The first bullet notes that all anticoagulants with VTE prophylaxis indications generally have the indications limited to certain populations of patients at risk for VTE. For example, patients undergoing hip or knee surgery. Conversely, all anticoagulants with VTE treatment indications have to date received indications applicable to the broad population of patients with VTE. That is, the treatment indication statements have not identified unique subsets of patients as the applicable target patient population.

Fragmin is a member of the class of low molecular weight heparin drugs and, as the third bullet notes, to date all approvals for this class of drugs have limited the usage to short periods of time, generally from one to four weeks.

The last couple of bullets on this slide summarize the clinical development programs of anticoagulants by noting that approvals for VTE treatment or prophylaxis indications, for the most

recently approved anticoagulants, have been based upon data from at least two adequate and well-controlled clinical studies. Heparin and warfarin are somewhat unusual in this regard due to the older regulatory history of these products and their extensive clinical experience.

[Slide]

One of the major regulatory precepts pertinent to the most recent approvals of anticoagulants is highlighted with the FDA guidance document, generally referred to as the evidence of effectiveness document. This document describes the number and nature of clinical studies the FDA generally expects to be submitted in support of the definitive evidence of a drug's efficacy.

In general, the document cites three major pathways, as noted here. Firstly, the document notes that FDA usually anticipates that persuasive evidence of efficacy will be provided from two or more adequate and well-controlled clinical studies. That is, the FDA regards substantiation of efficacy findings from two or more clinical trials

as an important consideration in assessing the persuasiveness of a drug's efficacy.

Secondly, the document notes that in some situations independent substantiation of efficacy may be provided from clinical study data obtained in related situations. In this scenario definitive evidence of efficacy from a single study may be reasonably supported by the findings from another study or studies that supply the efficacy data for the drug in a related indication.

The third efficacy pathway consideration is shown at the bottom of the slide as denoted by the possible use of a single clinical study to provide the sole definitive source of efficacy. The guidance document generally concludes that in addition to a single study's necessity for robustness, the efficacy findings should be or such importance that another study would be unethical or impossible, as illustrated by the robust finding of a survival benefit in the treatment of a condition.

Please note that the last two bullets on this slide refer to situations where a single study

provides the bulk of evidence supporting a product's efficacy. As will be shown on the next slide, the guidance document provides special considerations for this single study.

[Slide]

This slide provides a quote from the efficacy guidance document that is especially pertinent to today's discussion. The document notes that, quote, in all cases, it is presumed that the single study has been appropriately designed, that the possibility of bias due to baseline imbalance, unblinding, post-hoc changes in analysis or other factors is judged to be minimal and that the results reflect a clear prior hypothesis documented in the protocol, end quote.

In other words, whether a single clinical study provides the sole source of efficacy evidence or whether the single clinical study is supported by findings from related clinical studies, the single clinical study should provide robust study findings.

[Slide]

This slide summarizes the current Fragmin indication, which is one related to two major areas, both prophylaxis indications. One indication is for prophylaxis of deep vein thrombosis in certain at risk populations. The other is for prophylaxis of ischemic complications in patients with unstable angina and non-Q-wave myocardial infarctions.

As noted here, the Fragmin dosages for the DVT prophylaxis are approximately 5000 units daily. This dose is approximately one-third of the dose proposed for DVT treatment, as will be shown on the next slide.

[Slide]

The proposed Fragmin indication is cited here as, quote, Fragmin is also indicated for the extended treatment of symptomatic VTE to reduce the recurrence of VTE in patients with cancer, end quote.

Also as shown, the proposed dose regimen consists of one month of higher dose Fragmin, 200 IU/kg/daily, followed by five months of Fragmin at

a dose of 150 IU/kg, with no daily dose exceeding 18,000 units.

[Slide]

This slide begins a series of slides concerning special considerations regarding the CLOT study. This study was entitled, quote, randomized comparison of low molecular wight heparin, dalteparin, versus oral anticoagulant therapy for long-term anticoagulation in cancer patients with venous thromboembolism, end quote.

This overview will focus upon three major areas as cited by the bullets. Initially, I will highlight certain unique study design features. Subsequently, I will highlight certain important CLOT study results. Finally, I will place the study findings and proposal in a regulatory context.

[Slide]

The major features of the CLOT study are summarized on this slide. The CLOT study was an international, multicenter study that used an open-label design and randomized patients in a 1:1

ratio between the study treatments. The specific study dosages will be shown on the next slide. The patient population consisted of cancer patients with an existing acute DVT and/or pulmonary embolus.

As has been previously noted, the primary endpoint was a comparison between the study groups in the time to first symptomatic recurrent VTE over the six-month study period.

[Slide]

The two study group dose assignments are highlight here, with the active study group consisting of one month of higher dose Fragmin followed by five months of lower dose Fragmin, and the control study group consisting of a few days of higher dose Fragmin, a time period during which subjects were begun on warfarin. Subsequently these patients were to continue on warfarin for the remainder of the six-month study. This group is referred to as the oral anticoagulation group or OAC group.

[Slide]

Certain important design features of the CLOT study are listed here. These include an open-label design where the two study groups inherently differed in patient anticoagulation monitoring, with the OAC group requiring regular INR blood monitoring. This type of monitoring may have resulted in the OAC group having greater healthcare provider contact and, hence, closer symptom monitoring than the Fragmin group. More intense symptom monitoring could result in a bias toward greater detection of symptomatic recurrent VTE.

This requirement for VTE symptoms in the definition of the primary endpoint meant that the endpoint results might be influenced by the occurrence of excessive numbers of deaths, especially for patients who died without experiencing symptoms of VTE.

Additionally, an excessive number of deaths could have impacted the primary endpoint due to the difficulty of diagnosing VTE, especially pulmonary emboli at the time of death or shortly

prior to death.

The final notation on this slide highlights the initial use of Fragmin in both study arms. In this context the usage assumes that Fragmin was superior to placebo in the initial treatment of VTE. Since the study was not designed to assess the safety and efficacy of this initial Fragmin usage, given the study's open-label design, assumptions about the initial Fragmin dosages safety and efficacy may have impacted subsequent patient management and symptom detection.

[Slide]

The CLOT study time lines and major protocol amendments are summarized here. The first patient was enrolled in early May, 1999. Approximately four months later the sponsorship of the study was changed and the primary endpoint was redefined from the co-primary endpoint comparisons or recurrent VTE and major bleeding to the single primary endpoint of recurrent VTE. This change was also accompanied by plans for re-estimations of the projected sample size and targeted sample size was

readjusted upward in 1999 and 2001. Subsequently, the last patient completed participation in the study in April of 2002.

[Slide]

This slide initiates a series of slides describing notable findings from the CLOT study. Firstly, the baseline characteristics are summarized here. In general, patients were balanced between the two study groups for important baseline characteristics. The patients were older, as evidenced by the median age of 64.

The last few bullets summarize the cancer status of the patients by noting that 90 percent of the patients had solid tumors; 75 percent of the patients had stage IV cancer; and 10 percent of the subjects had no evidence of cancer at baseline, as might occur with successful prior cancer therapy.

[Slide]

Patient disposition in the CLOT study is summarized here. Overall, 338 patients were randomized to each of the study groups. The yellow font highlights the especially important

observations. In general, approximately half of the randomized patient population discontinue the assigned study drug regimen during the study.

As shown in the first bullet, most of the study drug discontinuations were due to death, a rate of 17 percent in the Fragmin group and 7 percent in the OAC group. Conversely, study drug discontinuation due to occurrence of recurrent VTE was more common in the OAC group, the rates of study drug discontinuation due to VTE being 6 percent for the Fragmin patients and 14 percent for the OAC patients.

The table also notes that the rates for discontinuation due to bleeding were numerically higher for OAC patients, while the study drug discontinuations due to adverse events were similar between the study groups.

The "other" category at the bottom of the table refers to a broad range of various reasons for study drug discontinuation, with no notable imbalances evident.

[Slide]

As has been previously noted, the CLOT study's primary endpoint favored the Fragmin group as evidenced by this time to first recurrent VTE curve. Shown on the horizontal axis are the study days, while the VTE recurrence probability is shown on the vertical axis. The solid line indicates the Fragmin group and the hatched line the OAC group. As shown here, the p value associated with the treatment effect was 0.002.

[Slide]

As illustrated here, most of the treatment benefit was evidenced in the first month of the study, the time period during which the Fragmin group received the higher Fragmin dose. This table shows the primary endpoint result when categorized by study period. During weeks 1-4 the rate of recurrent VTE was 3 percent for the Fragmin group and 10 percent for the OAC group. The rates over the subsequent weeks were similar, 5 percent versus 6 percent. The total recurrent VTE event rates were 8 percent for the Fragmin group and 16 percent for the OAC group.

[Slide]

As previously mentioned, survival is required to experience VTE symptoms. Hence, mortality and VTE represent competing risks in the CLOT study. The bullets highlight some important considerations. Specifically, approximately 40 percent of all the patients were dead at 6 months, such that the death rate was 3 times greater than the recurrent VTE rate. This relatively high death rate indicates that death outcomes may importantly impact the study results. This impact may be evidenced in many sensitivity analyses and here I will highlight two data explorations as indicated by the last two bullets.

First, we will examine the imbalances in outcomes based upon categorical analyses of the VTE and death outcomes. Subsequently, we will examine the similarity of the two study group outcomes based upon comparisons of VTE-free survival or what may be referred to as clot-free survival.

[Slide]

Shown on this slide is a mutually

exclusive categorical analysis of death and VTE outcomes. For the patients who died but did not experience a recurrent VTE the rates were 33 percent for Fragmin patients and 28 percent for OAC patients. For the patients who had recurrent VTE and then died, the rates were 6 percent for Fragmin patients and 12 percent for OAC patients, an outcome that accounts for most of the treatment benefit events. For the patients who had recurrent VTE and survived, rates of 2 percent versus 4 percent. The last row lists patients who had neither death nor recurrent VTE, that is, the clot-free survival group, with rates of 59 percent for Fragmin patients and 56 percent for OAC patients.

[Slide]

This slide restates the categorical analysis in terms of the outcomes for the categories accounting for the major imbalances. As noted in the bullets, these categories both pertain to outcomes among patients who died. For patients whose death followed a recurrent VTE the Fragmin's

group rate was favorable compared to the OAC group, a 6 percent rate versus 12 percent rate, or a difference of minus 6 percent.

However, for patients whose death occurred without a recurrent VTE the Fragmin's group rate was unfavorable when compared to the OAC group's rate, a 33 percent rate versus a 28 percent rate, or a difference of plus 5 percent. The consequences of these imbalances are stated on the next slide.

[Slide]

The categorical imbalances associated with the risks for death and recurrent VTE suggest that inaccuracies in the diagnosis or detection of VTE near or at the time of death may importantly impacted the results. The higher death rate among Fragmin patients who did not have recurring VTE detected may have been related to less vigilance in the detection of VTE among Fragmin patients, perhaps related to investigator bias regarding Fragmin efficacy or less intense symptom monitoring.

Multiple hypotheses and exploratory analyses may be proposed to account for these findings. However, one exploratory analysis that may have special value is a comparison of the VTE-free survival outcomes or time to recurrent VTE or death curves between the study groups. This type of exploratory analysis has a straightforward clinical interpretation and largely resolves the competing risk considerations.

[Slide]

This figure shows the time to recurrent VTE or death, with study days shown on the horizontal axis and the probability of either recurrent VTE or death shown on the vertical axis. The hatched line represents the OAC group and the solid line represents the Fragmin group.

As you can see, the numerically favorable difference is seen as not statistically significant. The nominal statistical significance for the difference in the two curves is 0.20.

[Slide]

A few other notable exploratory outcomes

are highlighted on this slide. As shown in the first bullet, an outcome that examines the time to treatment failure, where treatment failure is defined as the time to recurrent VTE or discontinuation of the study drug due to death, showed similar outcomes between the study groups, with a nominal p value of 0.65.

Exploratory subset analyses are generally of very limited value. However, it is important to note that these analyses suggested no treatment effect among patients with non-metastatic cancer, as well as patients with hematologic cancer, an observation that may relate to the relatively small sample sizes with these patient subsets.

Lastly, the bottom bullet notes that hospitalization rates were similar between the study groups. In general, the favorable primary endpoint treatment effect would have been bolstered in importance if the hospitalization rates were also favorable.

[Slide]

The major efficacy finding limitations are

summarized here. In general, the robustness of the primary endpoint is called into question by three major observations: The competing risks of death with recurrent VTE; certain CLOT study design features, especially the differing patient management between the study groups that may have been associated with bias in symptom detection, especially given the open-label nature of the study. Lastly, the slide highlights the variable results among the sensitivity analyses that explore the VTE and death outcomes.

[Slide]

This slide begins a summary of the major safety findings from the CLOT study. These findings generally relate to the bulleted outcomes, the study drug discontinuations due to death; the rates of major bleeding; thrombocytopenia; and liver enzyme or bilirubin elevations.

[Slide]

As previously noted, the study showed an imbalance in the rates of patients who discontinued the study drug due to death. The rates were 17

percent for Fragmin versus 7 percent for the OAC group. However, the study also showed that the overall mortality rates were similar, 39 percent for Fragmin and 41 percent for the OAC group.

[Slide]

This slide explores one of the possible considerations for the imbalance in study drug discontinuation due to death rates. Specifically, the possibility that imbalance in study drug exposure times might account for the imbalance.

As shown at the top of the slide, the median study drug exposure time was 9 days longer in the Fragmin group. Specifically, the median was 176 days for Fragmin patients and 167 days for the OAC patients. The table estimates the crude death rates on a monthly basis among patients who were receiving the study drug during the month. The left major column shows the Fragmin group and the right major column shows the OAC group. The arrows highlight the crude death rates, with the first month showing a rate of 5.4 for the Fragmin group and a rate of 3.7 for the OAC group.

This higher Fragmin crude death rate is maintained throughout the study when analyzed according to the monthly exposure to the assigned study drugs. Hence, exposure time alone does not appear to account for the imbalance in rates of study drug discontinuation due to death.

[Slide]

This slide summarizes the first safety observation, a possible safety signal related to the imbalance in the study drug discontinuation rates due to death. As noted in the sub-bullets, the imbalance in study drug exposure does not appear to fully account for the imbalance. Other considerations may relate to variable patient management between the study groups and the possibility of a study drug effect. However, mechanisms for an adverse Fragmin mortality effect were not evident in the study data.

[Slide]

This slide summarizes the major bleeding outcomes. Overall, the study found a non-statistically significant numeric excess for

the Fragmin patients, rates of 6 percent versus 4 percent. In this table the rows show the major bleeding rates by weeks. Fragmin rates are shown on the left and OAC rates on the right. During the first week, a time period when patients were receiving the higher Fragmin dose in both study groups, the rates were 1.2 percent in both study groups.

During weeks 2-4, the time period when higher Fragmin dose was continued in the Fragmin group, the Fragmin rate was numerically higher, 2.7 percent while the OAC rate was 0.3 percent. During weeks 5-26 the rates were the same at 3 percent. Hence, the most notable differences in major bleeding rates were detected during the period of higher dose Fragmin administration, as detected during weeks 2 through 4.

[Slide]

Other notable safety observations related to the occurrence of thrombocytopenia and serum liver enzyme or bilirubin abnormalities. The table summarizes these adverse event findings according

to the severity grad3 e, with any severity grade shown in the left-most columns and grade 3 or higher severity grades shown in the right-most columns.

As shown, thrombocytopenia adverse events of any grade were detected in 11 percent of the Fragmin group and 8 percent of the OAC group. Grade 3 or higher thrombocytopenia adverse events were detected in 6 percent of the Fragmin group patients versus 3 percent of the OAC group patients. Subsequent rows show small numeric excesses in the rates of serum liver enzyme or bilirubin elevations, as illustrated by the finding for the ALT results. Specifically, any severity grade ALT elevation was detected in 40 percent of the Fragmin group and 31 percent of the OAC group, with grade 3 or higher events detected in 4 percent of the Fragmin group versus 2 percent for the OAC group. A similar pattern was seen for the other liver biomarkers shown in the table. Despite the small numeric imbalances in these rates, only one Fragmin patient and two OAC patients had the

assigned study drugs discontinued due to hepatobiliary disease.

[Slide]

Overall, the safety findings are most notable for two groups of findings, as shown on this slide. First, more patients assigned to the Fragmin group discontinued the assigned study drug due to death. Second, when compared to the OAC group, small numeric excesses were detected among the Fragmin group patients for the major bleeding outcomes and the adverse events of thrombocytopenia and serum liver enzyme elevations or bilirubin elevations.

[Slide]

This slide summarizes certain major observations from the CLOT study, as indicated by three areas, the study design limitations; the study efficacy findings; and the study safety findings.

The study design limitations are notable for the open-label nature of the study which may have impacted multiple aspects of the study, such

as VTE detection and patient management.

The study's primary endpoint was redefined from an original co-primary endpoint comparison of major bleeding and VTE rates to one of time to recurrence of symptomatic VTE. The study design required differing anticoagulant management between the study groups, with one group requiring regular blood INR monitoring while the other group did not. Finally, the study's primary endpoint required survival and was conducive to a competing risk with mortality.

As noted here, the study's major efficacy outcome was confounded by the competing risks of death and recurrent VTE. Another notable efficacy finding was that the treatment effect for Fragmin was evidenced in the first month of the study regimen, with no further gain evidenced over the subsequent months of the study.

The study's major safety concerns related to the excess in study drug discontinuations due to death among the Fragmin group, as well as the small excess for Fragmin patients in major bleeding rates

and adverse events of thrombocytopenia and certain liver test abnormalities.

[Slide]

This slide places the CLOT study findings in a regulatory context by noting that the CLOT study was submitted as the single clinical study providing the definitive evidence of safety and efficacy for the proposed indication of six months of VTE treatment among cancer patients. As previously noted, the CLOT study has an important limitation in data interpretation.

The second bullet provides a background for the proposed indication by noting that short-term regimens of Fragmin have proven efficacy and safety in other patient populations when the drug is used for VTE prophylaxis.

The last two bullets note unique regulatory considerations and that the proposed indication is specific for cancer patients with VTE, not the broad population of patients with VTE since safety and efficacy of the proposed dose regimen has not been confirmed for the broader

population of patients.

[Slide]

This afternoon our questions focus around four major areas, as outlined here. These topics include assessments of the CLOT study, safety findings and robustness of the CLOT study efficacy findings. Other topics include considerations related to the potential labeling of the product and potential need for additional clinical studies.

I thank you for your attention and turn the podium back to our committee's chair.

Questions from the Committee

DR. HUSSAIN: Thank you, Dr. Dmytrijuk. We are going to go now to the section dealing with questions and answers to the committee. As is the case usually, I would like you to let me know, or Johanna, that you have a question. We will acknowledge you and then you can ask your question. I will begin first with Dr. Hiatt. He had a question.

DR. HIATT: Thank you. A couple of questions actually. The first one was in reference

to either Dr. Eagle or Dr. Lee regarding the design of the CLOT study. In many other studies like this where you are looking at a symptomatic endpoint in a condition where there can be a lot of unrecognized disease, you could have included a fixed time point for screening using duplex ultrasound or some other measures, looking for pulmonary emboli in all patients, symptomatic or asymptomatic. I am wondering why you didn't consider that, particularly given this competing issue about people dying before the event versus not. That is one of my questions.

The second question was to note that the Fragmin group did get a total duration of higher dose Fragmin longer than the oral anticoagulation group, and I would like to hear some comments about that. I think I will just stop at that point.

DR. LEE: Thank you very much for the question. Perhaps if you wouldn't mind actually repeating the questions for me? The first one, in terms of why we didn't use routine screening to detect thrombosis, well, as I have already

mentioned, the study was designed to address symptomatic events. Symptomatic events are clinically relevant. These are events where the patients are coming in with a more swollen leg; with more shortness of breath. These are symptoms that compromise their quality of life and compromise their cancer treatment.

If we were to do a study that basically just screened patients routinely for ultrasound evidence of DVT where they didn't have symptoms, you can argue whether these are clinically relevant at all because now what are we going to do with the patients? They have absolutely no symptoms; it is not interfering with their life; and what does this mean in terms of their cancer therapy?

So, in contrast to prophylaxis studies or studies that are designed to evaluate the effectiveness of a new anticoagulant, we know that Fragmin is already an effective anticoagulant because it has a proven track record for the last 20 years. It is approved for primary prophylaxis. What we wanted to do is to look at whether Fragmin

will reduce symptomatic events, events that are relevant to the patients; important for their quality of life; important for how we manage them, not just because of thrombosis but because of their cancer care.

DR. HIATT: Just a comment with regard to this FDA presentation, if, in fact, the symptom was death and not a tender, swollen leg, then screening in all patients at a fixed time point could have rebuilt an imbalance in recurrence in asymptomatic thromboembolic events that could have been associated with an increased risk of early death.

DR. LEE: Well, I agree with you that often recurrent VTE can appear as a fatal event, fatal PE. But these were, in fact, actually relatively rare compared to the vast majority of patients who would represent with symptoms. Also, there have been previous studies in the thrombosis literature that have shown that it is impossible to basically screen for thrombosis and hope that a negative screening test will basically reliably predict that the patients will not develop recurrence. Because

these patients are having changing clinical status all the time so one week they might be quite well; the next week they are bedridden because of their chemotherapy or some other event in their lives. So, now your risk of developing recurrent thrombosis drastically changes.

So, if we had done ultrasound screening for VTE and DVT and it was negative, it doesn't really provide you with any security that the patient isn't going to die of a fatal PE later on. So, again, I have to disagree that screening would have really provided the patients with any greater safety, or provided a better answer to our question.

DR. HIATT: Then the other question, and then I will stop, was the difference in duration of the higher dose of dalteparin in the dalteparin group. They had about three weeks more exposure to 200 IU/kg than did the oral anticoagulant arm. Could you comment on that?

DR. LEE: Yes, like I said during my presentation, and I am sorry I didn't make that

very clear perhaps, the traditional treatment that consisted of initial therapy of five days of heparin followed by oral anticoagulant is basically designed that way because oral anticoagulants don't take effect for the first week. So, simply low molecular weight heparin or heparin is given for that first week to really bridge the gap when oral anticoagulants are supposed to take effect. So, that is why the traditional treatment is sort of separated into initial and long-term treatment.

For dalteparin, which takes effect within three hours, reaches peak levels within three hours of an injection, we don't need to do that initial and long-term treatment. It is monotherapy. We decided to give the full dose anticoagulation for the first month because we know that recurrent thrombosis is highest during the first month. So, it doesn't make clinical sense to stop this protection in a week just because traditional therapy, which is limited by oral anticoagulants long action--sort of long delay in taking effect. So, our regimen was really designed to basically

match the needs of the patient, whereas oral anticoagulant therapy totally fails to address the patient's needs and the clinical history.

DR. HIATT: Thank you.

DR. LEE: Thank you.

DR. HUSSAIN: Dr. Lee, while you are up there, I have a question for you. The early deaths observed on the experimental arm, were these fairly distributed across all subgroups?

DR. LEE: Sorry, if you could just explain that?

DR. HUSSAIN: As I understood from your presentation and Dr. Eagle's, there were earlier deaths in the experimental arm in the first 14 days. There were more deaths, and these were seen mostly in the first 14 days. Is that what Dr. Eagle presented?

DR. LEE: No, there was absolutely no difference in the rate of overall deaths throughout the entire period of the six months.

DR. HUSSAIN: So, what is the argument of the FDA then? What is the stuff we just heard

about more deaths?

DR. LEE: If I can have the Kaplan-Meier curve on overall mortality, please? I am sorry, I don't have the number of the slide but this was in the main presentation.

[Slide]

You can see that on the Kaplan-Meier curve there is absolutely no difference. I mean, the curves are virtually superimposable. So, I don't understand where you are getting this from.

DR. HUSSAIN: Perhaps you can explain because I am obviously confused.

DR. RIEVES: Thank you for the opportunity. In analyzing a clinical study, one of the aspects in analyzing the safety is the determination of the study drug discontinuation rates and the cause for the study drug discontinuation. It is important to frame our statement in that we are looking at study drug discontinuation due to death. On the case report form there were multiple options for site investigators to identify the reason for study drug discontinuation. As it turns out, twice as many

patients had study discontinuation due to death in the Fragmin group as in the oral anticoagulation group, and it is that potential safety signal that we are focusing on.

You are exactly right, the overall mortality is the same. The survival curves are the same. But the safety signal that may relate to study drug discontinuation due to death is different.

DR. HUSSAIN: But just so we understand, when you die you don't take drug. Right? So, if you died earlier, then that would be coded as you are dead and you didn't take the drug and that was the cause of stopping the drug. Does that not imply that there perhaps was imbalance in the amounts of deaths happening over time? I mean, did people code things differently? Could you please explain?

DR. RIEVES: Sure.

DR. HUSSAIN: Am I the only one confused about this or do others have similar issues?

DR. EAGLE: If we could show slide 44 from

the main deck?

DR. HUSSAIN: And could you please comment also, while you are up there, Dr. Eagle, about the 14 days, one day and all of that?

DR. EAGLE: Sure, no problem.

What we need to think about this study is that at randomization patients were entered who had cancer. The majority had metastatic cancer. They were followed over a period of 6-12 months to see what happens to cancer patients from the date of randomization, particularly from a survival point of view.

[Slide]

Here is the curve that shows that at any time points of the study patients had the same survival whether they were randomized to OAC, oral anticoagulant, or to dalteparin.

From that perspective, then the question you can ask is during their life from randomization, how long did these people get OAC or low molecular weight heparin. What we know and what has been presented is that patients get low

molecular weight heparin right up until the point they die. Why? Because when you look at patients who discontinued because of death there are more of them. Yet, overall there was no difference.

However, when we look at OAC, they lived the same. How long did they get oral anticoagulant therapy? They didn't get it up to the time they died. They got it up to the time where they couldn't swallow; there were problems with their treatment; they came up to the point where the palliation therapy was kicking in.

How can se show that? Because if I look at treatment discontinuation in that same life span more people are taking it up to the time they die in Fragmin; less people are taking OAC up to that same time point.

Not only that, if I then look at the actual time event that this decision on OAC is made, it is only that 14-day period where literally we are picking up. So, somewhere in those two weeks before the patient dies on the OAC arm the clinician is making the decision to stop the drug,

the discontinuation. So, then they tick the box to discontinue, whatever reason they decide, on OAC. With Fragmin they continue up till the patient dies and they tick that box.

So, now if I look at the reasons for discontinuation, I am really starting to pick out what clinicians were doing within this life interval that patients have with cancer. They are deciding sooner before the patient dies to stop OAC for other reasons. With Fragmin they are deciding to continue it in the same life interval right up until the event of death.

DR. HUSSAIN: I understand. Forgetting about what box they are ticking and all of that, in terms of absolute straightforward terms there was no indication--and I want an answer from you, yes or no--there is no appearance of increased death early or late between the experimental arm as compared to the regular arm. Right? In terms of real deaths, not anything else.

DR. EAGLE: No, that is the overall survival.

DR. HUSSAIN: Is that correct from your end?

DR. RIEVES: What is correct is that the overall mortality curves overlap each other.

DR. HUSSAIN: Okay.

DR. RIEVES: But that is a unique consideration that is different from the basis for study drug discontinuation. For example, our slide 28 is an important slide to examine. Part of our concern is that, given the database, we prefer not to use these post-hoc explanations as to patient management. Patients inherently differed in their management. Perhaps as a consequence of that, that may be one of the explanations for this observation.

[Slide]

But we are left with the data Fragmin group s they are shown in slide 28. This table is an attempt is an attempt to adjust for, quote, time on study drug. What is shown are the crude death rate columns comparing the Fragmin group to the OAC group. You can see that just solely based on the

time on study drug the Fragmin rates were fairly consistently higher than those for the crude death rates.

But, again, this is the safety signal that may be related to an aspect of study drug discontinuation due to death. Essentially, we have a question here. We do not have a solid answer as to why this observation is present. There are many possible explanations but, unfortunately, they are all post-hoc and subject to the post-hoc limitations.

DR. HUSSAIN: Thank you. Dr. Perry?

DR. PERRY: A question again for Dr. Lee, coming back to Dr. Hiatt's point. I agree that you screened reasonably well for symptomatic DVT but I don't think you have screened for pulmonary emboli. I was told repeatedly for the last 35 years that physicians commonly underestimate the incidence of pulmonary emboli.

So, unless you have autopsies on all your patients on both sides, I don't think you can tell me that you know how many people had pulmonary

emboli. Is that correct?

DR. LEE: I totally agree, and it is actually one of my pet peeves that I cannot get my colleagues to investigate patients when they do develop shortness of breath. But I am not an oncologist so I don't treat these patients with oncology problems. But I do see these patients daily in my clinic.

What happens is when these patients are close to their end of life, they have multiple symptoms--fatigues, shortness of breath--all of which can be attributed to their cancer or their chemotherapy. Physicians, families and the patients are reluctant to undergo these investigations. So, sometimes we are forced to not accurately diagnose these patients. However, in this study we did our best. We asked the patients to report to us when they developed symptoms. We called them every two weeks to ascertain symptoms. So, we tried our best to try to figure out as early as possible when they may develop these symptoms, and investigated them according to

pre-specified diagnostic algorithms.

So, we did testing whenever we knew these patients had symptoms suggestive of PE and DVT, and these were managed equally in the two arms.

DR. PERRY: But people with so-called asymptomatic PEs would have been missed in either arm.

DR. LEE: Yes, and they would be equally missed in both arms.

DR. PERRY: We assume that.

DR. LEE: We assume that, and that is the only way we can assume. Unless you think that one group of patients is going to under-report their symptoms to us, we can only assume that patients are going to report their symptoms as they were instructed to, and clinicians did their best to diagnose these cases because these are potentially medical emergencies.

I am a little bit sensitive to think that any of our investigators in the studies under-investigated patients to try to avoid diagnosing these events because it is not in the

clinician's interest, and certainly not in the patient's interest. I mean, we were treating these patients and we were doing the best that we could to try to minimize symptoms. As you see, 40 percent of these patients are dead at six months. So, their quality of life during this period is very important. When you have another blood clot, more swollen legs, more shortness of breath, it is very important to the patients and their families.

So, even though there was no difference in overall mortality, we reduced the risk of recurrent thrombosis by more than half in these patients, and that is absolutely important. Whether, you know, we under-diagnosed fatal PE or not, I recognize it. But it was equally missed, if that was the case, and we tried to use a regimen that was designed ideally to match the clinical history and the needs of these patients.

DR. HUSSAIN: Thank you, Dr. Lee. If we could please keep the answers brief, it will allow us to include more questions.

DR. LEE: Sorry. It is a passionate issue

for me so I do tend to go on.

DR. HUSSAIN: I understand that and we appreciate that. Dr. Perry, your final comment?

DR. PERRY: If you could go to slide 33, your slides? It is going to show that about ten percent of the patients have no evidence of cancer and about 12 percent of patients had localized cancer. Can you tell us any more about these? Patients with no evidence of cancer, what does that mean? Does that mean somebody had a mastectomy and had no evidence of recurrent disease but is on tamoxifen? And, the localized patients, is that somebody with a localized pancreatic cancer or stage I breast cancer? How do we know those seemingly very disparate people are randomized in balance?

DR. LEE: Right, if I may actually have the backup slide on the inclusion criteria, please, that would be very helpful.

[Slide]

As part of the study design, we a priori defined the patients with active cancer that would

be eligible for our study because we do recognize that there could be some subjectivity to this. So, the patients who were allowed in the study were patients with objectively documented acute symptomatic thrombosis of the lower limb and/or PE, and they also has active cancer according to this definition.

Now, you may disagree with it, being an oncologist, but from a thrombosis point of view, these are the patients that we see and we deal with, and these are the patients we have to treat when they develop thrombosis. So, these are patients with cancer diagnosed within the past six months.

So, it is possible, like you said, that they might have a mastectomy and so there was really no overt evidence of tumor at the time they were randomized to the study. Also, if they had recurrent or metastatic disease or if they had received cancer treatment within the past six months, they were also considered to have active cancer.

DR. HUSSAIN: Dr. Levine?

DR. A. LEVINE: I have several questions. The first involves the same issue as has already been discussed but I want to ask it in a more specific way. The problem to me is that the group on coumadin was seen far more regularly by the healthcare system and, therefore, the healthcare system had the opportunity to find subtle symptoms or to suggest to the patient, "gee, your leg looks a little swollen to me. Do you think so?" So, that is the crux of it to me.

In that regard, number one, how many of these events were diagnosed because the patient called you. Are you really symptomatic versus how many events were diagnosed by the phone interviews, versus how many events were diagnosed at an INR visit by a healthcare provider? So, that is my first question.

DR. LEE: If I can have slide 34 that was shown during my presentation?

[Slide]

This showed the frequency of contacts

between the two groups. As you can see, the scheduled visits were the pre-specified visits at one week, one month, three months and six months, and they were comparable. When you look at the telephone contacts, again, they are virtually identical. Lastly, if you look at the unplanned visits, these would be visits that were initiated by the patient's phone calls because they have symptoms or, for example, if they had INRs that were concerning. You can see, there was absolutely really no difference between the two groups overall. So, in terms of how they were managed and how disease may be picked up, there is really no difference.

DR. A. LEVINE: I think there is an error there. Are you saying that none of the patients on coumadin had any visits to check their coumadin? And, if they did have visits to check their coumadin, where does that play out there?

DR. LEE: Right, so the INRs were done usually at a local laboratory, convenient to the patients, and the results would be called into the

clinics. So, the patients don't actually come into the clinic to get their INRs done because they could be living very far away from the research center. So, the INRs are done and they were done at least every two weeks and sometimes more frequently, and they would be called in. Then the patients would be called at home with further doses of their coumadin.

DR. A. LEVINE: So, I still would say the same. In our place we have the whole coumadin group, and so forth, and they know the patients. They are the phlebotomists. They know them well. And, the bottom line is every two weeks, or whatever it is, the patients walk into their home clinic and somebody is going to say how are you? That, to me, is a real issue.

It is an issue as well because of what you have already alluded to. The fact is that cancer patients are at risk for asymptomatic DVT and that data is evolving now. So, little subtleties could very much say to me that you are going to find more DVTs in the coumadin group who come in all those

extra two-week visits. That is a huge thing for me.

Another issue relates to the telephone calls. Were those scripted interviews or how were those performed?

DR. LEE: Yes, basically for the telephone calls the nurses or the investigators followed standardized questions and asked them about symptoms of thrombosis, any bleeding issues, any AEs, whether they were still taking their study medications. So, they were standardized for the two groups.

Also, if I can have backup slide number 68?

[Slide]

This slide shows basically the INR controls for the group over the study periods. You can see that for the dalteparin the INR basically remains normal throughout the study, which is expected because dalteparin does outcome affect the INR. But when you look at the oral anticoagulant group, they certainly were maintaining therapeutic

levels throughout the entire study period.

Again, I understand why you are troubled by patients who are getting their INRs. There might be more questions asked about their well being so that triggered more investigations. But, again, even if you were triggering investigations, if they didn't have VTE those events are not included in the analysis.

The other thing is that we looked at the comparison of the local investigator's decision for diagnosis and the central adjudication committee, and basically there was absolutely no difference in the proportion of events that were reported to be positive in the two groups, suggesting that there wasn't over-investigation or under-investigation of the two groups.

DR. A. LEVINE: I have a question, I can't frame it quite yet but I will in a moment. I guess my question is this, you just said something that I will question, which is that there was no difference in the two groups as far as numbers of studies ordered, and so forth. Does that include

per the visits that you wrote there or does that also include per all of the coumadin visits?

I also assume that the tests would have been paid for by the study so it wouldn't have bothered anybody to order some extra tests if the patient had to be seen for an INR visit and had a subtle change.

DR. LEE: Well, the tests were paid by the study--I am not sure. The INRs were routinely done and they were not covered as part of the study. The study medications were provided to the patients in both arms. But any other testing was certainly considered routine for anybody who has a blood clot and needs to be on anticoagulant therapy.

The other thing is, I don't have the numbers. You were referring to the number of tests that were triggered by INRs, and so on, but, again, the nurses and the investigators were basically asked that when patients report symptoms they were following algorithms, going through specific testing of ultrasounds, VQ scans, spiral CGs and the patients were managed accordingly.

DR. A. LEVINE: I guess it would just make me feel better to know exactly how many patients were picked up at a coumadin visit because that would just answer it. That would make it kind of even to me.

Can I ask another couple of questions?

DR. HUSSAIN: Dr. Levine, can I ask you to ask one and then perhaps we will get others and then come back to you again.

DR. A. LEVINE: Okay. Then, my first question is in the study the dalteparin was used to treat active DVT in both arms. So my question is since this has not been tested before or approved before for the treatment of VTE, how many patients failed treatment, and how did you ascertain whether it was effective treatment or not?

DR. LEE: Is this to me or Dr. Eagle?

DR. A. LEVINE: To anybody. It is to anybody who can answer.

DR. LEE: As it was already outlined, dalteparin does not have an indication for initial treatment in the U.S. However, dalteparin is

recognized as standard treatment for initial therapy of venous thrombosis in Canada, many European countries and Australia. It has a track record for initial treatment of venous thrombosis. In this study we concentrated on long-term treatment and, as I showed in my slide, the patients received the same doses of dalteparin for that initial first week, which is traditionally considered as initial therapy.

So, even if you said, well, that is just placebo because this drug doesn't have regulatory approval to be used in this period, that is the same in both arms. But it would be hard to argue that this drug has no effect when, clearly, over the long-term it suppressed recurrent thrombosis by more than 50 percent compared to oral anticoagulants.

DR. A. LEVINE: I wasn't arguing that at all. I am just curious because in this country it is not approved. So, my question is what is the failure rate? Do you know that or did you ever look at that?

DR. LEE: Sorry the failure rate for?

DR. LEE: To treat the initial DVT. How did you prove that in different countries? I am just curious.

DR. LEE: Well, I think if you look at the recurrence, the number of recurrences during that first week, basically the numbers are comparable to what is reported in the literature for both the control arm and the experimental arm because they received dalteparin therapy. If I can have backup slide 59?

[Slide]

You can see here that during that first week the risk of recurrence is 1.5 percent in the dalteparin arm and 2.4 percent in the OAC arm. Now, they both received the same treatment during this time so these numbers would be comparable, and these are absolutely consistent with what is known in the literature. So, it certainly does not raise any suspicion that the dalteparin was not effective during this first week.

DR. A. LEVINE: Thank you.

DR. HIATT: Could I comment on that?

DR. HUSSAIN: Dr. Hiatt, if you don't mind waiting one second, I will get back to you. Dr. George has been patiently waiting.

DR. GEORGE: I have a question. I guess it is a statistical question so it might be for Mark Levine or Steve Piantadosi that you listed in your early slides.

There has been a lot of discussion here around competing risk analysis and I was just curious about why this wasn't basically built into the design and not included in the analysis in The New England Journal paper, not was much talked about it in the documentation that you provided, except to state that the reason you counted deaths as an independent censoring mechanism was because it seemed reasonable. There was no plausible reason why you would expect it to be anything other.

So, I guess my question is did you do some of the more standard competing risk analysis calculating cumulative incidence and tests based on

that? And, if you did, what were the results?

DR. PIANTADOSI: I am Steve Piantadosi, consultant to the company in biostatistics. Steve, I can't speak to the history, the early history of how the analyses were planned and done, but I can tell you, with regard to my involvement in the regulatory matters, that the competing risk issue was not thought to be a significant problem for estimating the primary outcome of this study, which is the relative risk of recurrent VTE in the two treatment groups.

There are two perspectives on this in the literature. One says that it might be important to try to estimate the absolute risk of venous thromboembolism corrected for the competing risk of death. However, there is a second perspective that recognizes that that is, in fact, unobservable. There are no circumstances under which an oncologist or other treating physician would be encountering a study cohort, or even an individual subject, who is completely free of the risk of death. So, there is only one observable here, and

that is the risk of recurrent VTE in the presence of death.

I believe that that is accurately estimated by the relative risk based on the randomization and intention-to-treat principle that was applied in the primary analysis here. Similarly, one could argue that the appropriate safety signal is based on the intention-to-treat analysis and overall mortality for exactly the same reasons.

This is state-of-the-art for these kinds of supportive care studies, as well as for these studies in venous thromboembolism. They are all done in the presence of various competing risks. Here the rate happens to be somewhat higher, but there is no expectation, no signal in the data or no biological reason to expect that there is a differential competing risk in the two treatment groups.

DR. HUSSAIN: We have several questions and we have just over ten minutes. So, I am going to ask that the questions and answers be brief,

please, so we can accommodate everybody. Dr. Grillo-Lopez?

DR. GRILLO-LOPEZ: I find the Kaplan-Meier curve for overall survival pretty convincing in terms of showing that the time to death, in fact, was the same for patients on either group. A couple of Kaplan-Meier curves are subject to what censoring rules were applied and I would feel much more confident if the sponsor could provide additional clarification around a couple of things.

First of all, were all patients observed until death? Have all patients died and, if not, is there any difference in the observation time between arms or in the drug exposure time between arms?

DR. EAGLE: So, if we could show slide 44 from the main deck?

[Slide]

I would just put in context here that the patients were treated for six months of therapy, and the arrow signifies then patients were followed for a further six months after they completed the

therapy period. Similarly, I would also add that the analysis was done well after the last patient visit at the six-month point. So, the median patient follow-ups--although I don't have that at hand at the moment--is certainly beyond the follow-up period here. So, this is an extended follow-up on survival.

DR. HUSSAIN: Dr. Hiatt?

DR. HIATT: I just want to make a comment about an earlier question on the standard of care for the initial treatment of venous thromboembolism. The cardiorenal panel has looked at some of this in the context of, for example, anticoagulation for patients with atrial fibrillation. I would just like to comment that some of the early data looking at the effects of benefit of coumadin versus placebo display quite point estimates and confidence intervals around the putative treatment effect.

But if you look at the VTE literature early on, particularly literature by Russell Hall, he did show in some early studies that, for

example, subcutaneous heparin versus intravenous heparin is different in that parenteral administration with the intravenous route was superior in preventing recurrence. A lot of those earlier demonstrated that the more rapidly you prolong the PTT and achieved adequate anticoagulation and sustained that, the lower the risk of recurrence.

In my comment around the high dose of dalteparin for a month in one arm versus a week in another was related to that thinking, that the more adequate and sustained higher level of anticoagulation early in the course of venous thromboembolism was related to decreased recurrence. I think that that could have contributed to some of the recurrence rate between the two groups.

But just back to the original comment, it is interesting when you try to look at standard of care in this area, and the FDA presentation related to that, it really goes back into historical kinds of controls and not as rigorously randomized trials

as we think about today.

DR. HUSSAIN: Thank you. Dr. Harrington?

DR. HARRINGTON: My comment follows Dr. Hiatt's earlier remark and, actually, his later remark as well. This is a question perhaps about the study that maybe you wished you had done when you had seen the data. If you look at your curves on slide 36 which show the very large separation in the rate of VTE on the two arms, those curves suggest to me that the real differences in those two populations are occurring in the first month, in fact, probably occurring between the first week in the first month.

So, one could infer, although this is observational, that the real effect here was the higher dose of your study drug over that first month. For me, that begs the question of the safety profile, the long-term use of your agent versus the OAC and what safety events you may have seen, say, beyond that one-month period in the population that was still receiving drug, and whether or not that long-term exposure leads to

different risk profiles in the two groups.

DR. EAGLE: So, I think we agree. In the first month it is not really high dose dalteparin we are talking about; it is continuation of what is recognized as initial standard dosing in most countries that the study was conducted in. Certainly, the maximum effect is in the first month.

In terms of the major bleeding side effects, the slides show that beyond that first month period there was really not a sustainable difference between the two groups. Therefore, the risk/benefit certainly was greatest I the first month. Continuing the therapy beyond that didn't provide any difference in that therapy and we are really comparing to the point that was made earlier, more continuation and, shall we say, sooner in anticoagulation in patients that are at very high risk of recurrence.

DR. HUSSAIN: Mr. Schwartz and then Dr. Levine.

MR. SCHWARTZ: My question is to the

sponsor. My impression is that DVT leads to death often in cancer patients so the expectation from the consumer then might be that this study should show a difference in mortality overall, if that is true. Yet, it is showing on difference. So, I am wondering if you can comment on that.

DR. EAGLE: So, if we do look at the actual documented fatal PEs, they were numerically lower in the dalteparin group compared to the standard of care, recognizing that this study was more designed to look at the recurrence of symptomatic VTE and not really designed in a way to really bring that out.

DR. HUSSAIN: Dr. Levine?

DR. A. LEVINE: A couple of questions quickly, number one, I wanted to go back to the equivalence of the two arms and I had two questions in that regard. Chemotherapy itself may activate the coagulation system and be associated with DVT. So, my question is what numbers of patients on each arm were actively on chemotherapy? The second is what numbers of patients on each arm had central

venous lines, which can also be associated plaque? When was that equivalent?

DR. EAGLE: Because that is about chemotherapy, let me get Dr. Levine, had of the steering committee to address some of those issues.

DR. M. LEVINE: Hi, Dr. Levine. In fact, I reported in The New England Journal many years ago the association between chemotherapy and thrombosis. In this trial the two arms were very well balanced in terms of the number of patients on cytotoxic therapy and hormonal therapy. It is about 80-90 percent, completely balanced. And your second question was?

DR. A. LEVINE: As far indwelling central lines.

DR. M. LEVINE: Well, we talked about stratifying and so on, and it was less than 20 percent. Now, you have to remember that this study was started in 1999, finished recruitment several years later, and at that time people were using fewer central line catheters. In addition, the United States entered 147 patients in the trial but

the remainder were from other parts of the world where, at that time, central lines were less common.

I would say that now I think all our experience around the world is that many, many, many patients are using central lines.

DR. A. LEVINE: But my only question was were they equivalent in both arms?

DR. M. LEVINE: Yes.

DR. A. LEVINE: Then, a quick one is what was the incidence of HIT in the study arm?

DR. M. LEVINE: Agnes can answer that, but in the handouts they showed thrombocytopenia but the number of patients with diagnosed HIT, you know, with serotonin and so on and so forth, was just a couple--how many? Two or three?

DR. LEE: If I can have background slide 85, please?

[Slide]

During the study there were three patients that were reported in the adverse events as possibly having HIT. These are the three cases in

detail. Basically, only two of the patients had HIT antibodies that were detected to be present when the tests were done. However, both of these patients received unfractionated heparin so it is possible that the antibodies were actually generated as a result of that.

If you look at the first patient, patient 207-002, the onset of the thrombocytopenia is at 22 days, which is beyond the usual period when we expect HIT. However, that is what the investigator decided the drop in platelet count may be related to. The patient was certainly receiving chemotherapy. HIT antibodies were not actually sent off for but the study investigator decided to stop study medication.

For the next patient the onset of thrombocytopenia was at 12 days and the patient was not receiving any chemotherapy. HIT antibodies were detected, however, this patient did receive unfractionated heparin prior to study enrollment. So, when the patient was first diagnosed with DVT or PE they were started on unfractionated heparin

before they entered the study. Again, as a result of the drop in platelet count, study treatment was discontinued.

The last case was a little bit strange in that the onset of drop in platelet count was actually in the seventh month after randomized. In fact, the patient had already completed six months of treatment with Fragmin therapy, and at this point the patient was receiving chemotherapy. When they came in, they suspected recurrent thrombosis and the investigator, in fact, put the patient on unfractionated heparin. So, it seems odd that he or she would have reported possible HIT and, yet, administer unfractionated heparin as being the treatment. So, certainly in the three cases I think really it is arguable whether they were confirmed cases.

DR. HUSSAIN: Dr. Rodriguez?

DR. RODRIGUEZ: In slide 37 where the subgroup analyses are described, it was mentioned by several of you that the hematologic patients were sort of out of sorts, and it was alluded that

the group was very small and you couldn't make any statements about it. But really what did happen? Did they have more recurrence of thrombosis? Did they have worse survival? I wasn't quite clear how they stood out from the other patients.

DR. EAGLE: We haven't broken hematological out by survival. But if we can show slide 37 so everyone can see what we are discussing?

[Slide]

Effectively, if you look down the right-hand side of the screen you can see the number in the sample size, recognizing this is a subgroup analysis and the smallest subgroup in this whole study is the hematological group, again, recognizing it is a group of biologically different tumors, unlike the other groups where they are biologically the same.

Also, I would comment that this is based on four events, and four events only, with zero in OAC and four in dalteparin. Basically, I couldn't tell you the breakout in that small subset of DVT and PE.

DR. HUSSAIN: Dr. Hiatt, do you have any final comments before we adjourn?

DR. HIATT: Yes, if I could make one final comment.

DR. HUSSAIN: Please do.

DR. HIATT: Thank you. The open-label nature of this study--I will again reference some of the cardiorenal experience here. A couple of years ago we were reviewing ximelagatran for approval for prevention of VTE, treatment of VTE, and use in atrial fibrillation. There were two studies that we reviewed for atrial fibrillation, SPORTIF III and SPORTIF V. SPORTIF III was open-label for all the reasons that the sponsors articulated. SPORTIF V, though, was randomized, double-blinded where they did the sham measurements for INR and things like that.

It is a slightly different situation but I would like to make one point. In SPORTIF III the point estimate really favored ximelagatran versus standard of care, which was warfarin. That is the open-label study. In SPORTIF V the point estimate

went in the opposite direction.

I think to really understand what is going on with a symptomatic endpoint, which is what this VTE endpoint is clearly, you have to have double-blinding. I just think that there are biases that are apparent here and they were clearly articulated at the cardiorenal meeting two years ago, well described in the minutes of that meeting. And, the differences in design of these two studies was simply the open-label versus fully blinding and the conclusions of the studies were very different, and the committee voted based on Sportife 5, not SPORTIF III. That is my comment.

DR. HUSSAIN: Thank you. Very brief, really brief, please.

DR. PIANTADOSI: Very brief. I was involved in some of the adjudication for SPORTIF. We are not talking about atrial fibrillation. We are not talking about one pill compared to a placebo pill. We are talking about cancer patients. It is very difficult to double-blind them for six months where they are getting dummy

pills, dummy injections. It is a different population.

DR. HUSSAIN: And I think we recognize that. I would like to thank all who participated in the discussion this afternoon. We are going to go now for a brief break. We will get back here at 3:30 and begin with the open public hearing. Thank you.

[Brief recess]

Open Public Hearing

DR. HUSSAIN: This session begins with the public hearing. Prior to that, I will read the 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 that it is important to understand the context of an individual 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 competitor. For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. Thank you.

MS. CLIFFORD: Our first speaker is Mr. Steve Walker and Frank Burroughs.

MR. BURROUGHS: Good afternoon. I am Frank Burroughs. I am president of the Abigail Alliance for Better Access to Developmental Drugs. Some of you in this room know the Abigail Alliance.

I am going to try to briefly and succinctly talk about the ACCESS Act which was brought up at the last ODAC meeting. Again, I want

to thank you for being here. Also, the ACCESS Act was brought out in a recent piece in The New England Journal of Medicine.

The ACCESS Act would provide access to investigational drugs for cancer and other life-threatening illnesses--key words here--that show early sf and efficacy. Unfortunately, incorrect information is going out to the public about the ACCESS Act. It is important to read and understand the ACCESS Act to understand current FDA laws and regulations.

The ACCESS Act does not apply to just any investigational drug. The ACCESS Act applies to drugs that show--again key words--early safety and efficacy. Here is an important point. Every drug that the Abigail Alliance and others have pushed for earlier access to are now approved by the FDA. Of course, there are more drugs in the pipeline for cancer and other serious life-threatening illnesses where we need earlier access.

A few critics of the ACCESS Act over and over again use the ill-fated bone marrow, high dose

chemotherapy treatment in opposing the ACCESS Act. This is a completely bogus counter to the ACCESS Act. No clinical trial was required for this ill-fated therapy. A bone marrow, high dose chemotherapy was a combination therapy using a medical procedure and FDA approved drugs, and was not an individual investigational drug. As explained in the ACCESS Act, early access tier-1 drugs all require clinical trials and are part of the clinical trial process. The bone marrow, high chemotherapy treatment is not a tier-1 drug.

The ACCESS Act will actually increase clinical trial enrollment. With the use of modern science and modern statistical tools, placebos are not needed for clinical trials for cancer and other serious life-threatening illnesses.

Another point that is in the ACCESS Act, a patient must first try to enroll in a clinical trial before getting tier-1 access. With earlier access to investigational drugs for cancer and other serious life-threatening illnesses, we will have larger populations in the investigational

process and this will increase data on safety and efficacy.

The liability issue has been brought put. There is an easy answer to this. The liability issue is clearly addressed in the ACCESS Act.

The public clearly wants better access to investigational drugs for cancer and other serious life-threatening illnesses. What the public wants is clearly brought out in a recent poll done by the National Consumers League. Many cancer advocacy organizations and other organizations for serious life-threatening illnesses have endorsed the ACCESS Act and the number is growing.

Finally, let me finish before Steve Walker, our chief advisor, talks. There needs to be better representation of people who are fighting for their lives on the ODAC. The power to choose members should be broader based at the FDA and not ultimately up to one person. I am sure you will understand this, new and even opposing ideas can lead to progress and knowledge.

In closing, please remember to read and

understand the ACCESS Act. Thank you very much.

DR. HUSSAIN: Thank you, Mr. Burroughs.

MR. WALKER: My name is Steve Walker. I am chief advisor to the Abigail Alliance. I receive no compensation for my work as an advocate and I pay my own expenses for my advocacy work.

By way of my background, I have a bachelor's degree in geology and a master's degree in marine science. I am an environmental consulting business owner with 23 years of experience, and I am the widow [sic] of a wife who died of colon cancer. So, I have seen this system from the inside. And, I am a regulatory expert as well.

I am here today to speak to you about some concerns we have regarding the relationship between ODAC and the FDA. As a result of having nominated an eminent oncologist to this board, we learned how the selection process works. We found that it is not as transparent and probably not as effective as it should be. Our experience in researching some of the issues between ODAC and the FDA also led us

to ask the question whether the relationship between ODAC and the FDA is too close.

So, I am going to explore two questions today. Does the Office of Oncology Drug Products have too much control over ODAC? And, is ODAC too close to the Office of Oncology Drug Products? Now, it may seem like the same question but it isn't and we will find out why.

Before moving forward, I wish to make it very clear that I am not questioning, nor is the Abigail Alliance questioning the integrity, the qualifications, the intentions or the motivation of anyone working at FDA or anyone sitting on this board past or present. But the information we are going to provide comes in some cases from individuals whom I will identify as the sources of that information.

The first thing I am going to talk about is how ODAC members are selected and who selects them. Most of the people in this room know something about the nomination process. Certainly the members and everyone at the FDA do. I am not

sure if the audience knows about it, but there are really three steps. There is a nomination process which is an excellent process. It is very transparent. You can get on the web page and find out how to do it. Anyone in this room can nominate anyone you want to the ODAC. There is a screening process that takes place based on some requirements in the charter. How that happens is murky but you can find the information. But the selection process is completely opaque. You can't find that out.

As to the process in participating in the nomination process, we found out nominations are sent to the division. The division decides who they want. Of course, the other side of that decision is they decide who they don't want. The division is the Office of Oncology Drug Products. So, the people who come to this advisory committee for advice pick the members of this committee. Now, there are levels to the selection process but the ultimate decision is made by the Office of Oncology Drugs for subsequent approval by someone

in the Commissioner's office.

I inserted this slide just as a confirmation. Our nominee received a letter from the office and the letter thanks the nominee for offering to serve and refers to the ODAC as, and I quote, the Oncologic Drugs Advisory Committee at the Food and Drug Administration, Center for Drug Evaluation Office of Oncology Drug Products. One might argue, looking at the laws and regulations, that this committee doesn't actually reside under the Office of Oncology Drug Products. This letter is from, and signed by Dr. Richard Pazdur, the Office of Oncology Drug Products Director. So, unless this letter is an exception, the decisions are made in the Office of Oncology Drugs.

Now, to understand why this might be a problem we also have to look at what else the office controls about advisory committee meetings. The office controls when to convene a committee, the subject and drugs to be discussed, the content, and I think we saw earlier today with the Fragmin presentations from both sides the clear spin of the

FDA briefing documents--and that is the right word.

They also control who sits and votes as members in any particular meeting. They control who sits and votes as consultants. And, they control what questions are posed for a vote. And, as we all know, they decide what to do with the advice they get from ODAC.

To put this situation in further perspective, we need to look at the laws and regulations that govern advisory committees, and the law is the Federal Advisory Committee Act. It is very clear the advisory committee will not be inappropriately influenced by the appointing authority or by any special interest but will, instead, be the result of the advisory committee's independent judgment.

Now we look at the regulation, and the regulation is entirely consistent with the law and goes further. The regulation says that committees will be utilized to conduct public hearings, which we believe is a very important part of the advisory committee process because it is the public's only

window into the inner workings of the FDA review process. Voting members should not be representatives of the group that nominated them, nor should they represent any group they are affiliated with. For example, someone who belongs to the American Society of Clinical Oncology should not be coming in here with the talking points of the American Society of Clinical Oncology. Their independent judgment should be based on their own experience and expertise.

The committee should be balanced fairly with respect to points of view regarding FDA's duties. When I look around this table and I look at the membership of this committee, I see universally people with resumes that look very much like the director of the Office of Oncology Products, all from academic institutions or NCI centers; all clinical trialists. I don't see a community physician in here. I don't see a country oncologist on this board, and they have view points about what happens here. And, the committee should be constituted in ways to assure that its advice

and recommendations are the result of the advisory committee's independent judgment.

So, it is quite clear that the intent of the law and the regulation is that the purpose of an FDA advisory committee is to provide balanced, independent advice in a manner open to the public.

The second question I am going to talk about, which I think is also a very important question, is should the Office of Oncology Drug Products control the membership of ODAC? Actually, this is the same question. And, does this practice compromise the independence of ODAC? Anyone who manages people knows that a manger over time puts his stamp on everything he manages or she manages. And, over time memberships expire on this committee and the Office of Oncology Drug Products picks its members, and the view points could conceivably get closer and closer together until suddenly there is no dissent on any fundamental issue.

Next I am going to address some concerns regarding what appears to be a too close,

arm-in-arm relationship between ODAC and the Office of Oncology Drug Products. I said I was going to put some names up here, and this is where I do it. Before moving on, I wish to repeat that I am not questioning the integrity or motivation of any of the fine people, past and present, who have served on this committee or who work at the FDA. But in order to make the points I am about to make, mentioning these names is unavoidable.

At the last ODAC meeting three members came to the end of their terms. These are the three members, Dr. Martino was the chair. In his parting thanks, which certainly was appropriate because being a member of this committee requires a great deal of effort and time and sacrifice and anyone who agrees to do it deserves our thanks. So, I have no problem with them being thanked. Speaking collectively of the three, Dr. Pazdur commented that they had developed a very close working relationship with many at the FDA.

Speaking regarding Dr. Martino, Dr. Pazdur noted that she was always available to FDA staff

for consultations or to simply bounce off ideas. Speaking of Dr. Cheson, he commented that Dr. Cheson had consulted on numerous occasions outside of ODAC meetings on end of Phase 2 meetings and provided official and unofficial consultations with FDA staff. Finally, speaking of Dr. Reamon, he commented that his assistance with end of Phase 2 meetings and other difficult questions and issues was much appreciated.

Where I am going with this has much more to do with the relationship than it does with the persons. It shows that between the Office of Oncology Drug Products and ODAC there is a close internal working relationship. It doesn't conjure up an image of an arms-length relationship which is what is required by the statute and the regulation. Instead, it is, rather, a very close, routine working relationship taking place out of the public view.

It raises I think some very important questions, and we can all think of our own questions about what this means. Are members of

ODAC working directly with FDA on regulatory strategies for specific INDs outside the public meeting process? Do ODAC members work with FDA on active INDs prior to scheduling of meetings for an NDA or BLA for those drugs? They assist and attend end of Phase 2 meetings. I think we have an answer to that. Somehow they are involved. Have any of the drugs they have worked on with FDA been later brought before ODAC for its advice?

There has been a lot of talk about conflict of interest with members and I don't put much stock in a doctor having worked on a clinical trial and received somehow $10,000 or worked in a department that received money from Pfizer to work on another drug and the doctor didn't work on that drug but he was in the department. I have been a scientist for 23 years and I just haven't really seen that, and I don't think anybody on this board is influenced by the fact that they worked on a clinical trial or they did some consulting.

But I think this is a real conflict of interest. I think you can't be both an outside

advisor and an inside consultant. How can a committee provide balanced outside, independent advice to FDA? The committee roster and agenda are entirely controlled by the FDA staff asking for that advice. I think the answer is, well, individually you can be but as a committee it is very difficult to make the argument that this committee is outside and independent.

How can any member or the committee as a whole provide outside, independent advice to FDA if some or all of the members also work out of the public view directly with FDA to set agency policy or strategies regarding INDs that may eventually come before the committee? And even if it not a specific IND that comes before this committee, if you are working on a similar drug or similar development program that advice is going to translate into others. Then you come here to this meeting, and you are thinking back on what you told the FDA two years ago about a drug you were commenting on, and a similar drug is in front of you and you don't want to change your mind even

though it is a good drug.

I think what we saw today in this last presentation on Fragmin is how important this process is. I can be against approval of a drug. Some people probably think I am never against approval of a drug but sometimes I am. This drug should be approved. They won. They did simple, straightforward, perfectly understandable analyses and, as a care giver, I know what it is like to have to stop medication when a patient is dying. What you, guys, did was an incredible fishing expedition for subgroup analysis and post-hoc subgroup analysis looking for a data set that would give you a negative number. We would never know that happened had we not had this meeting today. So, that is how important this is.

This relationship also creates procedural problems. Deliberations of advisory committees are by law and regulation to be open to the public. The only way they cannot be is through a closed committee meeting process for which there are very specific rules, or through a specific formal

assignment from the FDA to a member of the committee. This is in the law and regulations, by the way. I am not making this up. You can get the links to these regulations on the FDA's own advisory committee web page.

Informal conversations, the chairman at the end of a phone call, that is not anticipated as being a function of the Oncologic Drugs Advisory Committee. The law and regulation are very clear about what the function of this committee and every committee that advises the FDA is. The ODAC is not supposed to be a part of, an extension of, or a tool of the Office of Oncology Drug Products. ODAC is intended to advise and instruct the office from a vantage point that is clearly outside and independent of the FDA, in a manner openly visible to the public.

We are one of the groups that, when we think something is wrong, we try to propose what to do about it. We think, first, we need to remove any and all nomination and selection tasks for ODAC members and other voting members from the Office of

Oncology Drug Products and probably from CDER. It needs to be in an independent office whose goal is to properly run advisory committees in accordance with the letter and the intent of the law and regulation. It absolutely cannot be under the control of the people who come to this committee for advice.

Again, everybody on this committee is from an academic center or NCI. Every one of you is engaged in conducting clinical trials. Where is the person who knows how to model as opposed to doing statistics? Where is that country oncologist who doesn't have access to clinical trial drugs? They have a stake here. Their patients have a stake. Why is there only one patient representative when the patients? There should be two so at least you get different points of view from patients.

Require that all nominations to ODAC be a matter of public record, including identification of both the nominating and nominated parties. I doubt if anybody here would have a problem with

that, but that is the way it should be. And, we should know everyone who is nominated, or at least everyone who is nominated and survives the initial screening process. If somebody nominates a plumber, obviously they may be a great plumber but they are not going to get on this committee. I don't need to know if somebody nominated a plumber. But if that thing makes it through the screening process I want to know. I want to know who is making the decisions and who is being rejected and who isn't. That tells us whether the system is working.

We think that there should be a limit on all interactions between FDA and ODAC committee members to the open committee meeting process. That is the intent of this board, to be a window to the FDA. It is one of the primary reasons for the existence of advisory committees, excluding, of course, those rare occasions where there might be a specific formal assignment to a member and, as we saw today, the FDA can certainly use the help, or in a closed committee process as defined in the

laws and regulations.

We need to end ODAC member participation in FDA internal proceedings regarding active INDs, such as end of Phase 2 meetings. While you are sitting on this committee you just simply shouldn't be there.

Imagine a scenario of a sponsor walking into an end of Phase 2 meeting hoping to ask for accelerated approval based on a compelling Phase 2 trial, and sitting next to the director is the chairman of ODAC. Now, I don't know if this ever happened. I hoped it never happened. But if the director is saying one thing and the chairman of ODAC is backing up that opinion, the sponsor has lost before they have even started. And, one of the functions of this committee is that it is sort of an appeals process and that is eliminated if the members are working inside.

Post all committee vacancies no less than six months prior to the vacancy opening up on the FDA's advisory committee web page. I did see on the roster that the terms are on there but it

wouldn't hurt to just have a link to when these vacancies are up so if somebody wants to nominate someone, they can get it in time. What I head was that it takes months to process a nomination, which means you have to get your nomination in three or four months before the vacancy.

Make the advisory committee member selection process and duties more transparent, and do it right now. I should not have had to find out by trying to use the nomination process--call to find out about the status of our nominee and then find out that our nominee had been rejected by the office, and then have to chase around in the agency, making phone calls to my contacts there trying to confirm if that is, in fact, how it works. In fact, that is what we did. I should be able to go to the advisory committee web page and find, from nuts to bolts, every step that happens in this process.

I will leave you with I think a very clear and concise thought, and I hope that you all leave here today thinking about what the function of this

committee really is, especially at the FDA because I don't blame committee members for being nominated and being selected and doing their job in the context that the FDA tells them they are supposed to do their job. But I do blame the FDA for letting the administration of this advisory committee get so far off track. They have the regulations. They have the laws and they know the intent, and it shouldn't have happened and we need to do something about fixing it, and we need to do it quickly. The member selection process, administration and utilization of advisory committees by FDA should be reformed to ensure that the intended balance, independence and transparency to the public is achieved at every single meeting, with every single appointment, and with every single decision. Thank you.

DR. HUSSAIN: Thank you, Mr. Walker.

MR. WALKER: I will answer questions if anyone has any.

DR. HUSSAIN: Unfortunately, we are going to have to go the committee discussions but we

appreciate your comments.

Questions to the ODAC and ODAC Discussion

So, we will begin the discussion among the members of the committee. During the discussions we can entertain questions to the sponsor, if there are any. We have a long list of questions that we have to vote on and address, and some of it requires some discussion so I am going to ask that we perhaps take half an hour to have the discussions of the committee and then begin the voting process question by question, and perhaps discuss these questions as we get to them.

Dr. Zalkikar, from the FDA, had some questions that she didn't get a chance to ask in the earlier session, to the sponsor, I believe.

DR. ZALKIKAR: No, my question is not to the sponsor, but I just want to draw the committee's attention to the efficacy analysis in this application. The primary efficacy endpoint is recurrence of VTE and when you see those Kaplan-Meier curves, one has to remember that the deaths are used as a censoring mechanism. That is

based on the assumption that the two failure processes, which are VTE recurrence and death, are independent. You know that is not true because the death reduces the probability of subsequent VTE recurrence to zero. So, we would like to hear the committee's discussion regarding the meaningfulness of the primary analysis, efficacy analysis, whether it should be just the efficacy analysis or the primary endpoint, the way it was defined by censoring deaths, or whether it should be really the analysis of the composite of the VTE recurrence and death.

DR. HUSSAIN: Can I perhaps ask Dr. Harrington or Dr. George to comment on the questions that were raised?

DR. HARRINGTON: I can comment but I know Steve raised it earlier.

DR. GEORGE: Well, the issue with competing risk is not so much the independence of death, but it is that if, in fact, there are these competing risks you can have a situation--if your purpose is to estimate the cumulative incidence of a cause or

a failure cause, in this case the VTEs, if you have a lot of competing risk as you do with deaths, your overall cumulative incidence, which it looks like is what they did here and that was my question earlier, it looks like what was done in the paper-I couldn't completely reconcile with the fact that there was a lot of censoring due to deaths.

That is, the final answer for the six-month cumulative incidence of the cause of VTE looked to be about the same as you would get if you treated deaths truly as a competing risk and not counted it as censoring. That is probably because they were balanced about the same in both groups. But it doesn't always work out that way. That is why I asked if it had been done and I couldn't reproduce it exactly.

A more important feature may be what Steve mentioned, that the relative risk shouldn't be affected in a major way by that analysis. So, I think a more important issue here in the analysis has to do with is the accurate certification of those events. That is, if there is even a chance

that there was a differential false-negative rate in the groups, especially caused by things that might have occurred near death, there is potentially a problem. And, it doesn't have to be very big. That is one of the issues that concerns me.

That is, what I am talking about here is we know that we missed some VTEs. That is inevitable. We always do in these classifications, whether it is because you are waiting for a symptom that you didn't see or something, but you miss them. Presumably you miss them in both groups. The question is, is there a differential missing. This is the false-negative kind of thing. If, in fact, for some reason, either due to the way the observations were done or stopping treatment, or things that happened near to the time of death, if, in fact, there was a higher percentage missed on, say, the Fragmin group that is a problem. The issue is it doesn't have to be very big because there were so many deaths; there were so many of these competing deaths. My rough calculations are

if the differential were about ten percent it would completely change the results.

These are things that we have no data for on this study. So, that is all hypothetical. If you assume though that they are the same in the two groups, then there is not a problem. Although the incidences, of course, are lower, presumably the relative risk would still be about the same.

DR. HUSSAIN: Dr. Harrington, anything to add?

DR. HARRINGTON: No.

DR. HUSSAIN: I actually have a question to the FDA. First of all, is there a low molecular weight heparin that is approved in this indication in cancer patients?

DR. RIEVES: No. There are four drugs that are on the market with treatment indications in VTE but they are in the broad population of patients. There are no subsets indications. For example, there are no indications in neuromuscular disease, cardiac disease, cancer--

DR. HUSSAIN: But not in this indication?

DR RIEVES: In a broad population, that is correct.

DR. HUSSAIN: And these agents, we are all using them anyway. Any questions from the committee members? Yes?

DR. RIEVES: Dr. Hussain, before we move to the questions directly, I would like the op to briefly frame the very first question because that is coming from the trenches, from the review staff, and one of the charges to the review staff was to resolve this issue and we have had a great deal of challenge with that issue.

There are two aspects of this question, the very first question, is it safe; potential safety signal, given the situation that we have a single study. We have products on the market that are safe and effective for the treatment of VTE. The review team in general, in reviewing the data, anticipated that the rates of study drug discontinuation and the basis for those study drug discontinuations would be balanced between the study arms. Or, if they are not balanced, then the

imbalance is readily resolved by this study data. For example, study drug discontinuation due VTE is readily explained.

On the other hand, the challenge here is that we noticed that for the study drug discontinuation due to death there was a fairly marked imbalance. It is a much higher rate in the Fragmin group.

The review team considered the possibility that may be because of the different patient management. Cancer patients can't continue oral anticoagulant therapy, for example. In an attempt to address that issue we analyzed the outcomes looking at the exposure times. As out table showed, the review team was left with the observation that we could not account for the study drug discontinuation due to death imbalance based on exposure time.

So, in that situation the review team came away with the observation that this is an unresolved issue. So, this lack of a resolution is open to many hypotheses as to why it may have

happened, and that essentially forms the basis for the question to the committee. Your opinion with respect to how important is that issue, that unresolved issue.

DR. HUSSAIN: This is a question to the sponsor. Again, as I understand it, it is a coding issue we are talking about that gives the impression that there were more discontinuations secondary to death in the experimental arm.

DR. RIEVES: In a sense that is right. That is a large part. It may tie into coding. There are multiple explanations for it and, unfortunately, we have not been able to resolve that based on the database.

DR. HUSSAIN: Have you looked into did this come from one investigator, from one group of patients, from one nurse, from something that would explain it perhaps?

DR. EAGLE: No, it was reported across the study. It wasn't particularly one investigator. Again, I would emphasize that we are talking about the last 10-14 days for that differential in the

survival, and that is about the differential that occurred in median exposure as well. So, we are really talking about just a few days difference. And, discontinuation is really defined by saying I am only counting patients up to the day they took the medication. If they die the next day I won't count it on that analysis. You know, cancer death is a predictable event. So, therefore, there is potential that doctors would be informally censoring, stopping treatment a day or two before, in which case they would come off that therapy and not be counted for other reasons.

DR. HUSSAIN: Dr. Rieves, while we are on this subject, what potential speculative points could you make?

DR. RIEVES: Right, as has been described, the patients were managed differently between the two study groups inherently with respect to oral anticoagulation versus Fragmin. Conceivably, there may be factors that are simply not in the database that are subjective physician management decisions that were not captured in the study database. That

may explain it.

On the other hand, of course, as reviewers, one of the considerations is that it might be a study drug effect. So, it behooves us in the trenches, reviewing the data, to resolve that possibility and, unfortunately, we are in a situation where we do not have resolution of that issue.

DR. HUSSAIN: Dr. Bukowski?

DR. BUKOWSKI: I am trying to understand what kind of a study drug effect it could be given the drug we are dealing with, which has been utilized quite widely, perhaps not for six months the way it was in this trial but utilized. So, do you have any speculation on what it could be?

DR. RIEVES: Well, we have attempted to look--for example, one of the important considerations here is notice that it is not simply the drug itself as to whether it is safe and effective; it is the drug regimen. The drug regimen that is under consideration here is approximately three-fold higher in terms of dose

than the prophylaxis, which is the marketed dose at the current time. So, considerations, for example, are could the higher low molecular weight heparin alter potassium outcomes? We have not been able to resolve the issue essentially. It is not explained by higher bleeding rates. Essentially, we are left with an unresolved issue.

Given the track record, especially in cardiovascular diseases, we have to have a relatively healthy skepticism when we have a single study signaling a possibly very important safety signal. As you well know, with the CAST study and so many other cardiovascular studies, a single observation has led to cumulative concerns over time.

DR. HIATT: Can I comment on that?

DR. HUSSAIN: Yes, please.

DR. HIATT: There are examples in cardiovascular medicine where an anti-thrombotic agent could be paradoxically pro-thrombotic. I don't think that is going on here at all. What I find interesting is that the real hypothesis that

is being tested is a superiority hypothesis, and I think if you express it in terms of event-free and alive you gain superiority. But if you are looking at--sorry. If you are looking at event-free survival they really look equivalent, in my mind. If you just look at the single endpoint of VTE without the concern of the death censoring possibility, then you get superiority. So, the worst, in my mind that it could be is equivalent to standard therapy if we are worried that potentially there could be a differential in events that were asymptomatic and not picked up.

The only explanation they could come up with is that particular one, that, for some reason, there was a higher sort of silent thromboembolic event rate near the time of death in people on dalteparin. The only way to pick that up would be to do a study where you have routine surveillance occurring throughout the study and that didn't happen.

But I don't think it is a pro-thrombotic mechanism. I also think the agency came up with

the conclusion that it wasn't a hemorrhagic mechanism either.

DR. HUSSAIN: Dr. Hiatt, what is the routine surveillance that you are mentioning? What would have to be done?

DR. HIATT: Well, I think in other studies like this you could at, say, three months and six months just do a duplex ultrasound in everybody. That way you would capture whether there is a differential. I think the assumptions by the sponsor are that there really isn't a bias in the reporting, and that all symptomatic patients presumably have an equivalent rate of asymptomatic thrombosis as well, and/or they had asymptomatic and it didn't really matter because they didn't contribute to the endpoint. But if death was confounded, then there could have been a differential, and the only way to resolve that would be to have some screening mechanism. Duplex screening would not be unreasonable. Spiral CT might get to b a little more expensive. VQ scanning is inherently inaccurate. But there are

mechanisms to do that where you could have resolved this particular issue.

DR. HUSSAIN: Dr. Harrington?

DR. HARRINGTON: Thank you. So, this issue of the deaths while on treatment is certainly an important one and I guess I need some clarification here from the FDA on their table on slide 28 because, for me, the interpretation--even though I am a statistician, I am still getting confused by these data.

So, let me ask specifically about one of the lines and it might help me understand things. I think the main question here is are people dying more rapidly apparently while on a particular agent, or are they dying more rapidly having been exposed to one of the two treatment arms?

[Slide]

In the first line in that table where there are 17 versus 11 deaths with less than one month's exposure, among the 11 are all 11 of those on the oral anticoagulant arm patients who died while on that arm, or does that include patients

who died having been exposed for less than a month but, say, were exposed for a week, came off therapy but then died during week three or week four? How did you count deaths here and what did you do to censor those deaths?

DR. RIEVES: This is a table that we had requested the sponsor compose for us. This is a table on-treatment deaths.

DR. HARRINGTON: On-treatment deaths?

DR. RIEVES: These are on-treatment deaths. Perhaps, Dr. Hussain, at your discretion, the sponsor may want to address this because this was one of our attempts, our directives to the sponsor to try to resolve the issue and this was one of the analyses that resulted.

DR. HARRINGTON: That helps me understand this table. This table then does not really resolve whether exposure to the drug increased the death rate. It still is consistent at least with the presumption or the assumption that patients on the oral anticoagulant may be taken off that sooner in the course of their disease and may die

subsequently, whereas people still may have stayed longer on the Fragmin arm and died while on treatment.

DR. GAFFNEY: If I may comment on this? My name is Michael Gaffney. I am a statistician with Pfizer. I think this is a critically important thing to understand for the committee and I can address it through Dr. Harrington's issue with slide 28, particularly the first line.

The first thing to say is that FDA is completely right to see this as a signal and to ask the question about it. However, where we disagree completely is that the data of this CLOT study does not provide an answer. There is an answer within the CLOT study which explains this apparent discrepancy in their on-treatment analysis.

If we go their slide 28, in that first line there they have 17 deaths on Fragmin and 11 on OAC. These are the ones, as people have indicated, where they ticked the box that treatment was stopped because the patient died. What you don't see in that interval is that there were overall 25

deaths in month one on Fragmin and 31 on OAC.

Now, what is the explanation for that? The explanation is censoring due to the benefit of the drug. There were 12 VTEs on Fragmin in that time point and 34 on OAC. Of those 34, 8 of those patients subsequently died within that interval, the 30-day interval. For the 12 patients that were on Fragmin, 3 of them died. So, if we just take as an explanation the benefit of the drug, the apparent discrepancy in on-treatment mortality is completely wiped out. It is 20 versus 19.

As you go down that time interval, the explanation for the discrepancy changes from VTE because the probability of VTE goes down dramatically, but is answered by the clinical management issues that both Dr. Lee and Dr. Craig Eagle have spoken to. So, there is no mortality difference. There is an explanation within the data and the committee has to understand that.

DR. HUSSAIN: Just so that we understand this, when I look at these death rates they look to me higher in the first month or less than one month

in the experimental arm. How do you explain that away? Presumably when a patient went on treatment they didn't come off treatment like three hours after. So, they started and within the one month they are still on study.

DR. GAFFNEY: Right.

DR. HUSSAIN: So, for the first month, the second month and the third month there is what looks like higher death rate.

DR. GAFFNEY: The reason why there is a higher death rate, particularly in the Fragmin group relative to the OAC, is because deaths were censored disproportionally, and they were censored primarily because, the way the protocol was run, as soon as a patient had a recurrent VTE they were taken off the treatment. There were 34 recurrent VTEs in that one-month interval in the OAC group. Eight of those patients died subsequently within that 30-day interval. There were 12 in the Fragmin group and 3 patients subsequently died within that interval. If you add those to the ones that were counted there, it is now 20 versus 19.

So, there is a very biased censoring mechanism going on for two reasons in this trial. One is the benefit of the drug in preventing VTEs and the second one is the clinical management that we have heard about, having to remove patients from the oral treatment prior to the death.

DR. HUSSAIN: Thank you. Dr. Link?

DR. LINK: Maybe it is clarified. So, this is basically deaths on study versus deaths. So, you got taken off study so you are not a death anymore. The lay pediatrician got it!

[Laughter]

DR. HUSSAIN: That makes two of us! I finally got it! Yes, Mr. Schwartz?

MR. SCHWARTZ: Thank you. When I looked at the material we were given prior to this meeting, this table also struck; it was startling. I searched the literature. I should note that there is more to this table because in the materials we received it extends through month seven through eight, and in the investigational arm there were virtually zero deaths and also in the control.

So, I looked for study drug effect in the literature. I didn't find anything direct, but I did see something that was indirect that I thought was startling but, of course, I am a lay person and I will leave it to the committee to judge the significance. In Thrombosis Research, 2001 Dr. Rickles writes: Thrombosis in cancer appears to be an over-exuberant host response in an attempt to limit tumor growth. It is a leap, of course, to connect the study drug effect to that, but indirectly it seems plausible to me that in dealing with the thrombosis we may be inadvertently increasing the risk of cancer progression.

DR. HUSSAIN: Dr. Lyman?

DR. LYMAN: I don't know if this helps at all, but we are in the midst of a comprehensive, systematic review under the auspices of the American Society of Clinical Oncology in supportive clinical practice guidelines for VTE prevention in the cancer population, and this includes reviewing all randomized, controlled trials in medical primary and secondary prophylaxis, as well as

surgical secondary prophylaxis, limited to cancer studies. While that is an ongoing process, it has not been published and the guideline process is under way, we have found nothing in all of the trials that we have identified, and we feel the search is complete at this time, that would raise concerns in the context of nothing being found there. I find it reassuring that this explanation as a drug effect seems less compelling I a body of evidence that suggests the lack of such events. So, I think we need to keep this in the context of a wealth of randomized, controlled trial literature as opposed to, you know, something that might be identified in a laboratory finding.

DR. HUSSAIN: Dr. Harrington?

DR. HARRINGTON: This is by way more of a comment and it cycles back to something that Dr. George said earlier. So, now that Dr. Link and I both understand what is going on in this table, essentially what happens in this table is that a biased ascertainment of an endpoint can lead to apparent differences which are not real. So, here

the biased ascertainment was death, and the ascertainment bias was either using patients just on study versus using everybody.

Of course, the flip side of that coin that I think is the conundrum for the sponsor is if there had been a biased ascertainment in the VTEs for perhaps another reason, perhaps not for censoring due to death but because of timing of the measurements or the aggressiveness with which symptoms are measured, then the same thing could be happening. There could be an apparent difference in the VTE rate that is there maybe partially due to a biased ascertainment.

For me, I think that is the key issue. It was raised by Dr. George earlier. He did a back of the envelope calculation and said ten percent ascertainment bias rate in the Fragmin arm versus the OAC false-negative rate might lead to the results we are seeing here. So, I guess, although it was raised earlier, I think quite articulately, what I would like is for the sponsor just to come back to this point a little bit and give us

whatever they know, whatever they believe about the equivalence of the ascertainment in the VTEs on the two arms. I know you have done it before but, for me, it is the critical point. I would like to hear it just one more time, why you believe you have minimal ascertainment bias on those two arms.

DR. EAGLE: I will get Dr. Lee to address that issue.

DR. HARRINGTON: Fine.

DR. LEE: Thank you. I will try to keep it brief. As I said, we contacted patients every two weeks and we instructed the patients to contact us when they have symptoms. When they contacted us, that triggered pre-specified algorithms for investigations. So, basically, the investigators, nurses were mandated basically per protocol to investigate all the symptoms that were reported by patients.

Now, it is possible that some patients under-reported their symptoms and some patients are, you know, more concerned about their symptoms. But I don't really understand how that could

really differ between the two arms.

Also, when we look at the adjudication results, the centrally adjudicated results by blinded reviewers, experts looking at thrombotic outcome events, and so on, and compare that to the local investigators there was absolutely no difference in the true positives, false positives, false negatives. They were identical in the two treatment groups, suggesting that there was no under-reporting or over-reporting of the two sides at all.

Lastly, these are symptomatic events. Patients are unlikely to go away and say okay, my leg is painful and swollen and I am short of breath but, if you are not going to do tests, I am just going to crawl away and ignore them. They are going to call you. They are going to harass you. They are going to say I need testing done. This is uncomfortable; do something about it. So, it is very unlikely, to me, that the investigators could have ignored these symptoms because they were primarily triggered by patients.

DR. HARRINGTON: So, just one follow-up question then. You had a nice algorithm, an every two-week schedule and an algorithm for following up reports on that.

DR. LEE: Right.

DR. HARRINGTON: Do you know between the two treatment arms how many of the symptomatic events were reported out of cycle in the OAC arm versus, at the two-week boundaries, on your Fragmin arm?

DR. LEE: Well, what I can say is that every time a patient reports symptoms and they get investigated, it would have triggered an unscheduled visit.

DR. HARRINGTON: Do those differ by arms, the unscheduled visits?

DR. LEE: Absolutely not. I showed that I a slide for the frequency of contacts for all the unscheduled visits, and that has to be registered because the patients have to come in for testing. They can't just do it by phone. So, they have to come in for testing. So, on slide 34 now, the

unplanned visits are the same in the two treatment groups.

DR. HUSSAIN: A question to the sponsor, are there any planned trials to look into this further, or is this the trial that you want to use for the expanded indication?

DR. EAGLE: This is the trial that we feel is significantly providing evidence of efficacy that we want to use.

DR. HUSSAIN: Dr. Link?

DR. LINK: I just have one question. So, this has been approved already for this extended treatment in other countries? Is the extended treatment the same as this?

DR. EAGLE: Yes, that is correct.

DR. LINK: The same schedule?

DR. EAGLE: Correct.

DR. LINK: So, do you have any sort of reports from those of untoward effects in the last five months of treatment?

DR. EAGLE: Again, this has only been happening in the last 6-12 months and at this point

we have no data to answer that question.

DR. HUSSAIN: Dr. Grillo-Lopez and then, Dr. Hiatt, if you have any final comments before we go to the questions. Dr. Lopez?

DR. GRILLO-LOPEZ: Since I am the industry representative and not allowed to vote, I would like to express my opinion.

This study clearly met the primary endpoint and the FDA, in their presentation, used exploratory analyses to call into question the validity of the primary endpoint and the results. Exploratory analyses are traditionally not allowed by the FDA, the sponsors are not allowed to use exploratory analyses in relation to an endpoint or its results. And, the FDA should apply that rule to themselves, just like they apply it to the sponsors.

Now, the pattern, when I make a controversial comment like that, is that Dr. Pazdur immediately asks for a turn so I expect he will do that. You might put him on the list after me.

DR. HUSSAIN: Dr. Hiatt is after you.

DR. GRILLO-LOPEZ: I have one more thing to say. I believe that, yes, there was a potential red flag with death. In my mind, the most telling and the most important slide is the exposure slide number 44, the Kaplan-Meier graph for overall survival. It shows that overall survival was the same for both groups. Thus, the time to death was the same for both arms of this study and, therefore, death is not a factor affecting the primary endpoint.

Now, I had some concerns, which is why I asked my question earlier on because coming to that conclusion depends on whether the censoring rules have any effect on this. Was there any imbalance, particularly in observation time or exposure to drug in the two arms of the study? But after speaking with Dr. Levine and Dr. Rickles, they assured me that there was no significant difference in the two groups in terms of observation time or exposure to drug. Therefore, I have to conclude that this is a very valid Kaplan-Meier curve and the conclusions that can be drawn from it are

valid. Because of all of the above, if I had a chance to vote, I would vote positively on the questions posed by the FDA.

DR. HUSSAIN: Thank you. Dr. Hiatt?

DR. HIATT: Just a final clarification. I am looking at the sponsor's slides and I see that death was counted both as an outcome event and a couple of slides later as a safety event. Is the sponsor viewing mortality as a possible modifiable endpoint or really as a safety endpoint? The reason I ask is if it is an outcome event, then I think ITT is the best way to look at it. If it is a safety event, then on-treatment is probably the more conservative approach.

DR. EAGLE: In the study it was looked at as a secondary endpoint effectively but again, of course, mortality can then be classified subsequent to that analysis as a safety endpoint. But it was designed to be a secondary outcome measure.

DR. HIATT: Thank you.

DR. HUSSAIN: Thank you. Dr. Pazdur, Dr. Rieves, any finally comments before we go to

questions?

DR. PAZDUR: When it comes to exploratory analyses and it comes to safety, and we are dealing with the potential of deaths here that are unbalanced potentially or unexplained signal, I should say, I don't think the issue is whether it is an exploratory analysis or not. I think we, as a public health agency, have an obligation to bring this out to the American public for discussion. Initial t DR. HUSSAIN: Just out of curiosity, the dose that you are using in the study, have you used it in any other indication?

DR. EAGLE: Again, as has been acknowledged, in the immediate treatment for VTE the initial treatment has been used in that setting, again, emphasizing that is in an up to ten days setting.

DR. HUSSAIN: So, this is not a unique dose in this setting?

DR. EAGLE: Not at all but, again, emphasizing that in the U.S. it is certainly not approved for treatment of VTE at that dose but in

many other countries where the study was conducted it is approved.

DR. HUSSAIN: Thank you. Can we have the questions up perhaps so we can begin? We have multiple questions to answer. The first one deals with the safety.

The question specifically that we are asked to vote on is do you regard the study drug discontinuation due to death finding as sufficient to preclude the approval of the application until the issue is resolved with additional clinical studies?

The safety concerns are summarized on a slide and in your handout. Do you want to discuss any point here or do you feel like you are ready to vote? All right. So, Dr. Hiatt, I am going to ask you to give us your vote and briefly, perhaps in one sentence, if you are voting yes or no why you are voting yes or no.

DR. HIATT: Well, the overall mortality risks are obviously superimposable

DR. HUSSAIN: You are going to have to say

yes or on first. Do you regard the drug discontinuation due to death as sufficient to preclude the approval of the application until the issue is resolved with additional clinical studies?

DR. HIATT: I will vote no.

DR. HUSSAIN: And do you want to, please, explain briefly?

DR. HIATT: It is unexplained and the sponsor said they didn't plan to do any further studies. I think what allowed me to vote no is that if you look at event-free survival--if you look at the proposed labeling which claims superiority, I am a little comforted by that finding. But I do think it is unresolved. I think it should be resolved but does it raise it to the level where you would not approve this for the indication, I will vote no.

DR. HUSSAIN: Thank you. Mr. Schwartz? For the people answering, please identify your name and then give your vote.

MR. SCHWARTZ: Karl Schwartz. My vote is no.

DR. HUSSAIN: Any reason for voting no?

MR. SCHWARTZ: In and of itself, this is not enough but there are other questions I have. I am also on the fence about this. It was something that concerned me. I think the explanation is plausible so I wouldn't rule out approval based on this alone.

DR. HUSSAIN: Thank you.

DR. GEORGE: Stephen George. I vote no. I find the whole issue of this study drug discontinuation due to death both misleading and sort of a red herring. It is off base, to me, in that it obscures some of the other more important issues. I mean, remember, it depends on the definition of what discontinuation is, one day, two days, 14 days, those kinds of things. So, I find none of the things I heard, they were either just confusing or not compelling to me. There are more important issues that we need to address.

MS. HAYLOCK: Haylock. I would also vote no, primarily for the same reasons as Mr. Schwartz and Dr. George.

DR. LYMAN: Gary Lyman. I would vote no, reiterating what Stephen George just said and, again, placing it in the context of other trials which have failed to raise any concerns about this. I think the explanation offered is plausible and likely to be the explanation for this.

DR. HUSSAIN: Hussain, and I vote no. I am comfortable with the survival curves or the death curves that were shown, and then all the other reasons that were cited earlier by other colleagues.

DR. HARRINGTON: Harrington. I vote no for the same reasons.

DR. A. LEVINE: Levine. I vote no.

DR. LINK: Michael Link. I vote no.

DR. RODRIGUEZ: Rodriguez. No.

DR. BUKOWSKI: Bukowski. No.

DR. PERRY: Perry. No.

DR. HUSSAIN: What is the tally? Unanimous, no.

The second issue deals with the efficacy. You have the language stated on the slide. The

question that we are being asked to vote on is considering these endpoint limitations, does the CLOT study provide substantial evidence of effectiveness?

Considering that we probably don't need to discuss this, I am going to begin with Dr. Perry and ask him to vote.

DR. PERRY: I was hoping for a comment. All of us can design a better study but that is why we have committees because none of us can design the ideal study ourselves.

DR. HUSSAIN: That is true.

DR. PERRY: I think they did a very good job and I vote yes.

DR. BUKOWSKI: Bukowski. Yes.

DR. RODRIGUEZ: Rodriguez. Yes.

DR. LINK: Link. Yes.

DR. A. LEVINE: Levine. Yes, but I definitely have reservations. This clearly is not as clean as it should have been and could have been.

DR. HARRINGTON: Harrington. I vote yes,

but I don't believe the study has proved the benefit for long-term use of this agent.

DR. HUSSAIN: Hussain. If I may answer that, it is impossible when everybody dies in six months. I don't know how you would prove long-term benefit when you have hospice type patients, to be honest with you. You can scratch that because I am not supposed to comment. My vote is yes. That is it.

DR. LINK: David, did you mean long-term like the additional five months?

DR. HARRINGTON: Yes, I meant the additional five months.

DR. LYMAN: Gary Lyman. I vote yes, the study limitations notwithstanding.

MS. HAYLOCK: Haylock. Yes.

DR. GEORGE: George. Yes.

MR. SCHWARTZ: Is it the primary endpoint?

DR. HUSSAIN: The question specifically deals with considering the endpoint limitation, does the CLOT study provide substantial evidence of effectiveness.

MR. SCHWARTZ: So, that is singular, endpoint, primary endpoint.

DR. HUSSAIN: The primary endpoint, yes, being the reduction in the risk of clots.

MR. SCHWARTZ: Yes.

DR. HUSSAIN: Thank you. Dr. Hiatt?

DR. HIATT: Oh, I will vote yes, with some reservations.

DR. HUSSAIN: So, we have a unanimous yes, with multiple reservations that were cited by the different individuals.

The third issue that we have to deal with is the issue of safety and efficacy. This question specifically says if we provide favorable responses--which I take that we have--to the preceding safety and efficacy questions, that is, no to safety question one and yes to efficacy question two, the question that we are being asked to vote on is does the totality of the CLOT study's safety and efficacy results provide a benefit-to-risk relationship sufficient to warrant approval of this supplemental marketing

application?

Does anybody want to discuss this briefly before we go for a vote? Dr. Perry is shaking his head. He does not want to discuss. So, please, let's vote. Dr. Perry?

DR. PERRY: Yes.

DR. BUKOWSKI: Bukowski. Yes.

DR. RODRIGUEZ: Rodriguez. Yes.

DR. LINK: Link. Yes, but I do share Dr. Harrington's concern about the safety and efficacy of the second five months of therapy after the initial therapy.

DR. A. LEVINE: Levine. Yes, but I agree. It is the first month that is convincing to me, not month two through six.

DR. HARRINGTON: Harrington. Yes.

DR. HUSSAIN: Hussain. Yes.

DR. LYMAN: Lyman. Yes.

MS. HAYLOCK: Haylock. Yes.

DR. GEORGE: George. Yes.

MR. SCHWARTZ: Schwartz. Yes.

DR. HUSSAIN: Dr. Hiatt?

DR. HIATT: I think yes if we believe that these deaths are not contributing to the endpoint of interest, but we will come to labeling in a minute. I think that the overall risk/benefit can be dealt in with some labeling issues so I will vote yes too.

DR. HUSSAIN: Thank you. Dr. Rieves, you want us to continue with the rest of the questions? Correct? Okay. So, there is the issue now of labeling. The statement is up there. I am going to read it briefly.

The CLOT study includes predominantly patients with advanced, metastatic cancer. Exploratory subset analyses did not support an apparent treatment effect within the subsets of patients with hematologic malignancies or patients with non-metastatic cancer.

The question for the committee to vote on: If marketing approval is recommended, should the product label limit the indicated patient population to a subset of cancer patients, for example, only patients with metastatic,

non-hematologic cancer?

Do you wish to discuss this or go to a vote? Vote? Dr. Hiatt?

DR. HIATT: I didn't see any convincing evidence of limiting this to any particular population of patients with malignancy. I am a little uncomfortable with the subgroup analysis and assuming that hematologic malignancies are somehow discrepant. So, I don't think that is a question that I am uncomfortable with.

But in the labeling discussion I would comment that the proposed indication does indicate that it is for the treatment of symptomatic VTE. I think the word "symptomatic" is key. I don't see any claim in the label for superiority over standard care. Is that correct?

DR. HUSSAIN: So, would you vote yes to limiting it to certain population or no?

DR. HIATT: No.

DR. HUSSAIN: You would not limit it to a certain population?

DR. HIATT: I would not, and I don't know

if it is appropriate formatting here but I am a little concerned. I just want to clarify that the label does not claim superiority in the labeling consideration.

DR. HUSSAIN: Mr. Schwartz?

MR. SCHWARTZ: Schwartz. Yes, I think the sponsor has already expressed an interest in doing a study for hematological cancers and I think it is needed.

DR. HUSSAIN: Dr. George?

DR. GEORGE: I am not sure I understand the question. A yes vote would be we are voting to limit it?

DR. HUSSAIN: Limit it.

DR. GEORGE: Limit it. I would vote no, although I have a little comment. I certainly don't put much stock in those subgroup analyses but I am concerned about the type of patient mix that was on this study. We didn't discuss that a lot; we got into it a little bit. But I am a little bothered by just being this generic cancer group when, you know, there is such a mix. I don't know

what I would have done if I were doing it but it is such a mix that I don't know whether the term just for cancer patients is really appropriate.

DR. HUSSAIN: Miss Haylock?

MS. HAYLOCK: Haylock. No.

DR. LYMAN: Lyman. No. I would like to certainly see more post-marketing data on these specific categories, that is, the patients with more limited disease and the hematologic population.

DR. HUSSAIN: Hussain. Yes, I would vote to limit it to the subsets that appear to benefit from it, particularly because if there is any question on safety the patient groups that did not appear to benefit should not be subjected to it considering that they have other alternatives.

DR. HARRINGTON: Harrington. I would vote no, not to limit it. The subgroups are small, analyzed post-hoc and we don't know how to interpret that.

DR. A. Levine: Levine. No. I also would like further data from the company but would not

vote based upon the subset analyses which aren't really valid.

DR. LINK: Link. I agree. No.

DR. RODRIGUEZ: Rodriguez. No.

DR. BUKOWSKI: Bukowski. No.

DR. PERRY: Perry. No. I think if you had a localized pancreatic cancer, localized lung cancer you are probably at higher risk than with many other metastatic cancers and so I can't see splitting hairs right at the moment.

DR. HUSSAIN: So, we have ten no and two yes. Ten who are not in favor of limiting. Do you still want us to discuss the final question, Dr. Rieves?

DR. RIEVES: The final question is not relevant. The feedback has been extremely useful.

DR. HUSSAIN: So, this is question number five: The CLOT study was conducted among cancer patients and included predominantly patients with advanced, metastatic cancer. Limitations in the study design are cited above.

I am not sure what you want us to address

in this discussion portion, Dr. Rieves.

DR. RIEVES: This is contingent upon marketing approval not being recommended. Actually, perhaps if we have maybe five minutes--

DR. HUSSAIN: Yes, we do.

DR. RIEVES: --to touch on the subject of the, quote, extended treatment. For example, one of the considerations is that cancer patients with a clot, VTE, may be at risk for recurrent clots the remainder of their lives. So, conceivably, the drug could be continued for a considerable amount of time. The definition of "extended" is open to many interpretations. So, it would be useful to hear from the committee members should that extended definition be a six-month period of time or, conceptually, should we consider it broadly, just unlimited such that it is undefined and open to physician discretion? So, feedback in that respect would be very useful.

DR. HUSSAIN: Dr. Perry?

DR. PERRY: In the patient population I deal with that has a hyper-coagulable state, until

and unless we have an effective therapy for metastatic pancreatic cancer, prostate cancer, lung cancer, etc., those people are going to be at risk the rest of their lives. To say that we could stop after six months and leave them at risk of clots, to me, is just untenable. So, I think there are other people who are going to be at risk for a certain period of time and then their problem is going to be taken of. It is hard for me to envision that right at the moment, but there will be some. So, for the moment I would say indefinite for those people who have an ongoing indication, a hyper-coagulable state.

DR. HUSSAIN: Dr. Rodriguez?

DR. RODRIGUEZ: Well, just following perhaps on that, you bring up a very important issue. Unless a malignancy is active, there are some patients who do get cured--I mean, limited stage breast cancer, lymphomas, etc. It would be a huge detractor in quality of life to have these people on treatment even for six months. I mean, the curves seem to suggest that the greatest

benefit from this occurred during the first four to six weeks of treatment. Outside of someone who has a demonstrated pro-coagulable state, I wonder if the prolonged treatment for six months is even necessary. Perhaps six to eight weeks may be a more appropriate therapeutic strategy.

DR. HIATT: May I comment on that?

DR. RODRIGUEZ: See, that is the unique situation where we know that there is a therapeutic risk of coagulation. That is the same as your patients with pro-coagulable state. They have a reason to be on the anticoagulation.

DR. HUSSAIN: Dr. Hiatt?

DR. HIATT: Yes, I have two comments. There is a number of cardiovascular trials where there is early benefit and then people say, well, maybe we should stop the drug in a month or six months. When you try to analyze those data, it is pretty compelling that you should keep them on long term.

The second comment is that in this indication, in all the guidelines I am familiar

with, these kinds of patients would be considered high risk for the rest of their life and it wouldn't make sense to stop them. So, I would advocate for long-term therapy.

But the final comment is that there are a couple of things that I think were sort of not addressed clearly, and that has to do with the LNT abnormalities, thrombocytopenia, and if there is going to be long-term therapy I think labeling and perhaps post-marketing surveillance should address these potential risks.

DR. HUSSAIN: Dr. Hiatt, in the cardiovascular studies have people looked at, say, shorter duration, not necessarily just the one month but perhaps three versus six or six versus twelve or some kind of duration?

DR. HIATT: Yes, there is an example which is the CURE study where all the benefit seemed to occur in the first month. Then, what people would do is stop one of the anti-platelet drugs after 30 days. The post-hoc analyses looked at that data and the current guidelines recommend 9-12 months.

This is just as an example. If you try to figure out if you could somehow account for the early benefit with a continued benefit of doing anti-platelet therapy out beyond the first month, and it appears that there is. So, I wasn't terribly bothered by the separation of the curves fairly rapidly early on and then they seemed to be rather parallel after that. I don't think you can unbundle those data. No one is ever going to do a study where you compare three months to six months, or something like that. Given the underlying substrate of these patients with the high mortality risk, unless we have some convincing evidence that the death related discontinuations were thromboembolic in nature, I think long-term is probably the answer.

DR. HUSSAIN: Dr. Bukowski?

DR. BUKOWSKI: Remember, ten percent or more of the patients had no evidence of disease. They were free of their cancer. That perhaps is a group that is different and perhaps doesn't need the long-term anticoagulation. So, I think it

would be very interesting to see a study somehow address that question. Is it necessary, especially in the low risk group, for example the patient who has had their surgery and is in the postoperative period and getting adjuvant therapy, or some such thing.

DR. HUSSAIN: Dr. Harrington?

DR. HARRINGTON: Notwithstanding the compelling clinical arguments for continuing anticoagulant therapy in this population, this study does not support or argue against the long-term use because both groups were getting treatment, nor does it support the particular choice of an agent, Fragmin versus another oral anticoagulant. So, I am not sure that this study provides enough evidence for the labeling to say that this agent has been proven to be beneficial for long-term use, or even suggest that it is beneficial for five months or longer use.

DR. HUSSAIN: Dr. Lyman?

DR. LYMAN: I would hate to have the labeling take it out of the realm of clinical

judgment, and there are guidelines, as I mentioned, under development, as well as NCCN guidelines that call for durations of 3-6 months of management for a DVT; 6-12 months for a PE. Then continuation should be considered if the patient has advanced, unresponsive cancer or certain high risk factors, and they are defined in that. So, I would rather see that dealt with in terms of guidelines than in restrictive labeling that might handicap the management of an individual patient.

DR. HUSSAIN: Can I ask the sponsor--this may not be a politically correct question but I am going to ask it nonetheless. In the setting of an end of life situation, which is what we are dealing with, I guess the concern I have is the cost. The cost of drug administration, the cost in a situation where we are not curing these patients and they are ultimately dying of their disease. I just can't imagine what the cost of Coumadin versus your drug is. I think that is a real question and I would hope that we, collectively as a group, deal with that, understanding that resources are going

down; they are not going up.

Do you want to comment on that in terms of how you view things? For example, why not put people on Coumadin and if they relapse switch them to the drug, as opposed to ahead of time putting them on the drug?

DR. EAGLE: So, you are really getting into the issue of the CLOT study saying put them on an inferior treatment and then when they fail that put them on dalteparin.

I guess really the cost we need to think about is not just the cost of drug; it is the cost of the person and the health and treatment of that person. These patients are going to get recurrence. They have alterations in their cancer therapy, quality of life, visits to doctors, more investigations, all because they have recurrence in that area. Also, on top of that, we need to remember there is monitoring involved in warfarin, collection as well as regular blood tests, not necessary with dalteparin; ease and convenience; family members of cancer patients taking time off

to work to actually take their relatives to the doctor to be seen and managed with warfarin. So, all these things become less and less of an issue.

So, when you are talking about the cost we really need to focus on treating the patient and what that cost to the person is. I think that is more relevant.

DR. HUSSAIN: Thank you. Dr. Rieves, did you get all the answers you want?

DR. RIEVES: Yes. Yes, it was extremely useful. We appreciate the discussions, not typical type of discussion for this type of product I think but it was extremely useful. Thanks, everyone.

DR. HUSSAIN: Thank you. With that, I would like to thank the committee members and all the audience for their patience, and good evening.

[Whereupon, at 5:00 p.m., the proceedings were recessed, to resume on Thursday, September 7, 2206 at 8:00 a.m.]

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