FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE

WEDNESDAY, JUNE 20, 2012

8:00 a.m. to 12:00 p.m.

Morning Session

FDA White Oak Campus

Building 31, The Great Room

White Oak Conference Center

Silver Spring, Maryland

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. WILSON: Okay. I'd like everyone to take their seats. We're going to go ahead and get started in about 30 seconds.

Okay. I'd like to call the meeting to order. I'd like to start with each member introducing themselves into the record. If you could please state your name and what your specialty is, where you're from, the usual. And we'll go ahead and start on the right side. Thank you.

DR. FINGERT: Good morning. My name is Dr. Howard Fingert. I'm a medical oncologist and a hematologist. And I'm industry representative from Millennium, the Takeda Oncology Company.

DR. DIEHL: Lou Diehl from Duke University. My subspecialty is in lymphoma and hematologic malignancies.

DR. VOSE: Julie Vose, University of

Nebraska Medical Center. And my specialty is in lymphoma and hematologic malignancies.

DR. LOGAN: Brent Logan, biostatistician from Medical College of Wisconsin.

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

DR. MENEFEE: Michael Menefee, medical oncologist and hematologist at Mayo Clinic, Florida.

DR. FOJO: Tito Fojo, medical oncologist, medical oncology branch, National Cancer Institute.

DR. BUZDAR: Aman Buzdar, medical oncologist from M.D. Anderson, Houston.

DR. WOZNIAK: Antoinette Wozniak. I'm a medical oncologist from the Karmanos Cancer Institute in Detroit.

DR. KELLY: William Kelly, medical oncologist, Thomas Jefferson University, Philadelphia.

DR. SEKERES: Mikkael Sekeres, medical oncologist, Cleveland Clinic.

DR. WILSON: Wyndham Wilson, medical

oncologist, NCI.

DR. BRIGGS: Caleb Briggs, designated federal officer, ODAC.

DR. FREEDMAN: Ralph Freedman, gynecologic oncologist, M.D. Anderson Cancer Center.

DR. LOEHRER: I'm Pat Loehrer, medical oncologist from Indiana University, Melvin and Bren Simon Cancer Center.

DR. ARMSTRONG: Deborah Armstrong, medical oncologist, Johns Hopkins in Baltimore.

DR. ZONES: I'm Jane Zones. I'm a medical sociologist. And I'm affiliated with the National Women's Health Network and Breast Cancer Action.

DR. ARSCOTT: Karen Arscott, neuromuscular medicine physician, two-time lung cancer survivor.

DR. LEE: Kyung Lee, statistical reviewer, FDA.

DR. HERNDON: Jeanne Herndon, medical officer, FDA.

DR. ROBIE-SUH: Kathy Robie-Suh, medical team leader, FDA.

DR. FARRELL: Ann Farrell, acting division

director, Division of Hematology Products, FDA.

DR. PAZDUR: Richard Pazdur, director, Office of Hematology and Oncology Products.

DR. WILSON: Thank you and welcome.

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

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

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

I'd like to remind everyone present to please silence your cell phones and other electronic devices if you have not already done so. The committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

We now will have a conflict of interest statement read.

Conflict of Interest Statement

DR. BRIGGS: Hi. I'd first like to identify the press officer, Stephanie Yao.

Stephanie, if you could please stand. Thanks.

The Food and Drug Administration, FDA, is convening today's meeting of the Oncologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees, SGEs,

or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

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

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special

government employees and regular federal employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today the committee will discuss New Drug Application 203213, with established name semuloparin sodium injection, application submitted by Sanofi-aventis, U.S. LLC. The proposed indication for this product is for the prophylaxis of venous thromboembolism, VTE, in patients receiving chemotherapy for locally advanced or metastatic, pancreatic or lung cancer, or for

locally advanced or metastatic solid tumors with a VTE risk score greater than or equal to 3. This is a particular matters meeting during which specific matters related to Sanofi's semuloparin sodium injection will be discussed.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Howard Fingert is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Fingert's role at this meeting is to represent industry in general and not any particular company. Dr. Fingert is employed by Millennium.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the

participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue.

Thank you.

DR. WILSON: We will now have a brief presentation from Dr. Pazdur.

Member Appreciation

DR. PAZDUR: June is the month of weddings, graduations, and proms. But we're not going to have a prom here, and we're certainly not going to have a wedding. But we do have a graduation of some sort.

On behalf of the FDA, I would like to take a brief moment to recognize four of our committee members whose terms expire at the end of June. Drs. Ralph Freedman, Dr. Kevin Kelly, and Dr. Patrick Loehrer have served on the ODAC over the past 3 or 4 years, and their commitment and service to this committee has been beyond reproach.

Dr. Wyndham Wilson has also served on the ODAC since May of 2008, serving as chair of the committee from July 2010 to the end of his term in June.

During their years of service as ODAC members, their professionalism and guidance was vital to the regulatory drug review process. Their involvement in the review process, however difficult, allowed the hematology and oncology divisions to provide safe and effective products for cancer treatments to the American public in a timely manner. In appreciation of their services, FDA will present a plaque to each of the retiring members.

Dr. Wilson, could you come up and get your plaque? And let's have a round of applause for Dr. Wilson.

(Applause.)

DR. PAZDUR: We really appreciate his tenure at ODAC; a sincere personal thank you on this part.

Dr. Freedman, if you'd like to step up. And again, let's have a round of applause.

(Applause.)

DR. PAZDUR: It's a long trip from Houston every quarter here, and I appreciate it.

Dr. Kevin Kelly, round of applause.

(Applause.)

DR. PAZDUR: Again, thank you for your service and your dedication.

And lastly, Dr. Patrick Loehrer, we appreciate your service. And, again, I know it's difficult to come here from Indianapolis on a routine basis, but we appreciate your efforts.

(Applause.)

DR. PAZDUR: Thank you for all of their efforts. We really appreciate all of our ODAC members. It's a tremendous time commitment on their part. Remember, this is in addition to their day job, so to speak, so we really appreciate all of their efforts and excellent advice that they've given to us throughout the course of the years. Thank you.

(Applause.)

DR. WILSON: Maybe I can speak for myself

and I suspect for the other retiring members. And that is that I feel that it's really been a privilege and honor to be able to participate in this important process. And I think it is especially key because getting drugs approved is a very important process that involves assessing risk-benefit, and it's not always that easy. So I just want to say that it's certainly been my personal honor to have been able to serve. Thank you.

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 advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue, such as consulting fees, travel

expenses, honoraria, and interests in the sponsor, including equity interests and those based upon the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation 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 presentation, it will not preclude you from speaking. Thank you.

We will now proceed with the sponsor's presentation.

Sponsor Presentation - Richard Gural

DR. GURAL: Thank you. Good morning. Dr. Wilson, members of the advisory committee, Dr. Pazdur, FDA, ladies and gentlemen, my name is Richard Gural, and I'm vice president for regulatory affairs for Sanofi. On behalf of Sanofi, we are pleased to be here today to present to the committee an advancement in the field of thromboprophylaxis and ambulatory cancer patients receiving chemotherapy.

VTE is an important complication in cancer patients and those receiving chemo. The current standard of care remains the treatment of VTE rather than the prevention. One of the main reasons for this is that no anticoagulant has demonstrated an acceptable benefit-risk profile for the prophylactic use in ambulatory cancer patients. Semuloparin has been developed to meet this medical need.

Semuloparin is an ultra-low molecular weight heparin. It was designed to have a reduced mass, using a unique depolymerization generation process. The high anti-Xa/IIa ratio of 80 was intended to result in an improved benefit-risk profile. Semuloparin has a long half-life with a low peak to trough ratio, allowing for once-a-day administration.

The semuloparin NDA relies on the data from a large phase 3 program. The pivotal study, SAVE-ONCO, was a randomized controlled clinical trial that included 3,212 cancer patients receiving chemotherapy for locally advanced or metastatic

solid tumors. The phase 3 program with semuloparin was also conducted in a surgical setting. These studies provide supportive evidence of the antithrombotic activity for semuloparin and provide additional safety information in approximately 4,900 patients.

At the time of the original NDA submission, the proposed indication reflected the overall SAVE-ONCO study population. During a post-NDA submission meeting with the FDA, there was a request to narrow the indication. The new proposed indication is for the prophylaxis of venous thromboembolism, VTE, in patients receiving chemotherapy for locally-advanced or metastatic pancreatic or lung cancer, or for locally-advanced or metastatic solid tumors, with a VTE risk score greater than or equal to 3.

In today's presentation, we will hear from Dr. Khorana of the University of Rochester. He will describe the medical landscape and how VTE prevention needs to become an important medical consideration for many cancer patients. Next,

Dr. Lawson will present the positive efficacy data from the pivotal phase 3 study, SAVE-ONCO, and the overall safety profile of semuloparin, and information on the surgical studies also conducted. Dr. Zaks will then discuss the proposed indication and specifically its rationale, efficacy, safety, and benefit-risk. Dr. Bunn of the University of Colorado will then discuss the implications that SAVE-ONCO has on medical practice. I will then return to answer any clarifications that you might have.

With that, Dr. Khorana, if you could, please. Thank you.

Sponsor Presentation - Alok Khorana

DR. KHORANA: Good morning. My name is Alok Khorana. I'm a medical oncologist and currently an associate professor of medicine and oncology at the James P. Wilmot Cancer Center of the University of Rochester. I co-direct the GI cancer program for the university, so my clinical practice is heavily focused on gastrointestinal malignancies. And surely the complication of VTE in my patients that

have driven my decade-long research career focused on risk assessment and the prevention of cancer-associated thrombosis.

This research program is supported by the NIH, including the NHLBI and the NCI, the V Foundation, and the Wilmot Foundation. Sanofi is compensating me for my time and expense to attend this meeting, but I have no financial interests in its outcome or in the company itself.

VTE is frequent in cancer patients, particularly those receiving active systemic therapy. And in recent years, there has been a steep increase in the rates of VTE with increased rates between 28 to 47 percent. VTE can manifest as either deep venous thrombosis or pulmonary embolism. But with current medical technology cancer-associated VTE can be discovered as often based on symptoms as it is incidentally on scans. Emerging data indicate that patients with VTE have similarly adverse outcomes, regardless of whether the diagnosis was based on symptoms or whether it was found incidentally.

Prior public health policy efforts by the Joint Commission, by the surgeon general, and guidelines by ASCO and NCCN, have all focused on prevention of VTE in hospitalized patients and in surgical patients and the immediate post-surgical period. But cancer care has shifted to the outpatient setting and so has the occurrence of VTE.

We reported at ASH last year, on a cohort of nearly 18,000 cancer patients seen in the United States between 2006 and 2008, 996, or approximately 5 and a half percent, of these patients develop VTE. The overwhelming majority of VTE, 78 percent, occurred in the outpatient setting. Thus, if public health efforts to reduce VTE were to continue to focus solely on the inpatient and surgical settings, we would miss a large majority of preventable cases.

Amongst cancer outpatients, the current standard of care is to treat VTE when it occurs but not attempt to prevent it. But treating of VTE once it occurs has consequences for patients with

cancer. A diagnosis of VTE can lead to delay or discontinuation of systemic therapy, and it can lead to hospitalization, which may be prolonged.

Once you get the first VTE, there's a 9 to 21 percent risk of recurrent VTE, and patients need to be on anticoagulation for at least 6 months and often longer in the setting of active disease when receiving active treatment. There's also high risk of bleeding, up to 12 percent, with full-dose therapeutic anticoagulation as opposed to prophylactic anticoagulation. And finally, there's a real risk of mortality. In one large registry analysis that we conducted, 3 and a half percent of deaths in patients with cancer receiving chemotherapy were in fact caused by cancer-associated VTE.

Now having sort of described the phenomenon of VTE in cancer patients, it's also important to recognize that not all ambulatory cancer patients are equally at risk for VTE, and there's a wide variation in risk, depending on various risk factors. And so targeting prophylaxis toward

patients with highest risk is the most optimal way of preventing VTE.

One of the traditional and historically most important risk factors for VTE that every oncologist recognizes is the site of cancer. In this recent representative study of over 30,000 United States patients, conducted by Dr. Lyman from Duke University, all patients receiving chemotherapy -- patients with pancreatic cancer, lung cancer, and other gastrointestinal cancers -- had amongst the highest rates in this cohort. Note also that rates of PE, or the proportion of diagnosis that is PE versus DVT, can also differ. For instance, in this analysis, PE was particularly frequent in patients with lung cancer.

Site of cancer of course is important, but it's just one of several risk factors for cancer-associated VTE. And given the high degree of variability and VTE risk and the multifactorial etiology of VTE in cancer, my collaborators and I focused on the development of a risk assessment

tool to identify patients particularly at risk for VTE. We evaluated a multitude of risk factors, including patient related factors described here, including demographics, performance status, and comorbid conditions; cancer related factors, including the site and stage of cancer; treatment related factors, including the type of chemotherapy and supportive care agents; and laboratory-based risk factors.

The utilized data from a large prospective U.S. registry of cancer patients initiated chemotherapy, and these patients were followed for the first three cycles of treatment, of various treatment related complications, including VTE. Dr. Gary Lyman from Duke University was the principal investigator of this registry and a collaborator on this effort, which was funded by the NCI.

We were able to initially derive from a duration cohort of 2,701 patients, and a score was developed. And this score once developed was tested in an independent validation cohort of 1365

patients from the same registry.

The risk score comprises five simple clinical and laboratory variables shown here. These include the site of cancer, which could be very high risk, such as pancreas and stomach, and a score of 2 would be a sign for those sites, or high risk, such as lung, lymphoma, gyn cancers, and some GU cancers, with the exception of prostate. And a score of 1 would be a sign for those high-risk sites. Other variables included competence of the CBC, such as the platelet count, the hemoglobin, and elevated leukocyte count, and morbid obesity. And all of these latter variables were assigned a score of 1.

In our original paper, which was published in Blood in 2008, we showed that the risk score was in fact able to identify two very distinct populations. There's a high-risk population shown on the right side of the graph, which had a rate of VTE, which was substantial, 7 percent or so in both the development and validation cohorts, in a period of 2 and a half months. There was also a low-risk

population shown on the left, which had a rate of about 1 percent or less. And prophylaxis would likely be very beneficial for the high-risk population and likely not be of benefit for the low-risk population.

A significant proportion of patients were also classified as intermediate risk, and here there was not much difference between scores of 1 and 2. And this is a population that deserves further study in terms of additional VTE risks. The risk score as it stands, however, has now been externally evaluated by several research programs, including those of the prospective Vienna CATS study, the Southern European New Drugs Organization, the Memorial Sloan-Kettering Cancer Center, and many others. And this risk score has now been verified in an additional 4,000 patients.

Now given the known high rates of VTE in cancer patients, multiple randomized clinical trials have in fact attempted to evaluate the benefit of outpatient venous thromboprophylaxis using a variety of agents. And the most recent

studies have focused on the use of low-molecular-weight heparins.

Results from the most recent 2012 Cochrane meta-analysis are presented on this slide. Although most of the trials are relatively small, overall, the meta-analysis does show that low-molecular-weight heparins are in fact effective in reducing the risk of VTE, but this benefit is offset by an increase in the absolute risk of major bleeding.

Guidelines panels evaluated VTE prophylaxis in this emerging data over the past few years as well. I was one of the authors of the 2007 ASCO guidelines, and at the time we were unable to recommend prophylaxis for ambulatory patients until better strategies for risk assessment were available. And since then, we have developed and validated the risk score that I just discussed.

Recent revisions of guidelines from NCCN and ESMO both recommend consideration of VTE prophylaxis, but this is a very soft recommendation, again, given the lack of an optimal

risk-benefit ratio. But both of these guidelines do in fact refer to the risk score that we developed as an appropriate tool to identify patients who would benefit from prophylaxis.

In conclusion, VTE is a frequent complication in cancer. In 2012, it occurs mostly in outpatients. It is increasing in frequency. The current standard of care is to treat but not to prevent VTE, and this has consequences for cancer patients. These include the high risk of recurrent VTE, a high risk of bleeding on therapeutic anticoagulation, increased healthcare resource utilization, and a small but real risk of mortality for patients. Primary prevention of VTE can be considered when an anticoagulant demonstrates a favorable benefit-risk ratio in this setting.

Thank you.

Sponsor Presentation - Francesca Lawson

DR. LAWSON: Good morning. My name is Francesca Lawson from clinical development at Sanofi R&D. Semuloparin was assessed in a clinical development program consisting of 15 phase 1

studies, one dose-ranging study, and two distinct phase 3 VTE prevention programs, one in oncology and one in mostly short-term surgical settings. The oncology program is based on the pivotal phase 3 SAVE-ONCO study. The phase 3 surgical studies provide supportive evidence of the antithrombotic efficacy of semuloparin in various high VTE risk settings and provide exposure data in approximately 4900 additional patients.

With respect to SAVE-ONCO, patients were randomized to either placebo or semuloparin, 20 milligrams subcutaneously, once daily. This study was placebo controlled because no drug is indicated for primary thromboprophylaxis in ambulatory cancer patients. The primary efficacy endpoint was the composite of VTE and VTE-related deaths.

The study hypothesis was that VTE would occur in approximately 4 percent of the patients in the placebo group, and the time of prophylaxis with semuloparin would lead to a relative risk reduction of 50 percent, resulting in a 2 percent event rate

in the semuloparin group. Given these assumptions, the group size needed for a power of 90 percent was about 3,200 randomized patients.

Study treatment was administered for the duration of the initial chemotherapy. Study treatment was to be continued regardless of any changes or delays in chemotherapy if this occurred within the first 3 months. In the case of changing chemotherapy after the first 3 months, study treatment was to be discontinued.

Patients were eligible for the study if they were initiating a course of chemotherapy and if they were considered a high risk of VTE due to stage of cancer, local advanced or metastatic, or the site of cancer. Enrollment was not based on the Khorana VTE risk score because this score had not been published or independently validated in 2007 when the study was designed. Key exclusion criteria included poor performance status, contraindication or requirement for anticoagulation, and severe renal impairment.

The primary efficacy endpoint was the

composite of symptomatic DVT and any pulmonary embolus occurring during the efficacy analysis period. This is defined as the period from randomization up to three days after last injection of study drugs. DVT had to be symptomatic, and the clinical diagnosis had to be documented by venography or compression ultrasound.

Pulmonary embolism included non-fatal PE and VTE-related deaths. With respect to non-fatal PE, if the event was symptomatic, the clinical diagnosis had to be documented by imaging. VTE-related deaths included fatal PE; for example, confirmed by autopsy and unexplained death. All events had to be confirmed by an external blinded adjudication committee that reviews all imaging tests.

Overall, 3,212 patients were randomized. The most common cancers were lung and colorectal. Two-thirds of the study population had metastatic cancer and one-third had locally advanced cancer. Median duration of study treatment was approximately 3 and a half months in both treatment

groups, and 152 patients received semuloparin for actually 3 months.

This slide shows the result of the primary endpoint. Semuloparin significantly reduced by 64 percent the composite of VTE or VTE-related deaths with P value less than 0.0001. In this slide, the gray line shows events in the placebo group, and the yellow line, events in the semuloparin group. The lines start diverging at the beginning of the treatment period, and the treatment effect was maintained over time.

The robustness of the primary efficacy analysis was confirmed by all sensitivity analyses, including the analysis on the per protocol population, the analysis of VTE of all-cause deaths instead of VTE or VTE-related deaths, and the analysis under assumption of informative censoring, as this was raised by FDA as a potential issue. These last analyses were independently performed by Dr. Scott Emerson of the University of Washington.

The treatment effect was consistent across individual components of the primary endpoint,

symptomatic DVT, and PE. The hazard ratio for symptomatic DVT was 0.32, and the hazard ratio for PE was 0.41. The treatment effect of semuloparin on the primary efficacy endpoint was consistent across tumor location in Khorana VTE risk score. In this slide, the vertical dotted line depicts the point estimate on the primary endpoint for all patients. The point estimates in subsets of patients, according to the location of the primary tumor and the degree of VTE risk, are all on the left of 1.

Important for our discussion today is the different risks of VTE according to the location of the primary tumor. Looking at the primary endpoint in the placebo group, we see the patient with lung and pancreatic cancer at the highest incidence of VTE, 4.2 percent in lung cancer, 10.9 percent in pancreatic cancer. The Khorana VTE risk score was prognostic of VTE risk in SAVE-ONCO. The incidences of the primary endpoint in the placebo group were 1.3 percent in patients at low VTE risk, a score of zero; 3.5 percent in patients at

intermediate risk, a score of 1 or 2; and 5.4 percent in patients at high VTE risk, a score of 3 or higher.

The secondary endpoint of SAVE-ONCO was overall survival assessed at 12 months after randomization or at study end, whichever came first. SAVE-ONCO did not demonstrate an improvement with semuloparin on overall survival. The hazard ratio was 0.96, and the 95 percent confidence interval ranged between 0.86 and 1.06.

Let's now review the safety results. In SAVE-ONCO, the primary safety outcome was bleeding, and all bleeding events were adjudicated by a blinded external adjudication committee. Clinically relevant bleeding was defined as overt bleeding requiring medical intervention. This occurred more frequently in semuloparin compared to placebo. This difference was mostly driven by non-major bleeding.

The incidences of major bleeding were similar in both treatment groups: 19 events, 1.2 percent in semuloparin, versus 18 events,

1.1 percent in placebo. In accordance with the criteria of the International Society on Thrombosis and Haemostasis, ISTH, major bleedings included fatal bleeding, symptomatic bleeding into critical areas or organs, and overt bleedings requiring two or more transfusions or resulting in a hemoglobin drop of at least 2 grams per deciliter.

This slide shows bleeding as reported by the investigator for all bleedings adjudicated by the external blinded committee as major. The first three sites -- cerebral, vitreous and pericardial -- correspond to critical organs according to the International Society on Thrombosis and Haemostasis. The FDA in their briefing book considered the splenic hematoma also to be a bleeding into a critical organ.

In the placebo group, the vast majority of the major bleedings consisted of gastrointestinal hemorrhages. Four of the 15 GI bleeds in the placebo group were fatal with none of the 7 GI bleeds in semuloparin fatal. Overall, six patients experienced a fatal bleeding in the study, 4 in the

placebo group and 2 in the semuloparin group. That includes one patient who committed suicide, reported as traumatic hemorrhage, and a patient who experienced acute respiratory failure and convulsions, suspected by the investigator to be due to bleeding brain metastasis, but no imaging was performed.

Our overall assessment of the risk of bleeding hinges on the totality of events designated as major by the external blinded adjudication committee in accordance with the criteria established by International Society on Thrombosis and Haemostasis.

Bleeding events were also independently adjudicated based on NCI toxicity criteria. In semuloparin, a higher incidence of bleeding, grade 1 or 2, was observed. These bleedings are mild or moderate, and at most require noninvasive intervention. Slightly more bleeding, NCI grade 3 or 4, occurred in semuloparin, while more bleeding, NCI grade 5, that's fatal, occurred in placebo. Therefore, the same incidence of 1.4 percent was

observed in both treatment groups for bleeding, NCI grade 3 or higher, which include events that are medically significant, severe, life threatening, or fatal.

Overall, the rate of treatment-emergent adverse events were similar between the two treatment groups. This included adverse events that were serious, led to death, or to permanent discontinuation. On treatment and post-treatment, deaths occurred with similar incidence in semuloparin and placebo. Cause of death was adjudicated by a blinded external committee as fatal pulmonary embolus, fatal bleeding, cardiovascular death, or other. The deaths adjudicated as other were generally due to progression of patients' underlying malignancy or infection.

A review of the heparin-derived class effects showed there was a higher incidence of ALT elevation in semuloparin compared to placebo, but the percent of patients with ALT and bilirubin elevation were similar in the two treatment groups.

Thrombocytopenia, systemic allergic reaction, an adverse event of hypokalemia also occurred with similar incidence in the two treatment groups. There were no cases of drug-induced liver injury, heparin-induced thrombocytopenia, or semuloparin associated severe systemic allergic reaction.

The efficacy and safety of semuloparin is reported by data in approximately 4900 patients exposed to semuloparin in surgical studies. The semuloparin surgical program consisted of one placebo-controlled study and four enoxaparin controlled studies. The primary endpoint of all studies was a composite of both symptomatic and asymptomatic VTE or all-cause death. The placebo-controlled study, SAVE-HIP 3, demonstrated a superiority of extended prophylaxis with semuloparin for the prevention of VTE after hip fracture surgery.

Three short-term enoxaparin-controlled studies compare semuloparin and enoxaparin for the prevention of VTE after major orthopedic surgery. In all three studies, the rates of the primary

efficacy endpoint were lower in the semuloparin group compared with enoxaparin, but the treatment effect reached statistical significance in SAVE-HIP 1 only. This is likely the result of setting a very high bar for a target relative risk reduction of 40 to 45 percent, as shown in this slide in the red dots over enoxaparin. A meta-analysis of the three orthopedic studies shows that the rate of the primary endpoint, in blue in the forest plot, was significantly lower in semuloparin compared with enoxaparin.

Another short-term study, the SAVE-ABDO study, compared semuloparin and enoxaparin for VTE prevention after major abdominal surgery. Here enoxaparin was initiated before surgery while semuloparin was initiated only following surgery. Within this design, noninferiority could not be demonstrated. The incidences of primary endpoint were 6.3 percent and 5.5 percent in semuloparin and in enoxaparin, respectively. Nevertheless, semuloparin clearly exhibited thromboprophylactic activity since previous studies in patients

undergoing major abdominal surgery have reported rates of any VTE or death ranging from 20 to 30 percent in the absence of thromboprophylaxis.

In conclusion, all five surgical studies provided evidence of antithrombotic activity of semuloparin in setting at high risk of VTE.

With respect to the bleeding profile of semuloparin and enoxaparin, the meta-analysis of the three orthopedic studies, shown in blue in the forest plot, suggests that semuloparin had an overall similar incidence of clinically relevant bleedings and a favorable trend in the point estimate for major bleeding, 0.57, although we did see some variability in the risk of bleeding between semuloparin and enoxaparin in the individual orthopedic studies.

In the major abdominal surgery study, semuloparin caused less bleeding. But this observation is impacted by the fact that semuloparin was initiated postoperatively, while enoxaparin was started before surgery.

In conclusion, SAVE-ONCO showed a highly

significant 64 percent relative risk reduction on a composite primary endpoint of VTE or VTE-related death and a consistent treatment effect in all subgroups, including the site of the primary tumor and the Khorana VTE risk score. The surgical studies provide supportive evidence of semuloparin antithrombotic activity in settings at high VTE risk. The safety profile of semuloparin is as we expected for a heparin-derived compound with no unexpected safety issues identified.

Throughout the clinical development program, 7,600 patients were exposed to semuloparin. In cancer patients receiving chemotherapy, no increase in major bleeding or bleeding when NCI grade 3 or higher was observed.

Now to discuss the benefit-risk of semuloparin, my colleague, Dr. Zaks.

Sponsor Presentation - Tal Zaks

DR. ZAKS: Thank you, Dr. Lawson.

Good morning. My name is Tal Zaks. I'm a medical oncologist from Sanofi oncology, and I'm an adjunct associate professor of medicine at the

University of Pennsylvania School of Medicine.

Semuloparin can safely prevent venous thromboembolic events in cancer patients receiving chemotherapy. The assessment of benefit-risk took into account both the primary endpoint, prevention of VTEs, and major bleeding as the most significant adverse event. Major bleeding was chosen because the clinical implications of a major bleeding event are similar to that of a VTE or VTE-related death.

As shown on the curve, treatment with semuloparin was associated with 39 events compared to 73 events on placebo, yielding a hazard ratio of .53 and an upper limit of the 95 percent confidence interval of .78. If we express the benefit to risk of semuloparin versus placebo as the numbers needed to treat versus the numbers needed to harm, 46 patients need to be treated with semuloparin to prevent one VTE, while over 1700 patients need to be treated to cause one excess event of major bleeding. If benefit to risk is expressed as absolute risk difference, for every 1,000 cancer patients treated with semuloparin, 22 VTE or

VTE-related deaths would be prevented at the cost of less than one more major bleeding event.

The SAVE-ONCO study met the primary endpoint as has been designed. Semuloparin use led to a significant 64 percent relative risk reduction on the primary endpoint of any VTE or VTE-related death, and this translated into an absolute risk reduction of 2.2 percent. Furthermore, this treatment effect was consistent across all subgroups. While the magnitude of benefit was as had been postulated, post-NDA submission, the FDA has asked to revise the indication. We therefore propose to narrow the indication to patients who are even at high risk of VTE. Since there was a consistent treatment effect by both site of primary tumor or VTE risk score, this approach is statistically valid and does not inflate type I error.

In order to identify the subset of the SAVE-ONCO population with a higher VTE risk, we look at the literature, the current guidelines, and the placebo arm of the SAVE-ONCO study, and we

considered the VTE risk score according to the cancer type and the Khorana VTE risk score. This approach is consistent with the notion that some cancers are intrinsically associated with a high VTE risk, while others are associated with significant risk only when additional risk factors, such as obesity, anemia, or thrombocytosis, are present.

This score is relevant because it was developed and independently validated in cancer patients receiving chemotherapy. Furthermore, it is recognized in two recently revised oncology guidelines -- the NCCN and ESMO -- as the recommended way to identify ambulatory cancer patients receiving chemotherapy who should be considered for VTE prophylaxis. Finally, it was also prognostic of VTE risk within the SAVE-ONCO study.

To identify the patients expected to be at highest risk for VTE, we first looked at the recent literature. As depicted on the left and previously shown by Dr. Khorana, data from a large U.S. claims

data base identifies patients with cancers of the lung and pancreas as having the highest risk of VTE and at a magnitude similar to that found in patients who fall into the high-risk VTE category in Dr. Khorana's study.

The incidence of VTE on the placebo arm of SAVE-ONCO, as shown in the gray bars on the right, is consistent with these data. By limiting the proposed indication to patients with longer pancreatic cancer, regardless of Khorana VTE risk score, are those with solid tumors and high VTE risk score. We include only half the patients enrolled in SAVE-ONCO, yet these patients experienced approximately 80 percent of the overall burden of venous thromboembolism.

In the proposed indicated population, semuloparin significantly reduced the primary endpoint of VTE or VTE-related death. The VTE incidence on placebo was 5.1 percent, and semuloparin significantly reduced it down to 1.4 percent. In this population at higher risk of VTE, the absolute risk reduction induced by

semuloparin was higher than the absolute risk reduction observed in the overall population.

As in the SAVE-ONCO population overall, thromboprophylaxis with semuloparin was associated with an increase in clinically relevant bleeding. Most of this difference was driven by difference in non-major bleeding. In this population, there were 13 cases of major bleeding with semuloparin and 11 cases with placebo. The benefit-risk in the proposed indicated population was analyzed assuming a consistency of effect for both VTE prevention and major bleeding with the overall study population.

In terms of numbers needed to treat versus numbers needed to harm, 30 patients need to be treated to prevent one VTE while 1500 patients need to be treated to cause in excess of one major bleeding event. The absolute risk reduction analysis shows that for every thousand cancer patients treated, semuloparin would prevent 33 VTE or VTE-related deaths, approximately half of which would be pulmonary emboli and would cause less than one more major bleeding event.

In conclusion, in the SAVE-ONCO study, semuloparin showed a favorable benefit-risk ratio in the overall study population that is further improved within the proposed indicated population. Specifically, this population has a higher baseline risk of thromboembolic events. The treatment effect of semuloparin is consistent, and with no increase in the risk of bleeding, this translates overall into a higher absolute risk reduction and a higher benefit-risk ratio, whereby treating 1,000 patients would prevent 33 VTE or VTE-related deaths at the cost of less than one major bleeding event.

To reflect on the impact of the SAVE-ONCO results on clinical practice is Dr. Bunn from the University of Colorado Cancer Center.

Dr. Bunn?

Sponsor Presentation - Paul Bunn

DR. BUNN: Dr. Wilson, committee members, guests, Dr. Pazdur, FDA staff, I'm pleased to have the opportunity to speak to you today, representing the view of a practicing medical oncologist. It won't surprise you that I'm not an expert in the

clotting cascade, but I do provide care for patients with advanced lung cancer who are included in the proposed label. With respect to my conflict of interest, I've received consulting honoraria for my time, but I have no financial interest in the company or the outcome of the meeting.

Many years ago, Trousseau recognized that patients with certain cancers had an increased propensity for clotting, including deep venous thrombosis and pulmonary emboli. He described the phenomenon, which now bears his name, in patients with adenocarcinoma of the pancreas. However, it was soon recognized that this hypercoagulable state was not limited to pancreatic cancer but also occurs in patients with a variety of other cancers. And it was subsequently recognized that the incidence of clinically important clotting was increased in hospitalized cancer patients, and more recently, cancer patients in the outpatient setting receiving chemotherapy.

The human cost of these thromboembolic events is high, and the economic cost of treating

these frequent complications is also high. The DVT or PE in a patient with cancer may be distressing. These patients have pain, may have swollen legs, difficulty breathing, palpitations, have a high degree of anxiety, and often a feeling of hopelessness. If they survive, they're going to receive subcutaneous injections for at least 6 months and often for the rest of their lives.

PEs and DVTs are not easy for the physician either. They understand that the risk of thrombosis is high and has increased in recent years but is difficult to quantify on an individual basis. A diagnosis of PE or DVT may delay chemotherapy. Continuous high doses of daily subcutaneous heparin expose patients to consequences of the treatment, including the risk of major bleeding and drug-drug interactions.

Personalized decision making and risk-benefit are not new. For all patients, we have to receive what's their major treatment, which platinum doublet, and we have to decide on support of care. And this may include the use of

inhibitors of bone resorption or marrow stimulating factors.

Oncology guidelines have recently recognized the high risk of VTE and morbidity associated with VTE in ambulatory cancer patients receiving chemotherapy. Thus, last year, both the NCCN and ESMO guidelines were revised, and they included the option of considering VTE prophylaxis and ambulatory cancer patients receiving chemotherapy, based on an evaluation of VTE risk. However, there are no drugs approved for the prevention of VTE and these ambulatory cancer patients at high risk for VTE, and there is a likelihood that reimbursement for such therapy would be denied.

The oncology guidelines do not provide any recommendation for any specific agent to use any dose or treatment duration primarily because the risk of major bleeding from current low-molecular-weight heparins offsets the benefit of reduced VTEs. And we know that data from non-cancer patients cannot be extrapolated to cancer patients.

While the FDA in their briefing book list large numbers of drugs approved for the management of VTE and "allows for the clinician judgment to match individual patient needs with options for therapy and with safety factors to consider for each drug and each patient," in reality, only one drug, dalteparin, is approved for long-term administration to cancer patients. And that's for the treatment of VTE and prevention of recurrent VTE. And it is associated with a high risk of major bleeding, even higher than that of Coumadin. The labels of all other drugs in the FDA briefing book contain no data on prolonged administration and no recommendation for patients with advanced cancer or their prophylaxis. If we're to practice evidence-based medicine, we should be able to offer these patients semuloparin.

Earlier this year, the SAVE-ONCO results, which was a well-designed, randomized, double-blind, phase 3 trial, were published in the New England Journal and had an accompanying editorial. SAVE-ONCO is the largest trial ever

done in this population and was designed to evaluate various risk groups, to evaluate safety as well as efficacy, and to determine if there was an effect on survival. In some studies, it indicated a small improvement in overall survival in patients receiving heparin.

The primary efficacy endpoint, reduction in VTE or VTE-related death was observed in the overall ITT population. The hazard ratio was 0.36. In patients with lung cancer, the hazard ratio was also 0.36, whereas it was 0.22 in patients with pancreatic cancer. And these differences were statistically significant with upper boundaries of the 95 percent confidence interval of .76 and 0.77. The majority of the VTEs occurred in these lung and pancreatic cancer patients.

Now, of course FDA regulations require that a drug must be safe as well as efficacious in patients with a proposed indication. As shown in the lower portion of this slide, there was an increase in clinically relevant bleeding with an odds ratio of 1.41, but this was driven by

non-major bleeding since the odds ratio for major bleeding was 1.05.

Now here, the SAVE-ONCO results for semuloparin are contrasted with the results of the Di Nisio-Cochrane meta-analysis that Dr. Khorana presented earlier. This comparison illustrates the favorable benefit-risk ratio produced by semuloparin. The top panel shows VTE and VTE-related death. The bottom panel shows major bleeding. And right at the top of each panel are the results of the meta-analysis.

The SAVE-ONCO results for the overall population and the target population are shown in orange. The efficacy risk ratio for VTE or VTE-related death was 0.62 for low-molecular-weight heparin. The hazard ratio for semuloparin was 0.36 in the overall population and 0.28 in the target population. On the safety side, major bleeding was increased in the low-molecular-weight heparin meta-analysis with a hazard ratio of 1.57. In SAVE-ONCO, the hazard ratio for major bleeding was 1.05 in the overall population and 1.20 in the

target population.

Thus, the results from the large randomized SAVE-ONCO trial showed efficacy that was superior to that reported with low-molecular-weight heparins and was associated with less bleeding complications than were reported with the low-molecular-weight heparin meta-analysis. Thus, the risk-benefit is now much clearer with semuloparin showing better efficacy and less bleeding compared to low-molecular-weight heparins.

Finally, it is important to consider the effect of these preventive majors on mortality. The SAVE-ONCO publication in the New England Journal was accompanied by an editorial. Its authors, Drs. Akl and Schunemann, had recently published a separate Cochrane meta-analysis, focusing on the effect of heparin derivatives on mortality in cancer patients. To look for trends, they pulled the results from their meta-analysis with those of the SAVE-ONCO study in a more recently reported study in 500 additional cancer patients, totaling 6,245 patients. The relative

risk of death at 12 months was 0.94 with a 95 percent confidence interval of .88 to 1.0.

When we look at the survival curves in the target population from SAVE-ONCO, the results are reassuring. In this population at high VTE risk, the survival hazard ratio is 0.88, and the upper bound of the confidence interval is 1.0. These results are consistent with the meta-analysis. The Akl editorial concluded that the findings suggest heparin derivatives induce a small survival benefit. I'm somewhat uncomfortable with that conclusion, but the data are certainly reassuring that there is no increased risk of early progression or death.

My clinical take on reviewing these data suggests the following conclusions. The SAVE-ONCO study that was conducted in more than 3,200 cancer patients provides compelling evidence for a favorable benefit-risk ratio of primary VTE prophylaxis in ambulatory cancer patients receiving chemotherapy. SAVE-ONCO results should lead to changes in clinical practice. And in particular,

VTE risk should be assessed in all cancer patients at the time of initiation of cancer chemotherapy. Cancer patients at high risk of VTE should be considered for routine thromboprophylaxis with subcutaneous semuloparin. Pros and cons of VTE prophylaxis should be discussed with each patient. And finally, treatment guidelines now will require reconsideration based on these results.

I personally would like to have the option to offer semuloparin to my high-risk patients because they would prefer to avoid the complications in the first place. And I'm pleased that this VTE prevention therapy is a proven option for high-risk patients. Thank you very much.

DR. GURAL: Mr. Chairman, that concludes our formal presentation. We do have a number of other internal and external experts with us today. So if you have any clarifying questions at this time, we'd be pleased to answer them.

DR. WILSON: Thank you very much.

We will now proceed with the FDA's presentation.

FDA Presentation - Jeanne Herndon

DR. HERNDON: Good morning. My name is Jeanne Herndon. I'm a medical officer in the FDA Division of Hematology Products, and I will be presenting the FDA clinical review for semuloparin.

The applicant's proposed indication is shown on this slide. Semuloparin is being proposed for the prophylaxis of venous thromboembolism in patients receiving chemotherapy for locally advanced or metastatic solid tumors. Please note that on January 31, 2012, following discussion with the agency, the applicant proposed a revised indication: prophylaxis of VTE in patients receiving chemotherapy for locally advanced or metastatic pancreatic or lung cancer, or for locally advanced or metastatic solid tumors with a VTE risk score greater than or equal to 3.

This slide shows the numbers of the FDA review team for this application. I will begin my presentation with the regulatory history and description of semuloparin, along with an overview of its clinical development program. Following

that, I will briefly review venous thromboembolism in cancer and current guidelines for prevention. I will then discuss the FDA clinical review of pivotal trial SAVE-ONCO in ambulatory patients with cancer with statistical review presented by Dr. Kyung Yul-Lee. Finally, I will conclude with a risk-benefit analysis and summarize the main issues pertinent to this application.

The initial IND for semuloparin was submitted to the FDA in March of 2006. On November 16, 2007, an end-of-phase 2 meeting was held between the applicant and FDA to discuss the design of phase 3 studies for the VTE prophylaxis development program. The pivotal trial for the indication under review was not conducted under an SPA agreement.

The proposed new drug, semuloparin, is a low-molecular-weight heparin that is derived from depolymerization of heparin. The average molecular weight distribution ranges between 2 and 3 kilodaltons. Similar to other low-molecular-weight heparins, semuloparin's mechanism of action is

through enhancement of antithrombin, which accelerates the inactivation of factor Xa and thrombin. It has preferential anti-Xa activity relative to anti-IIa activity.

This slide shows an overview of the semuloparin clinical development program. The applicant has conducted six phase 3 trials during development for VTE prophylaxis. A seventh trial in acutely ill medical patients was initiated but terminated early. Although a broad development program was originally pursued for VTE prophylaxis indications, the applicant is submitting only one trial, SAVE-ONCO, for registration. The remaining phase 3 trials were not reviewed by the FDA as part of the current NDA application for the cancer indication. However, I will briefly highlight the main findings from the applicant's analyses.

Shaded in gray in this table are the active control trials conducted against enoxaparin. Semuloparin failed to meet the primary efficacy endpoint in three out of four of the completed active control trials in patients undergoing knee

replacement, hip fracture surgery, and major abdominal surgery. Only one of the four enoxaparin controlled trials, SAVE-HIP 1, met the primary endpoint of any VTE or all-cause death, but did not meet the secondary efficacy endpoint of major VTE or all-cause death.

Shown at the bottom of the table, two successful trials of semuloparin were conducted against placebo control, which includes the current pivotal trial, SAVE-ONCO, in patients with cancer. The FDA review focuses on data from the SAVE-ONCO pivotal trial. It is noted, however, that patients with cancer were also included in the SAVE-ABDO trial, highlighted here, and conducted in patients undergoing major abdominal surgery.

An FDA exploratory analysis in the subgroup of patients undergoing cancer surgery revealed that more patients in the semuloparin arm experienced primary endpoint events of any VTE or all-cause death compared to enoxaparin. Although the analysis is exploratory, this subgroup comprised 81 percent of subjects in this large trial of over

4,000 patients.

The clinical setting in SAVE-ABDO differs from the indication sought by the applicant. However, it is the only other supporting trial of semuloparin in patients with cancer. The trial overall failed to demonstrate noninferiority of semuloparin to enoxaparin, with an odds ratio of 1.16 and the upper bound of the 95 percent confidence interval, 1.59, failing to meet the prespecified, noninferiority margin of 1.25 for the primary endpoint, suggesting that semuloparin may not be as effective as enoxaparin in this setting.

Listed on this slide are the anticoagulant agents that are currently approved in the United States for the prophylaxis of venous thromboembolism. Among low-molecular-weight heparins, the currently available agents for VTE prophylaxis include enoxaparin and dalteparin. Please note that the prescribing information for each of these anticoagulant drugs listed on this slide provides for specific indications of use, including treatment and prophylaxis.

The decision to initiate anticoagulant therapy in a patient remains an individualized decision between patient and physician. This decision is determined on a case-by-case basis, and clinicians are encouraged to consider the individual benefits and risks for each patient. Currently, no agents are approved specifically for the proposed indication in ambulatory patients with cancer.

In patients with cancer, venous thromboembolism occurs at an incidence that ranges between 4 and 20 percent. It is the second leading cause of death in this population. VTE risk level varies considerably among patients with cancer. This variation in risk is attributable to differences in tumor, therapy, and patient-related factors. Despite an overall increase in VTE risk on the other hand, bleeding complications from anticoagulation are also increased in patients with cancer and have been observed to be as high as twofold the risk of bleeding in patients without cancer.

A current set of guidelines recommended by the American Society of Clinical Oncology in 2008 for VTE treatment and prevention in patients with cancer recommends the following: anticoagulant use is indicated in the treatment of diagnosed VTE, and extended is treatment is recommended for the prevention of VTE recurrence. Routine prophylactic anticoagulation is not recommended for patients with cancer, except in hospitalized patients, those undergoing major oncological surgery, and in patients receiving thalidomide- and lenalidomide-based therapy.

As reflected in the ASCO guidelines, data on the use of prophylactic anticoagulants to improve survival in patients with cancer who do not have VTE is inconclusive and is not recommended. Practice guidelines issued by other groups, such as NCCN and ACCP, issued in 2011 and 2012, reflect similar recommendations. Thromboprophylaxis is not recommended for routine use in ambulatory patients undergoing chemotherapy, except in selected patients at high risk.

Approval of this application would thus in effect change current practice and set a new standard of care that affects a large number of oncology patients in the United States. Hence, in a meeting between the sponsor and FDA, post-submission of the NDA, the agency requested that the sponsor identify and narrow the proposed indication to a target population that might benefit from the proposed treatment.

I will now discuss the applicant's pivotal trial, EFC6521, hereafter referred to as SAVE-ONCO. SAVE-ONCO was a multicenter, phase 3, randomized, double-blind placebo controlled trial conducted between June 2008 and November 2010. The trial enrolled 3,212 patients with cancer who were to receive chemotherapy for locally advanced or metastatic solid tumors.

Patients were randomized 1 to 1 to receive either placebo or semuloparin, 20 milligrams daily, by subcutaneous injection. Randomization was stratified by region, location of primary tumor site, and stage of disease. Treatment was started

at the initiation of chemotherapy, and it was continued for a minimum of 3 months and until the change of antineoplastic regimen, unless chemotherapy was permanently discontinued earlier, due to disease progression or toxicity.

Eligibility for this trial included adults with metastatic or locally advanced solid tumor. The applicant chose the following types of cancer for study: primary tumors of the lung, pancreas, stomach, colon, rectum, bladder or ovary. Patients were to be initiating a new course of chemotherapy with minimum intent of 3 months.

Importantly, please note that study enrollment was limited to patients who did not require VTE prophylaxis. Due to the placebo controlled design, high-risk patients who were deemed to require prophylaxis with approved anti-coagulants were excluded from the study.

The primary endpoint of the trial was time to first occurrence of any component of a composite endpoint of VTE events, from randomization up to three days after the last dose. All VTE events

were confirmed by a blinded, central, independent adjudication committee and were designed as follows: symptomatic deep vein thrombosis of the upper or lower limbs, including central venos catheter-related thrombosis, nonfatal pulmonary embolism, and VTE-related death, consisting of fatal PE or unexplained deaths.

All clinical diagnoses were to be confirmed by imaging within 72 hours. For DVT, either by abnormal ultrasound or venogram, and for PE, by either spiral CT scan, pulmonary angiogram, or ventilation perfusion scan, deaths were adjudicated by central review as either VTE related, fatal bleeding, or other. Bleeding adverse events were also adjudicated centrally and will be discussed further in the safety section.

The main secondary endpoint was overall survival at one year or end of study of earlier. The study was designed to have 90 percent power with a sample size of approximately 3,200 to detect the hypothesized 50 percent relative risk reduction for semuloparin versus the assumed placebo event

rate of 4 percent at a significance level of alpha of .05. Sequential testing of the secondary endpoint overall survival at one year was to be performed at an alpha of .05 if the primary endpoint was significant.

The demographics and baseline characteristics of patients enrolled in trial SAVE-ONCO, including age, gender, race and renal status, were generally well-balanced between treatment arms. Of note, more than 90 percent of patients in this trial had an ECOG performance status of either zero or 1, indicating a patient population with only mild or no restriction of physical activity. Forty percent of patients had an ECOG score of zero, defined as fully active with no restriction in activity.

Primary tumor types for both treatment arms are listed on this slide. Thirty-seven percent of patients had lung cancer, and 29 percent had colorectal cancer. Thirteen percent and 12 percent, respectively, had gastric or ovarian cancer, while 8 percent had pancreatic cancer. The

majority of patients enrolled in the pivotal trial were from Eastern and Western Europe. Patients from North America comprised 6 percent of the SAVE-ONCO study population.

The presence of additional VTE risk factors other than cancer are listed on this slide. Note that more than half of patients in the trial had no additional risk factors and that nearly 90 percent had no more than one additional risk factor, such as the presence of a central venous catheter, use of hormonal therapy, history of DVT or PE, chronic respiratory or heart failure, venous insufficiency, obesity, or advanced age greater than or equal to 75 years.

Due to the heterogeneity of cancer diagnoses in the enrolled study population, patients in trial SAVE-ONCO received varying concomitant chemotherapy. The most common agents included platinum compounds and pyrimidine analogues. Treatment arms were balanced with respect to concomitant chemotherapy agents received. The median total duration of chemotherapy was

3.1 months, with 93 percent of patients receiving one chemotherapy regimen.

The median duration of study treatment in both arms was approximately 3 and a half months. Note that over one-third, 36 percent of patients in the trial, did not complete the study treatment period. Approximately 18 percent of subjects overall requested discontinuation of the study treatment, which involved daily repeated self-injections subcutaneously. This rate of subject requests for discontinuation of study treatment was not related to poor compliance or loss to follow-up.

At this point, I will turn the presentation over to the primary statistical reviewer, Dr. Kyung Lee, who will present the FDA analysis of efficacy data from the pivotal trial.

FDA Presentation - Kyung Lee

DR. LEE: Good morning. I am Kyung Lee. I will present the efficacy results and statistical issues of the SAVE-ONCO study. The primary endpoint was time to VTE or VTE-related death.

This analysis used the statistical method that accounts for competing risks. Competing risks are events whose occurrence precludes or greatly alters the probability of the main event from occurring. In this case, those associated competing risks were non-VTE-related deaths while patients were being followed for the primary endpoint. Gray's test was employed for the primary analysis.

This slide describes patient follow-up according to the protocol. There were no scheduled assessments. Assessments were performed only in the presence of symptoms. There were no assessments or adjudication beyond three days after the last dose. Subjects without documented VTE were censored as three days after the last dose, even when no assessments were done.

Almost all events occurred within the first 4 months. For each treatment arm, we see percentages of events, competing risks, and the censoring by month. The black-filled bars are the percent censored. The amount of early censoring overwhelms the number of non-events in both

treatment arms. 33.4 percent of patients in the semuloparin arm and 31.5 percent in the placebo arm were censored within the first 3 months of the study. Approximately, half of all patients were censored by 4 months.

This graph shows the percent of patients remaining to be followed for the primary endpoint by month for both treatment arms. Less than 62 percent were followed for 3 months. Three months was the expected minimum time on treatment, according to the protocol. About 12 percent were followed for at least 6 months.

Now, the primary analysis. The number of VTE or VTE-related deaths was 20 events in semuloparin versus 55 events in placebo. Seventy-two of the total 75 events occurred in the first 4 months. No events occurred after 6 months. The hazard ratio was .36 favoring semuloparin. The results were statistically significant.

This table shows the components of the primary endpoint. Some patients had more than one component: symptomatic DVT, .7 percent in

semuloparin versus 2.1 percent in placebo; pulmonary embolism, .6 percent in semuloparin versus 1.5 percent in placebo; and any VTE-related death, .4 percent in semuloparin versus .6 percent in placebo.

Overall survival was a secondary endpoint. Subjects were intended to be followed for overall survival for a maximum of 12 months. The majority of subjects alive at 12 months had their follow-up for survival immediately discontinued. As follow-up was elective after 12 months, the FDA analysis of overall survival is limited to 12 months. The hazard ratio for overall survival was .95, which was not statistically significant.

This table shows the subgroup analysis by primary tumor and VTE risk score. The shaded regions of the table are the subgroups that are included in the sponsor's proposed indication. The observed variability of the event rate in the placebo arm suggests that patient population is heterogenous. These subgroup analyses were not prespecified.

The results of the primary endpoint analysis for patients with lung cancer, pancreas cancer, or VTE risk score greater than or equal to 3 are provided here. The number of VTE or VTE-related deaths were 12 events in the semuloparin arm versus 43 events in the placebo arm. The hazard ratio was .28. Here are the overall survival results for the subgroup in the revised indication. This analysis was not prespecified.

A common assumption in survivor analysis, including the method employed in this study, is that censoring is not related to the outcome of interest; in this case, VTE or VTE-related deaths. Common causes of censoring are patients reaching the end of the study period without having the event of interest and patients dropping out of this study.

Censoring is informative when the prognosis of the patient at their censored time is different from that of patient on the same treatment arm still being followed for an event. Informative censoring can lead to significant bias, as well as

increased variability in the evaluation of treatment effects.

In reviewing the survival data, we found that those patients censored early in the primary analysis had shorter survival times compared to patients having longer follow-up in the primary analysis. Informative censoring would violate an assumption under which the primary analysis was performed.

This graph will help demonstrate this point. Provided here are the Kaplan-Meier curvers for VTE or any death and for overall survival for the semuloparin arm. We see that the Kaplan-Meier curve for overall survival is below the curve for VTE or any death. For example, at 3 months, 94 percent of subjects are estimated to be alive and VTE free, and 90 percent are estimated to be alive as noted by the vertical line.

This is a contradiction. The percent alive should always be greater than or equal to percent who are alive and VTE free. This contradiction is due to the early-censored patients having shorter

survival times than patients with longer survival. This is suggestive of informative censoring. A similar pattern was observed in the placebo arm.

In summary, the primary endpoint time to VTE or VTE-related death was met with hazard ratio of .36. In the revised indicated population, the hazard ratio was .28, favoring the semuloparin arm. There was no difference in overall survival.

Several issues call into question the robustness of this trial. There were many patients censored early in the trial, but there were few events. 32.5 percent of all patients were censored within 3 months of randomization, and only 2.3 percent of all patients had events in that time. Note that 3 months is the minimum 3-month period for the study. Also, the premature censoring in both arms appears to be informative. Informative censoring would violate a basic assumption of the analysis.

The SAVE-ONCO trial just reviewed is the only clinical trial supporting this indication in this population. Although not in the same

population, the only other study, SAVE-ABDO, which included cancer patients, did not show noninferiority to enoxaparin.

Thank you. Now, Dr. Jeanne Herndon will continue the presentation with the safety evaluation.

FDA Presentation - Jeanne Herndon

DR. HERNDON: At this point, I will now present the FDA analysis of safety data from the pivotal trial.

The median duration of study treatment in trial SAVE-ONCO was approximately 3 and a half months in both treatment arms. The key safety finding of semuloparin in this trial was bleeding complications from therapy. I will discuss these first, as they were prespecified safety endpoints, and then discuss the remaining adverse events and safety findings overall.

All bleeding events in the pivotal trial were adjudicated by blinded independent central review, and were categorized according to the International Society on Thrombosis and

Haemostasis' recommended definitions, as follows.

Major bleeding was defined as fatal bleeding, symptomatic bleeding in a critical area or organ, such as the examples listed on this slide, or bleeding causing a decrease in hemoglobin level greater than or equal to 2 grams per deciliter, or leading to transfusion of 2 or more units of whole blood or red cells.

Clinically relevant non-major bleeding was defined as all overt bleeding events requiring a medical intervention and not meeting any of the criteria for major bleeding. All other bleeding events not meeting the criteria for these categories were classified as non-clinically relevant bleeding.

Overall in trial SAVE-ONCO, 20 percent of patients in the semuloparin arm experienced a bleeding adverse event of any category, compared to 16 percent in the placebo arm. A slight excess in the semuloparin arm was also seen for serious bleeding adverse events and bleeding adverse events leading to treatment discontinuation.

As adjudicated centrally, more subjects in the semuloparin arm, 2.8 percent, experienced clinically relevant bleeding events compared to the placebo arm, 2.0 percent. Approximately half of these events were adjudicated as major bleeding and half as clinically relevant non-major bleeding, but requiring medical intervention. Transfusion rates for red blood cells, platelets and other blood products were similar between the two treatment arms.

Similar safety findings were seen across subgroups as shown on this slide. This includes the applicant's selected subgroups for the revised indication in lung or pancreatic cancer or in patients with a VTE risk score greater than or equal to 3, which are highlighted in gray.

Major bleeding occurring in the pivotal trial is summarized on this slide. Although the total number of patients experiencing a major bleed was similar between treatment arms, six patients in the semuloparin arm were adjudicated as having symptomatic bleeding into a critical area or organ.

These cases included 2 pericardial bleeds, 1 intraocular bleed resulting in retinal detachment, and 3 intracranial bleeds of which one case was fatal. No patients in the placebo arm experienced bleeding into a critical area or organ.

In addition to the six adjudicated cases in the semuloparin arm, FDA analysis considers an additional patient who experienced life-threatening splenic hemorrhage to meet the criteria of symptomatic bleeding into a critical area or organ. This seventh patient developed abdominal pain on day 63 of semuloparin treatment. Despite a diagnosis of splenic hematoma, the patient continued to receive study therapy, resulting in progressive bleeding, requiring splenectomy on day 72.

Adverse events other than bleeding, both incidence and types, did not differ significantly between treatment arms. Overall, approximately 85 percent of subjects in the pivotal trial experienced treatment-emergent adverse events. As expected, the majority of adverse events were

related to chemotherapy received concurrently with study therapy.

Approximately 26 percent of patients in each treatment arm experienced serious adverse events. Types of SAEs were balanced between arms and, again, were attributable to concurrent chemotherapy or underlying disease. These included infection, cytopenias, malignancy progression, and gastrointestinal adverse events.

As discussed previously, an overall high mortality rate was observed in this study. Sixteen percent of patients in each arm died during this study, during the treatment period, and through follow-up to the last protocol visit. Observed deaths by one year were 40 percent in the semuloparin arm and 41.5 percent in the placebo arm, reflecting the advanced stage of disease in the enrolled population. Causes of death were similar between treatment arms, and there was no excess death due to bleeding complications in the semuloparin compared to the placebo arm. Of note, fatal PEs represented less than 1 percent of

on-study deaths in either treatment arm.

In summary, the benefit-risk analysis of semuloparin in the applicant's proposed indication, based on the single pivotal trial, SAVE-ONCO, considers the following. The clinical benefit from treatment consisted of an observed 2.2 percent absolute risk reduction in symptomatic VTE events over placebo, with a less than 0.2 percent reduction in VTE-related death. There was no difference in one-year survival, with approximately 41 percent of patient deaths observed by one year of study follow-up.

Risks associated with semuloparin treatment included an overall increase in bleeding adverse events. Although the numbers of patients in the overall category of major bleeding was similar between treatment arms, several patients in the semuloparin arm developed major bleeding into a critical area or organ not observed in the placebo arm.

With respect to the applicant's selected subpopulation, patients with lung or pancreatic

cancer, or VTE risk score greater than or equal to 3, a similar benefit-risk analysis is shown on this slide. Treatment benefit in the subpopulation consisted of an observed 3.7 percent absolute risk reduction in symptomatic VTE events over placebo. Patient mortality was higher in this subpopulation, with 47 percent and 53 percent observed deaths by one year. However, similar to the overall trial population, VTE-related death comprised less than 1 percent of patient deaths in each arm, and the absolute risk reduction was, again, 0.2 percent over placebo.

Risks associated with semuloparin treatment in the applicant's selected subpopulation were as discussed previously in the overall trial population. There was a slight increase in bleeding adverse events and major bleeding. However, critical organ bleeds occurred with semuloparin treatment, which were not observed in the placebo arm.

Considering the results of the SAVE-ONCO trial, this slide shows the estimated numbers of

patients that would need to be treated to prevent one VTE event, as listed on the left-hand column, or similarly to cause one semuloparin bleeding adverse event, listed in the right-hand column. For example, 46 patients would need to be treated to prevent one symptomatic VTE event of any kind. On the other hand, one bleeding adverse event would be caused for every 25 patients treated with semuloparin.

Similarly, over 100 patients would need to be treated to prevent one pulmonary embolism. And for roughly the same number of patients treated with semuloparin, one clinically relevant bleeding event would be caused by therapy. In particular, note that nearly 800 patients would need to be treated with semuloparin in order to prevent a single VTE-related death. By contrast, for every 227 patients treated with semuloparin, one critical organ bleed is caused by the proposed therapy, meaning that for each VTE-related death prevented, 3 to 4 critical organ bleeds are caused by semuloparin therapy.

This next slide shows the same benefit-risk analysis calculated in the same manner for the applicant's selected subpopulation, patients with lung or pancreatic cancer or a VTE risk score greater than or equal to 3. Although the estimated numbers needed to treat to prevent one symptomatic VTE event or pulmonary embolism are lower than for the larger trial population, please note still that over 400 patients would need to be treated with semuloparin in order to prevent a single VTE-related death. By contrast, one critical organ bleed would be caused for every 206 patients treated with semuloparin, meaning that for each VTE-related death prevented, 2 critical organ bleeds are caused by semuloparin therapy.

In conclusion, the FDA review of this application has identified the following clinical, statistical and regulatory issues. The applicant presents a single pivotal trial to seek approval of semuloparin for a new indication without other supporting efficacy data. As no other anticoagulants are approved for this treatment

setting, the approval of this application would change the practice of medicine and affect a large number of oncology patients in the United States.

The efficacy of semuloparin is not supported by trials in other better understood VTE prophylaxis indications in orthopedic surgery and major abdominal surgery.

Second, the interpretation of clinical efficacy in the single, pivotal trial is compromised by a large proportion of premature censoring, 32.5 percent, which undermines confidence in the observed results.

Third, the magnitude of clinical benefit observed in the pivotal trial was modest, consisting of an absolute risk reduction of 2.2 percent over placebo, with less than 1 percent of subjects experiencing a fatal VTE event in each treatment arm, for both the overall trial population and also for the applicant's selected subpopulation, patients with lung or pancreatic cancer or VTE risk score greater than or equal to 3.

By contrast, high patient mortality was seen in these patients with advanced disease and was due primarily to underlying disease and non-VTE-related complications. Approximately 41 percent of patients overall died over one year of follow-up, with no survival advantage observed from semuloparin treatment. These findings call into question the clinical value of semuloparin in the proposed clinical setting.

Finally, although the applicant has proposed a revised, narrow indication in response to agency requests, it is unclear whether a target population suitable for treatment has been identified and adequately supported, based on subgroup analysis of the applicant's single placebo control trial in an heterogenous group of patients with cancer.

Considering these issues, we will be asking the committee to discuss the following.

Is there sufficient experience to inform the use of semuloparin for VTE prophylaxis in this previously untargeted population of patients with cancer?

Should the target population considered for this use be narrower than the population studied in SAVE-ONCO?

Based on the discussion, we will be asking the committee to vote on the following question.

Is there sufficient demonstration of a positive benefit-to-risk assessment to recommend approval of semuloparin for thromboprophylaxis in any population or subpopulation of patients with cancer? If yes, please define this population in your discussion after your vote.

Clarifying Questions from Committee

DR. WILSON: Thank you very much. We'll now take questions for the presenters. For those of you who have not served on the committee before, please raise your hand. Your name will be recognized by -- well, will be listed by Caleb, and I will call you in turn. However, I will start out.

One of the things -- I do think that -- I want to commend the sponsor for having done this large study. I think that the question at hand is

really extremely critical because, as has been stated, this will in many ways, if approved, lead to a potential change in practice that has not yet been recognized by the major groups out there. And so I think that we need to look at this very seriously.

I think we see from the entire study that the reduction in VTEs or VTE-related mortality was reduced from 3.4 to 1.2 percent. We also recognize that prophylaxis is not without its own complications. So I'm trying to come to grips with is there a group here that seems to benefit from this to justify, at least for myself, whether or not I would use it.

So I do see the sponsor has narrowed their indication to lung and pancreas or to patients that have a VTE greater than or equal to 3. My question is how they have arrived at lung and pancreas alone. I realize they're giving the relative incidences of VTE or VTE-related deaths in each group, but what percent of the lung and pancreas group had a VTE risk score greater than or equal to

3? In other words, is much of the lung and pancreas simply being driven by having a high VTE risk score, and should the risk score alone be a more appropriate narrowing of indication? It certainly seems to be what is being used or what is being stated as a potential endpoint to be considered in some of the guidelines.

DR. GURAL: Yes. Perhaps we could ask Dr. Zaks to address that question. Obviously, we have looked at this ourselves.

So Dr. Zaks.

DR. ZAKS: Yes. Thank you. If I could have slide EF-211? Thank you. Slide up, please.

Here you can see the incidence of VTE in the placebo arm, again, of the SAVE-ONCO study, either in lung cancer or pancreatic cancer, or if we look across, by VTE risk score. And certainly, I think there are a couple of salient points here.

First, the risk score overall holds up in that it identifies a higher population of patients at risk across the board in most of these solid tumors. Within lung and pancreatic cancer, at

least within SAVE-ONCO, the ability of the risk score to further distinction -- to further provide an assessment of risk is limited, and the majority of cases actually occurred in those who have the intermediate risk score. Of course by definition of these two cancers, none of these patients would fall into the low-risk category.

So this is really an alternative approach at looking at patients at high risk. Those with lung and pancreas have a substantial, intrinsic risk, and then those with the other solid tumors would be indicated if the risk was high.

DR. WILSON: Okay. Thank you. That was very helpful.

My second question really gets at is preventing a VTE really being useful, from a clinical point of view. We heard some very nice statements that preventing a clot prevents a delay in chemotherapy, prevents the use of full-dose anticoagulation that could then to lead to bleeding. But we didn't really hear any of the data, whether or not the projected benefits of

preventing a clot really were accomplished here, and I think that's because that was probably not captured. But I would like to know whether or not any of that was captured.

However, VTE-related deaths was one of the endpoints here. And I did want to get the company's perspective on this because it looks to me like there was a small reduction, only two cases, between the two groups, the placebo and the treatment group, of any VTE-related deaths. But from what I can tell here, every single one of these was due to an unexplained death, and none of them were due to a documented death due to a VTE.

I just want the company to confirm that.

DR. GURAL: There were a number of components to your question. We would ask first Dr. Lawson to address the specific concerns on the death-related, and then perhaps Dr. Bunn can talk about the clinical implications.

DR. LAWSON: Yes. Slide up, please. The adjudication committee, according to the manual, followed a very, very conservative approach. So

any death that was potentially, like a sudden death -- because no body had an autopsy -- that was compatible with a PE had to be adjudicated as VTE -- sorry, as PE, could not be ruled out. And so it was included in the VTE-related death.

In this slide you can see -- so we had overall 16 VTE-related deaths, 7 in semuloparin and 9 in placebo. And of those, only one was adjudicated as a PE in the placebo by the adjudication committee. All the others and all the ones in semuloparin were considered as unexplained death.

According to the investigator, 4 were fatal PE in the placebo and zero in semuloparin. So we really had the methodological issues because of course in a cancer study, we cannot perform autopsy, so we couldn't really assess PE. For the PE that was diagnosed, the non-fatal PE, that could only be diagnosed if it was confirmed by imaging. And in that case, we observed 80 percent reduction in incidence of PE, from 15 events in placebo, 3 events in semuloparin. And we note non-fatal PE at

the same pathogenetic mechanism. So it could be a surrogate endpoint for that.

I'll let Dr. Bunn comment on the clinical relevance of preventing an event.

DR. BUNN: In this trial, they didn't measure patients' symptoms. But certainly, we've all experienced people who have DVTs and PEs. One of the interesting features of why is the incidence of deep venous thrombosis and PEs increasing, I think it's for two reasons. One is the chemotherapy we use and the antiangiogenics and the central lines we use have increased. But also there's an increase in incidental PEs found by CT scanning. And certainly in lung cancer, these patients have routine CT scans, and incidental PEs are found. Now, incidental PEs have the same problem as a regular PE in terms of mortality and morbidity, and they also require treatment.

Now, when the FDA was talking about prophylaxis of approved agents, those are people who have a PE or a DVT, and they get treated. Okay? But then they get treated for the rest of

their life because that's prevention of a second recurrence. If you stop, there's a high risk of recurrence. It's much better to prevent it in the first place.

So when you look at low-molecular-weight heparins, the guidelines and evidence-based medicine don't suggest that they should be used, even though they've been proven to reduce VTE or VTE-related death. And the reason was because of the risk of bleeding. And here with this agent, we have a better risk-benefit ratio because there is a better hazard ratio for prevention of VTE and also a lower risk of bleeding. And I think the minor bleeding is nose bleeds and injection sites. And those are really of no clinical relevance.

So in my opinion, I treat people, and many of them get DVTs and PEs, and they're on heparin, a riskier heparin, for a long period of time. So I think that you've asked the right questions. I think the questions that you're asking are incredibly important. And if you're asking my opinion on the clinical relevance, I think it's

totally clinically relevant.

DR. WILSON: Okay. Thank you very much.

Dr. Buzdar?

DR. BUZDAR: Yes. I have a question and comment on the sponsor's presentation, which was slide number 36, which is actually bleeding as reported by the investigator, adjudicated as a major event.

If we look at it over there, the GI hemorrhage occurred in the placebo arm at twice the rate of the patients who were actually receiving anticoagulation therapy. There are 15 events in the placebo group and 7 events in the actual intervention arm. And if you look at it, the fatal events occurred in the placebo group, 4 patients in that subgroup.

If we take this out, then actually the safety profile becomes exactly the opposite, means that active intervention is causing more a significant event, because otherwise it does not make any sense why in the placebo arm there should be twice as many GI bleeds, unless they have looked

at it and there are differences or some explanation for twice as many events observed in the placebo arm.

That is exactly what the FDA point is, because if you look at it, all the other events, which could be potentially life-changing, like cerebral hemorrhage, vitreous hemorrhage, pericardial events, in the placebo arm there are zero.

Any explanation?

DR. GURAL: Yes, perhaps Dr. Zaks.

DR. ZAKS: Yes. I mean, these are the data as we found them in the study. I think that when one looks at a 3200 patient study, which is the largest ever conducted, and one looks at events whose rate is low, I think the point estimate for the confidence of what that hazard ratio is, is obviously difficult.

The number of cases here is overall very small. These were four cases on the placebo arm out of 1600 patients studied, in patients with advanced cancer. So I don't know that I have a

clinical explanation for those cases beyond that. But I would say that as far as a prespecified understanding of what one expects to see as far as major bleeding events and the reason that this was included is, first of all, the definition of a major bleeding event is an accepted one in the literature for anticoagulation agent. You've seen the data for the meta-analysis. And even in our own study, you can see that those events that are not bleeding into critical organs but the rest of them, actually contribute to mortality. And that's why we think including the overall major is important.

I think the question here really is, when one looks at the benefit risk, how does one assess the absolute increase in risk. And in that regard, it's a function of what is your point estimate for the hazard ratio and what is the relevant endpoint to use.

If I could have -- thank you. Slide up. The FDA has proposed looking at this through various angles of those bleedings that are all

clinically relevant, or all bleeds, or those that are just into critical organs. I think from a standpoint of the way the study was designed and our understanding of bleeding with anticoagulants, I think there are three levels at which one looks at this: all the bleeds, whether they're relevant or not, as the investigator reported them; and then the ones that the adjudication committee considered as clinically relevant, which was a small minority of them; and then within those that are considered clinically relevant, there are those that are considered major.

Now, what are those bleeds that are clinically relevant but non-major? And you can see them up here. These are really relatively minor events of hematuria, epistaxis, et cetera, things that do require a clinical intervention. But their clinical implication, if we look at the NCIC criteria, for example, they would be scored as grade 1 or 2. They wouldn't be the grade 3, 4 or even 5 that we associated with VTEs or VTE-related events. And that's a long-winded way of saying

this is why we chose the major bleeding as the most accurate comparator we felt to assess the benefit-risk here.

DR. BUZDAR: I think I still -- it doesn't answer the question of why there were twice as many GI bleeds in a patient population which is not receiving active intervention. And also, a post procedural hemorrhage, which was major, again, occurred in the patient population who is not receiving any anticoagulation.

So was there any difference in the population, that this patient population received a different type of systemic therapy, which put them at an increased risk of bleeding? There has to be some other explanation. If I was the sponsor, I would look at it in far more detail in these 15 patients, because that is what makes the safety profile exactly 180 degrees the other way around.

DR. ZAKS: So we looked in detail. I can say that the study was overall very well-balanced for all the major characteristics, as one would expect from such a large study. It was

multi-central; it was international. There are no other characteristics beyond to say that -- as one would expect the tumor types where one sees this.

I'm sorry. Could you bring that slide, please, back up? The tumor types would be more of the gastrointestinal tumors, where one would see a gastrointestinal hemorrhage.

Thank you. Slide up, please. And this is the distribution of those cases. But I don't think -- again, with a relatively small number of cases here, overall compared to the size of the study, I can't provide any further explanation than that.

DR. WILSON: Maybe you could enlighten us as to how "major" was defined and how that broke down among these various cases.

DR. GURAL: Dr. Lawson, if you could address the definition of "major" according to the guidelines.

DR. LAWSON: The major bleeding was adjudicated by an external committee in accordance with the ISTH guidelines. So in that respect, it

means all the fatal bleeding, bleeding into a critical area or organ, and bleeding that caused either a drop in hemoglobin of 2 or more, or regarding 2 or more transfusions.

So all the bleedings that occurred in SAVE-ONCO study were all submitted to the independent adjudication committee. And there was a two-membered adjudication committee, shared by Dr. Mark Levine at McMaster University. And there were two independent adjudicators who would review all cases. They would receive the hospital charge, the CRS.

Please, slide up. They received it for each event. It was the same committee that adjudicated the DVT/PE bleeding and the cause of death. And there was all the time two members that would assign the classification. And then if it was disagreement, there would have been another committee of two members. And then eventually, if disagreements still persisted, it would have been a consensus meeting.

DR. WILSON: Right. Thank you. But my

question was a little more specific. Did you look at the actual -- did you look at what the actual bleedings were? Like for the GI, were they upper GI? Were they major unit bleeds, gross bleeds? I'm just trying to get a little more understanding of Dr. Buzdar's question. This could simply be just statistical variation, but did you look at, I mean, the nature of these bleeds? These people dropped their hemoglobins a lot. Were they grossly -- having gross GI bleeds? Were they lower GI bleeds?

Do you have any of that? It sounds like the answer is no. If you don't have it, just say no.

DR. LAWSON: Do we have the information? I don't have a slide.

DR. WILSON: Okay, that's okay.

DR. LAWSON: Right, all the events.

DR. WILSON: That's fine. I was just trying to help try to get at this.

Dr. Sekeres?

DR. SEKERES: Thank you, Dr. Wilson.

I'm also going to be focusing on bleeding,

and I'm going to ask for clarification to a couple of slides. The first is actually FDA slide 47, where you drill down into bleeding into critical areas.

So I'm trying to just add everything up here. It looks like there are, by the sponsor analysis, 6 incidences of bleeding into critical areas, plus 13 patients who have a hemoglobin drop of 2 or need a blood transfusion to add up to 19. Within that hemoglobin fall of 2 or needing a blood transfusion, how does that intersect with the slides we've just seen that talk about major bleeds?

In other words, was major bleed -- is it possible that for some of these major GI bleeds, somebody dropped a hemoglobin of 2. And an investigator may have said, well, it may be a GI bleed, and then this was classified as a major bleed?

DR. ZAKS: So let me just clarify the question. You're correct in that that one splenic case was just simply previously captured as major

requiring transfusions. And now is major under bleeding in a critical organ, but it's still in the same denominator.

DR. SEKERES: Right. So the question is -- we're all trying to drill down into these major bleeds because, obviously, our recommendation here is all going to boil down to the potential benefits of preventing life-threatening DVT or PEs versus the risk of causing major bleeds in patients who have enormous competing risks in being treated for serious cancers.

When we see this number here, these 13 patients who were classified as having a hemoglobin drop of 2 or greater, or requiring a blood transfusion, how did those 13 patients intersect with the slide we've seen before of a list of patients who've had major bleeds? Is it possible on that other slide, where somebody was characterized as having a major GI bleed, that actually there may not have been a documentation of a bleed by endoscopy, but an investigator may have said, "Gee, their hemogloblin dropped by 2. This

may be a GI bleed."?

DR. LAWSON: Okay. Those were the terms reported by the investigator, but the dossier was sent to the independent adjudication committee. And the adjudication committee could only assign the criteria of major if it was overt bleeding documented. So even if an investigator had said maybe it was a GI bleed, unless it was documented proof of the bleed -- the hemoglobin drop, any support, if the patient was in cognitive shock -- it was not based on the investigator report.

DR. SEKERES: So how were these patients classified, then? If you have a patient who dropped hemoglobin by 2.4 but no evidence of bleeding anywhere, but needed a transfusion, was that patient classified as a potential major bleeder?

DR. LAWSON: It would have been adjudicated as non-major because that meant that there was a bleed requiring a medical intervention but not meeting any of the criteria for major. Because one

of the critical criterion for major was it had to be overt.

DR. SEKERES: So even if a patient had a drop in hemoglobin as a result of chemotherapy potentially, but someone put this as possibly --

DR. LAWSON: It could not be adjudicated as a major, according to the ISTH. It has to be overt.

DR. SEKERES: I would think that would be difficult to determine a posteriori.

DR. LAWSON: Excuse me? If the patient was -- with the fatal bleeding?

DR. SEKERES: Yes, whether the drop in hemoglobin was due to chemotherapy versus potentially a bleed somewhere.

DR. LAWSON: That's correct. So if the patient had a drop in hemoglobin, and then the investigator had performed assessment, an ultrasound, and identified an abdominal bleed, in that case, that would have been adjudicated as major. If the investigator was only a lab, of dropped hemoglobin, and no investigation was

performed by the investigator, that would have not been classified as major.

DR. SEKERES: So how would the adjudication board determine whether a rectal bleed was minor versus major? Because it looks like it falls into both categories.

DR. ZAKS: It would be a major if it would fulfill these additional criteria. So if it were looking at the dossier and there was felt that there was a description of sufficient hemorrhage and a drop in hemoglobin of greater than 2 units that was consistent with that clinical picture, that would be their determination of this to call it major. If there was no overt melena or hemorrhage that would coincide with the drop in hemoglobin, then it would not be adjudicated as such.

DR. SEKERES: So the drop in hemoglobin was the distinguisher between those two?

DR. ZAKS: Yes.

DR. LAWSON: I mean, when we say overt, the definition is either clinically or by imaging.

DR. SEKERES: Right, but it's a posteriori determination of overt. So it leads to some interpretation.

Moving on, I was hoping that you could put up FDA slide 31, but I'm going to ask the company to comment on this.

So I'm trying to add up all the numbers here. It looks like when you look at the symptomatic DVTs in lower limb for the placebo arm, they're a total of 25. But then you add up proximal and distal, and it adds up to 31.

Why the discrepancy?

DR. LAWSON: Because a patient could have more than one event. So if a patient had both a proximal and distal, or, for example, a patient could have also a DVT and a PE.

DR. SEKERES: So if that's the case then, are you mixing events with patients here, your numerator and denominator? So your denominator is patients, right?

DR. LAWSON: Number of patients with at least one event, is the overall, and then in all

the categories are the patients with that particular event. So, for example, if a patient had a proximal and distal, it would appear under both. But then on the total, under any VTE or VTE-related death, it would only count as one, because it's the number of patients with at least one event.

DR. ZAKS: This is always patients. There's no mixing of events.

DR. LAWSON: Yes.

DR. SEKERES: But there is mixing of events because under proximal and distal, 19 and 12 is 31.

DR. LAWSON: Yes.

DR. ZAKS: But if it's the same patient, then it's not counted twice.

DR. LAWSON: That's why it's not --

DR. SEKERES: I'm confused. I'm sorry. You have symptomatic DVT, lower limb is 25 patients. Then you have proximal versus distal is 19 and 12. So the 19 and 12 must be events, not patients.

DR. ZAKS: No, the 19 and 12 are distinct patients, but if you have a couple of these

patients who appears on both lines, because they had both events --

DR. SEKERES: If they had both proximal --

DR. ZAKS: -- then in the overall summation, that patient wouldn't be counted twice.

DR. SEKERES: But if you have a proximal and distal, it's still kind of funny math if you're looking at number needed to treat.

DR. ZAKS: Well, the number needed to treat is based on the overall events, and you can further hash it by symptomatic DVTs or by pulmonary emboli. We've not done an analysis of numbers needed to treat by every one of these individuals. But perhaps if I can -- if that answers the question, I can speak to the overall composition of the primary endpoint here.

DR. LAWSON: We have also looked -- in terms of the statistical significance of the study, we have also looked at the result. If you exclude, for example, the distal DVT, if that's what you're looking for.

DR. SEKERES: Well, I'm moving in that

direction.

DR. LAWSON: Okay.

DR. SEKERES: So, okay. I get the discrepancy in math. You have more than one event or a patient who may have more than one event. And you're saying that when you did your number needed to treat calculations, you took that into account and just still based it on patients and not the number of events.

So then let's move on to what I really think is for me the crux of this debate in potential benefit versus risk. And that is which of these DVT/PEs are really clinically significant --

DR. LAWSON: Yes.

DR. SEKERES: -- compared to events that may lead to nothing. For example, I treat patients who have central lines all the time. And sometimes they will get some swelling. If they have a PICC line, they may be imaged, they may not, and found to have a clot. The line is removed, and then I don't anticoagulate them because upper extremity clots don't tend to lead to significant clinical

events.

So there could be an argument made that you could subtract out upper limb DVTs from this and distal lower limb DVTs because they're much less likely to cause a clinically significant PE.

DR. ZAKS: So we did that analysis. If I could have the slide up? This pie chart shows the breakdown of the primary endpoint, again, as experienced on the placebo arm of this SAVE-ONCO study. And as you can see, the majority of events are PEs, most of which are symptomatic of course, and the proximal DVTs of the lower limb. Following that, you see any VTE-related death and the symptomatic DVTs of the upper limbs and the distal DVTs of the lower limbs, which make up less than 10 percent of the primary endpoint here.

If we take out the slice of the pie that's distal DVT or the slice of the pie that's symptomatic DVT of the upper limbs, the study retains its overall effect in terms of hazard ratio and high statistical significance. The same thing happens if you remove both of these primary

endpoints. And as you can see, they overall together make up roughly a quarter or less of the primary endpoint here.

DR. SEKERES: No. And I buy that, that there is still statistical significance if you subtract those out. But now we're getting into pretty crude numbers of number of patients needed to treat to prevent something that's clinically significant versus number of patients needed to treat to cause something clinically significant, meaning bleeding into a critical area. Thank you.

DR. WILSON: Maybe I'll just ask one thing to follow up on Dr. Sekeres. Given the fact that events were captured in that FDA chart, whenever they occurred, what was the overlap between proximal DVT and PE in terms of the numbers that were counted twice? In other words, is preventing proximal DVT -- what proportion of those people also were in the pulmonary embolism group? Because it's very standard to have a PE to do a Doppler of the lower extremity.

DR. ZAKS: So I believe there was minimal to

no overlap because the criteria here were not for asymptomatic DVTs, so they were for symptomatic DVTs for the primary endpoint here. So even if they had a Doppler and they were found to have a proximal DVT, if it was an asymptomatic diagnosis, it wouldn't have made it.

Slide up, please. And here you can see the breakdown. We had one patient, or three, depending on the group, which had both symptomatic DVT and PE. The majority of them had one or the other.

DR. WILSON: Well, you know, obviously, sometimes things can turn from asymptomatic to symptomatic, perhaps if something's found. But maybe I can ask in a different way. Among those patients that did have the PEs, what proportion of them had evidence of a lower extremity clot by Doppler?

DR. ZAKS: Can I have the slide back up? No, I'm not sure it's on there.

No. I think this is just the symptomatic cases. I understand the question. I don't have the information readily available, but we can get

it.

DR. WILSON: Okay. Thank you.

Dr. Logan?

DR. LOGAN: I had two questions. The first, you know, we're seeing here a very small absolute difference in the VTE incidence. And as the FDA has pointed out, there's this very high early censoring. And because of that high early censoring, the results in that very small incidence may be very sensitive to assumptions we have about the censoring.

My first question is, has there been any analysis of factors which may contribute to that early censoring? In particular, what is the censoring rate, the early censoring rate in this high-risk population that has been identified, as well as possibly by geographic region, and maybe other factors as well?

DR. GURAL: If I understand your question, we will have Dr. Emerson address from the statistical point of view. And I'm sorry. Could you repeat the second half of your question?

DR. LOGAN: What is the -- the censoring is mainly due to patients stopping treatment. What is the censoring rates in select subgroups of the population? In particular, the high-risk group that has been identified for this indication, and then also possibly by geographical region.

DR. GURAL: By geographical region. That's what I thought.

Dr. Emerson, please?

DR. EMERSON: Scott Emerson. I'm a professor of biostatistics, the University of Washington. And I am a paid consultant, but I have no other financial interests with Sanofi or with the outcome of this.

In terms of the patients who were censored, I'm not certain that I can address your question directly. We may have to have a Sanofi statistician. In terms of the profile of the patients who dropped off chemotherapy early, dropped off the semuloparin early, died, things like that, we see very similar distributions across here.

If I could have this slide up? This isn't directly answering your question in terms of other aspects, but these are the reasons that they stated for stopping therapy or that they were no longer contributing to the primary endpoint in terms of AEs or terms of having poor compliance. The other is mostly patient or investigator preference and issues such as that, and that's quite comparable across these groups in all things that we've examined.

Of course, the problem with informative censoring is not just whether these numbers look comparable, but whether there might be differential risks after this by all of these groups; that is to say that the patients who have a preference for dropping off the therapy on the placebo arm might act differently in terms of their eventual outcomes than the patients would on the treatment arm.

So I don't know if that is getting at your --

DR. LOGAN: Well, it doesn't really answer the question. I guess the question is, are there

patient characteristics that are driving this in particular. You might imagine that the patients that have a high risk of VTE, which is presumably who's been identified here, may be more likely to comply with the prophylaxis. So that's the question.

DR. EMERSON: So I'm actually going to answer the question in a different way. And that is to say, I'm going to move sort of to a bottom-line analysis. Rather than looking at what the baseline risk factors were in terms of whether the patients dropped off or not, the bottom-line analysis is to say what would have been their outcome had they stayed on. And that we can't know, but we can make assumptions about this and do a sensitivity analysis for the difference in risks that there might be.

So if I might have slide EF-374 up? The idea here is that the bottom line is not whether there were these differences in the data that we have, but really what's the differences in the data that we don't have. And I can't answer that

question, but what I can do is make assumptions about how bad that difference could be, and look to see whether this changed the outcomes.

So assessing these results in conjunction with the recommendations of the National Academy of Science report, as the FDA noted, the primary analyses here were predominantly missing at random, assuming that those patients who dropped off were behaving the exact same. But instead, we can do a sensitivity analysis to missing not at random. What if we had followed all subjects for the 6 months? What if there had been increased or decreased risk of VTE events after discontinuation of the drug? And what if those changes were different by arms?

If I could have the next slide up? And the results to the sensitivity analyses, the number that matters the most, truly, is the differential assumptions about the rate of VTE after discontinuation, and that's this 3.21. But I took values that I looked at and assumed what if the placebo group after discontinuation had a decreased

risk of VTE events -- about 11 percent decrease -- and on the semuloparin arm, what if it had been an increase by 185 percent of a 2.85-fold difference?

These numbers were chosen for a reason, somewhat in agreement with the adverse events that were reported during the safety follow-up period after stopping treatment for each of those arms. This would come up with that estimate. And based on these values and imputing the missing data under these assumptions, you could note that the average length of treatment during that 6 months would have been 3 and a half months, with 2 and a half months off therapy. The semuloparin would still be associated with a 40.5 percent decrease in VTE risk, with a P value of .025. And I'll note that if I pushed it further than this to actually increase the assumed increase in VTE events on the semuloparin arm to achieve a level .05 statistical significance, that would be a 3.66-fold increase. So this is the robustness.

I should make one additional comment here.

I chose the 6 months because that was more or less in keeping with what was experienced on the study in the following sets. Ninety-percent of subjects stopped semuloparin or placebo prior to 6 months. If, however, I moved it back to 4 months, or 3 months, which is when most of the VTE events occurred, I can in fact increase that differential events rate up to 6.2 at 3 months, and still have a P value less than .05.

So, Dr. Logan, I don't know that this is answering what the risk factors were, but this is instead the impact of what differential follow-up could be.

DR. LOGAN: Yes. I mean, I think it's important to keep in mind that the sensitivity analyses require a lot of assumptions here. The main issue is we don't know what happened. And my question really was, are there certain patients -- certain patient populations -- in particular, this high-risk group -- where we actually do have better follow-up than appears in the entire population.

But I think it's also important to keep in mind that the sensitivity analysis looks at a broad range of things, but the implication here is because there is a high censoring rate, the absolute risk difference may be substantially less than the already very small difference in risk.

DR. EMERSON: Can I have slide EF-375? So first I'd like to just speak to what the assumptions were in the analysis that I did. I did assume a proportional hazards model with a change point at the time of censoring. I have found that this is extremely robust to the mixture of reasons that there might be, that I am estimating the average increase in risk across the population, which, as you point out, is going to be quite varied. I will also note that the latest events that we observed in this trial was at 5 months, and so I extrapolate an exponential beyond that and then did multiple imputation.

But if I could also now just have slide EF-373 up --

DR. LOGAN: Perhaps we can just move on.

DR. EMERSON: Okay.

DR. LOGAN: I realize that there are a lot of assumptions built into this. Unfortunately, the issue is we don't know what's going on.

So the other question that I had was, I was a little concerned about the statement on sponsor's slide 48, which says that their selection of the subgroup does not result in any increase in the type I error rate for a demonstration of efficacy. I guess my understanding is that this is a post hoc subgroup analysis. I just can't imagine how that would be the case.

DR. EMERSON: Scott Emerson again.

Yes. The issue that we have -- if I could have this slide up, please? The issue that we have is efficacy. It was defined as a primary endpoint in the population overall. And as we noted -- if you've seen this slide before -- the examination of what the efficacy was among different populations by cancer site and by risk.

But we also noted that this relative risk that's extremely constant across all subgroups that

were examined, this is what allows us -- if I could put up slide EF-022. This is just the concept that for that same percentage that we observed across all these risk groups with no evidence of differences, it does matter what your baseline risk is. This is where looking at the data and looking at subgroups came in, not in terms of what the efficacy was on a relative risk scale, but instead identifying this high-risk population.

As was shown previously, looking at the placebo group, this identified what groups were. There's an element, looking through the data there. But if I might have this slide up. On the top, we look at what the sensitivity and specificity is for identifying the patients at highest risk, based on the placebo group. This was then independently confirmed with the dataset that Dr. Khorana had used to establish similar sensitivity specificity.

DR. LOGAN: But I think the point here is that selection of the -- even based on the baseline groups, you're picking the ones with the highest incidence, and that automatically has a potential

to bias the estimated treatment effect in the opposite direction, and the fact that you had the data available to you at the time that you were selecting the group.

So I think there are still concerns here about the post hoc subgroup analysis.

DR. WILSON: Dr. Fojo?

DR. FOJO: Thank you. I mean, I think there are a lot of apples and oranges here that are making it difficult for me to understand, including, for example, the data with regards to the incidence of DVT and so forth. It varies because in some cases, you're not sure whether it's over the lifetime of the patient or over the putative observation.

But in any case, I had one question real quick. How many assessments were done in the placebo group versus the treatment group, with regard to assessments looking for DVT, for pulmonary emboli, et cetera?

DR. GURAL: In fact, all of the -- these were all symptomatic, so prespecified time points

for assessment were not done. These are all symptomatic DVTs or PEs.

DR. FOJO: So the number of assessments was equal in both?

DR. GURAL: It was random. It was when the patients made the report, or the physicians.

Dr. Lawson?

DR. LAWSON: Are you asking whatever it was, the assessment by the investigator regardless of the adjudication? How many events to that adjudication?

DR. FOJO: Clinically, how many assessments were made? Obviously, the more you look, the more you find.

DR. LAWSON: So that's correct. That's why in order to avoid a problem, we asked -- the secondary point of the study was actually assessment of initiation of anticoagulation by the investigators after they assessed the VTE.

If I can have the slide -- slide up. This is the assessment by the investigators. So regardless of whatever time --

DR. FOJO: No. I don't mean assessment by investigators. I meant clinical -- how many had Dopplers, how many had spontaneous pulmonary -- CTs looking for pulmonary emboli, et cetera? Was that equal in both arms?

DR. LAWSON: Yes. This was similarly distributed.

DR. WILSON: Maybe I think what Dr. Fojo may be asking, number one, I think he's just asking for what it actually was --

DR. FOJO: Right.

DR. WILSON: -- what was collected. But also, if you have somebody on a clinical trial -- even though it's double-blind -- where the endpoint is looking for a clot, your sensitivity for finding that clot and cause something symptomatic is going to go up. I mean, there is no doubt that if you're worried about a clot, you're going to look a little bit harder.

So the question is, could all these numbers be inflated over what is really clinically relevant. And I think that is not something that

you can -- that's relevant to clinical practice. It's obviously I don't think a bias here because it was double-blind, but it is still a bias to clinical practice. And I think what we're trying to get a handle on is, is this reduction in venous thrombosis clinically relevant. And that I think is what's difficult to get around.

DR. GURAL: And perhaps I could ask Dr. Bunn to come and address a couple of those salient points.

Dr. Bunn?

DR. BUNN: Could we have slide 386? So I think the statistician -- I'm not a statistician, but I think he was concerned, Dr. Logan, about going from 4 to 2 doesn't seem very big, and what is the target population, and what does it really look like. And on the left here are the data from North America that were presented by Dr. Khorana for the three groups in the target population. And you can see the risk in the literature, thousands of patients as shown, from 7 to 12 percent. And then in the SAVE-ONCO placebo group, quite similar

numbers are seen.

Now, if we look at those patients who are from North America and Western Europe, we can see the white bars on the far right. The incidence in lung was 7.1 and greater than or equal to Khorana 3, 13 percent, and 18 percent in pancreas. And I think this is the population that we're talking about, and I think these are high risk.

DR. FOJO: Okay. Maybe we can -- I mean, this is not what I was looking for.

DR. BUNN: Oh. Sorry.

DR. FOJO: Actually, if you look at the gastric cancer, the differences between your data and the other data was not as tight. But I have one other question, in CC-46 that the company presented. This has been addressed. I think it bothers us all, what you're comparing here.

Do you have this similar type of plot, where you don't just consider major bleeding, but you consider also all other clinically -- what was it -- CRBE, clinically relevant bleeding events? How does that look when you do that? Because I can

see comparing a death to a major bleed, but I'm not comfortable with comparing a major bleed to a distal lower extremity, and upper extremity, as Dr. Sekeres was pointing out. So we need all bleeding to compare that. This is one of these apples and oranges things. You've biased it with everything in favor of clotting and only major bleeding in favor of toxicity.

DR. ZAKS: So a couple of points, if we keep that slide up. Three-quarters of these events are the lower-limb DVT proximal and the pulmonary emboli index. So the other group is a small minority, so you can sort of project -- I don't think we did this type of analysis by every subgroup.

In terms of the bleeding, really the assessment of risk is a function of two things. When you try to calculate the numbers needed to harm or the absolute risk, what really matters is what is the baseline risk you're looking at. And that depends on what is the risk, that's the clinically relevant one, and what is the hazard

ratio that you apply.

So we applied the hazard ratio as it was observed. And if we look at those -- and if we can have that slide back up, please. Okay. Thank you. So here's a different way of looking at it. This is time to pulmonary emboli or a major bleed. Okay? I think what's salient is how one looks at what is the excess risk, and that's a function of your baseline risk and the type of endpoint that you care about. And in this case, I can show you again why we took those clinically relevant but non-major and did not consider them to be of equal weight to the proximal DVTs, the PEs, and the events that we observed here.

DR. FOJO: So you don't have it. Okay. And then I had one other question. Why did you decide that -- so you would stop on-study participation, if you will, is that patients have progressive disease -- in many of the patients, that they had progressive disease. So then the indication is really limited to patients that are actively being treated, and in fact actively being treated for

just a few months, because we don't have the data as to what happens after they come off.

You know, patients who progress, at that point, we could all envision that they might have a high risk of bleeding because their disease is more advanced. We could also envision that they might have a high risk of clots, which might work to your benefit, or it might be more difficult because it gets to a point where maybe the prothrombogenic milieu is such that even your drug cannot do it.

So the way that the application looks is you want to continue this through the course of the patient's life, if you will. But you really have only very limited data over a very defined period of time, which is at most 3 months, or 3.4 months.

Why did you choose that approach?

DR. ZAKS: So let me perhaps clarify. The study as it was designed was to treat patients not for the duration of 3 months, but for the intended duration of that first chemotherapy. The 3-months time point was chosen because it was felt that patients who switched early chemotherapy have not

really benefitted from that line of chemotherapy. And so if the switch occurred before 3 months, and they went on a different chemotherapy, then they would continue semuloparin with that chemotherapy throughout the course. If chemotherapy was permanently discontinued in less than 3 months, then semuloparin and the study would be discontinued as well.

So that's the way the study was designed. And our proposed indication is for a period of 3 months, with the expectation -- and the 3-months endpoint is really driven in the study as well. The expectation is that this is a period of highest risk because the highest risk occurs early and risk drops over time. And that is substantiated by the literature of the timing of VTE risk over time in ambulatory cancer patients receiving chemotherapy.

DR. GURAL: And in fact the label is hopefully stating that once chemotherapy is stopped, then treatment with semuloparin would also stop.

DR. FOJO: I have one last question, but I

don't want to take more time. So if there's time, I'll come back, but I'll pass.

DR. WILSON: Okay. Well, let me just follow up on one thing that you brought up. And you put up a slide on historical incidences. And you made the point that your incidence was similar to the historical. And this really gets at I think a little bit about what Dr. Fojo was getting at, which is how hard were people being looked at, what's the true incidence, is everything inflated here?

So if you could put up that historical slide again --

DR. GURAL: Dr. Bunn, I believe this is your slide.

DR. ZAKS: Slide up.

DR. WILSON: So this may be an apples and orange. The historical data, U.S. ambulatory cancer patients, incidence of VTE, are these all VTEs or only symptomatic?

DR. ZAKS: These are symptomatic.

DR. WILSON: For the historical controls.

DR. ZAKS: Correct. I can invite Dr. Khorana to speak to that data. I believe he was an author on part of these publications.

DR. WILSON: And were they symptomatic, using a very similar definition to yours? Were they adjudicated, et cetera?

DR. KHORANA: So these are registry studies or claims datasets. So the one that reports our study was a cohort of patients getting chemotherapy. The doctors reported a VTE.

DR. WILSON: Okay. So this is not symptomatic. This is all VTEs, and it could have been picked up through incidental scans, et cetera, meaning that your symptomatic rates are probably inflated over what the actual true rate is, because they're very similar to the actual reported true rate that's probably a composite of symptomatic and asymptomatic. And this really gets at the fact that if you're doing a study where you're looking for reduction in VTEs, there's going to be a lot more sensitivity to looking for symptoms.

I simply wanted to bring that to the floor

because the relative incidences of these and how much this has really reduced that from a clinically significant point of view is really at the core of what we're looking at here. Thank you.

Dr. Wozniak.

DR. WOZNIAK: Yes, I have a couple of questions. The largest population were the lung cancer patients. There were almost 1200. And, you know, you're treating a lot of patients to benefit a few, so I was wondering if you looked at the lung cancer patients a little bit more and maybe tried to determine which ones were a higher risk -- for instance, does histology make a difference? Would you treat adenocarcinomas and not the squamous, et cetera? Was anything looked at?

DR. GURAL: Perhaps, Dr. Bunn. I think we have looked at that information.

DR. BUNN: Yes. This was looked at by histology. And if we could have the slide up, please. Shown here are the forest plots by the various histologies: adenocarcinoma, squamous, large cell and small cell or not otherwise

specified. And you can see in each -- each histology benefits the semuloparin.

Don't take that down yet, if you want to put it back up there? You can see that the rates --

DR. GURAL: Slide back up.

DR. BUNN: -- in placebo varied from 2.5 and then not otherwise specified, up 5.8 in the placebo arm for adenocarcinoma.

DR. WOZNIAK: Were any other things looked at other than histology? Type of chemotherapy?

DR. BUNN: Yes. If you could have slide 184? This is a similar forest plot by the type of chemotherapy that the patients received. There's obviously some variability, but in general, for every type of chemotherapy, it favors semuloparin.

DR. WOZNIAK: What about the site of metastases?

DR. BUNN: I don't have data on that.

DR. GURAL: Perhaps Dr. Zaks.

DR. ZAKS: No, we did not capture the site of metastasis. This was a study that didn't really capture tumor measurements as were used to capture

them in terms of studies that look at tumor sites and measurements and recess type criteria. We treated here both patients with locally advanced and with metastatic, but we don't have further granularity on that.

DR. WOZNIAK: Okay. My other question is about compliance. Some patients went off because of poor compliance. And I think there was about 18 percent or so who decided, I guess, not to participate anymore. How compliant were the patients that actually finished the study? Did they take it everyday? Were they 60 percent compliant? I know that with my patients, when they find out they have to give themselves an injection everyday, they're not too happy about that, even when they actually do have a reason for it.

DR. LAWSON: Well, almost 100 percent compliance in both treatment groups. The mean of standard deviation was actually 97 -- was the percent of compliance.

DR. WILSON: Okay. I want to thank the sponsors for being on the spot here. We still have

a number of more questions, but I think we probably all need to take a break here. So we're going to take a very short 10-minute break, and then we will resume the questions to the sponsor.

So if we could please reconvene at 10:45. Thank you. And, please, panel members, recall, do not discuss this among yourselves. Thank you. Bye.

(Whereupon, a recess was taken.)

DR. WILSON: Okay. Let's go ahead and get started. I would like -- the sponsor has indicated that they do have some additional information that was requested. So if the sponsor would like to go ahead and show us the slide. Thank you.

DR. ZAKS: Thank you, Mr. Chairman. Yes, I wanted to address the question -- I think it came up -- of different ways of calculating numbers needed to treat versus numbers needed to harm, assuming the various different endpoints.

Slide up, please. These are looking at either the PEs or the symptomatic DVT separately, combining both together, or then looking at --

DR. WILSON: There we are. Okay.

DR. ZAKS: -- sorry. Apologies.

So here we compare the various components of the primary endpoint, the symptomatic DVTs or the PES, in terms of the absolute risk reduction and the numbers needed to treat. And we looked at safety in various different ways, including the clinically relevant bleeding as the most conservative estimate, if you will -- though I would remind you of the list of what these actual cases are -- and then the major bleeding, the non-major bleeding, and the fatal bleeding events that we saw in this study.

So one can conduct these analyses in different ways. I think in any which way we look at, overall, our assessment is that there is a favorable benefit-risk here for these events. I've shown you the distribution of the pulmonary emboli and the symptomatic DVTs. If we look at the pulmonary emboli as a subclass, that was 45 to 50 percent of the events here. And 80 percent of those pulmonary emboli are symptomatic pulmonary

emboli.

So I hope that addresses the questions on the various analyses requested before.

DR. WILSON: Okay. Thank you very much.

Dr. Freedman?

DR. FREEDMAN: Thank you, Dr. Wilson.

I'm going to try to follow on the same theme of trying to understand the characteristics of the benefits and the extent of their risks here. It's a little unclear because we understand that in a study this size, it may be difficult to look at mortality. I mean, Kakkar required thousands of patients in order to look at the mortality.

So the question is what other benefits might there be here. And I was thinking one of the issues that could arise, obviously the severity of the event could also be looked at in terms of hospitalization requirements. So do you have any information about the median hospitalization requirement from a VTE event in the two arms? That's the one -- we can deal with that question first, then I have a follow-up.

DR. LAWSON: Yes. The number of patients who required hospitalizations during the study, due to a VTE, were 20 patients in placebo, 6 patients in semuloparin.

DR. FREEDMAN: And the duration, median duration of hospitalization required?

DR. LAWSON: This is just the number of patients that required at least one hospitalization during the period, and they were about half and half PE or DVT.

DR. FREEDMAN: Thank you. The other question relates to bleeding events. One can look at the severity of bleeding in terms of what type of intervention was needed in order to deal with it. For example, surgery, surgical intervention or interventional radiology in order to address bleeding. Do you have any information on that between the two arms?

DR. LAWSON: The ISTH does not classify the level of requirement for intervention. It's clinically relevant when they require contact unplanned with health petitioner, and then they

review the individual cases, as I said. But we do have the classification by NCI that takes that into account.

If I could have back my core slide from the NCI classification? Slide up. Okay. So these are the -- they were again adjudicated independently by the adjudication committee, according to the NCI criteria. And so here you can see the only ones that were imbalanced, where NCI, they were requiring either no intervention or minimal, local, and noninvasive intervention. Those would be grade 2. And those were increased in semuloparin, but they were very equally balanced. In grade 3, they require hospitalization, or urgent intervention would be grade 4.

DR. FREEDMAN: One other question. The risk of VTE, we've got a population -- as was mentioned by Dr. Fojo, you've got just a small window here that we're looking at patients as compared to how it would be in practice. In practice, they would be treated for a longer period of time, maybe, and also exposed to a variety of therapies. And

depending upon their situation, at a certain time, their risks may change. They may increase; for example, if they have to administer chemotherapy as inpatients, which is done less and less in this country, but in Europe, parts of Europe, what is the practice there? Do they do a lot of outpatient chemotherapy? Do they do as much as done here? Is it fairly balanced in the trial?

DR. LAWSON: Yes. Eight percent of the patients in the trial were hospitalized at the time of randomization because, again, it as worldwide. So in some countries, they do administer chemotherapy while hospitalized. We looked also at the effectiveness of semuloparin in patients after they've been hospitalized. And again, we have exactly the same efficacy, beneficial effect of semuloparin in a patient that required hospitalization not due to a VTE.

DR. FREEDMAN: And the comparison between North America and Europe, was it the same types of -- same degree of hospitalization for chemotherapy administration?

DR. LAWSON: Well, I have to -- the chemotherapy by geographical region --

DR. FREEDMAN: Yes.

DR. LAWSON: -- if you want to see --

DR. FREEDMAN: Well, what I'm getting at is if you add hospitalization to it, you may be increasing risk because patients are now --

DR. LAWSON: That's why we looked across the study in the efficacy of semuloparin in patients after they've been hospitalized, and that was -- throughout the study. And the efficacy of semuloparin was very significantly superior to placebo.

DR. ZAKS: If I could just make a couple of comments here. I think it's important to distinguish between the efficacy and the risks. So the efficacy of semuloparin was consistent across all the subgroups, across all the regions. And that is I think important when one starts to look at the different regions here. And, of course, there are some regional variabilities. You've seen a high risk in the North American and Western

Europe population. We see more central lines in these regions. Chemotherapy was, by and large, similar, perhaps with the exception of bevacizumab.

So there are some regional differences, but the efficacy overall of the drug is the same, and it's consistent across these regions.

Now, the other point I'd like to make, you asked about the time risk and whether the risk would go up. The literature -- actually, if I could have the slide of risk over time. The literature for these patients who come in the ambulatory setting to receive chemotherapy -- thank you, slide up -- decreases over time. And this is our best estimate. And these kinds of data are the reason why we picked that 3 months as the period for which we wanted to ensure the optimal chance of coverage.

DR. FREEDMAN: But patients who are getting extended chemotherapy may run into platelet issues, and their risk of bleeding might increase. So do you have a good understanding of that in relation to the -- from the data from the trial?

DR. ZAKS: Yes. At least as we saw it in the trial, we did not see a difference between the two arms. I will say one other point perhaps on the bleeding, because we've had a lot of discussion on major and non-major, and these are adjudicated bleeding events.

If we look to what the investigator termed as serious as another way of trying to capture the bleeding risk here -- and I think this was also in the FDA slides -- we have 30 patients versus 23 patients. So those are the serious adverse events. So let's leave the adjudication committee out of it. This is just looking at it through the lens of the investigator and what they think is serious.

DR. FREEDMAN: Last question here. So with time, did you find that the incidence of bleeding increased? When did the -- was there a peak frequency of bleeding issues in relation to the study?

DR. ZAKS: If I could have the slide up, please? So here's the time to event for a major bleeding event. And I think the -- you see the

large increase I think over the first period. But of course after time, you've got competing risks, competing events here, et cetera. But this is what the data shows.

DR. FREEDMAN: Thank you.

DR. WILSON: So maybe I could follow up on that. You've done a subset analysis of who you would be putting in for this indication, a VTE greater than or equal to 3, lung and pancreas. But I've not seen any breakdown of whether or not that group -- which is generally considered to be at a higher risk of clotting, and therefore is probably at a somewhat higher risk of bleeding. What's the breakdown of major bleeding events in that group? And specifically, did the FDA look at whether or not there was a disproportionate number of these critical bleeding events, intracranially, intraocularly, among the group that's being asked for, for the approval?

DR. ZAKS: Thank you. If I can have the slide up, please? This is the point estimate and the hazard ratios within the patients with lung

cancer, pancreatic cancer, or those with a VTE risk score of 3 or greater. And you can see the numbers there on the left as well.

So these are the major bleedings within this group. And the analysis that I showed in terms of the numbers needed to treat versus numbers needed to harm, they took into account a consistency of effect from the overall population. We can apply these hazard ratios to those analyses. One gets slightly different numbers, but it's the same ballpark in the sense that the numbers needed to treat is always a log less than the numbers needed to harm when you do that.

DR. WILSON: And did the FDA look to see whether or not symptomatic bleeding into critical areas or organs were disproportionately increased among the proposed indication group?

DR. HERNDON: Yes, we did. So among the 7 patients that developed critical organ bleeds, 4 of them were in that subpopulation. So 3 were in lung cancer patients and 1 in pancreatic cancer. Two were intracranial, 1 was intraocular, and 1 was

pericardial.

DR. WILSON: Okay. So if one actually runs the number, then the relative risk seems to be similar, whether or not you're in that group or not, which was what my question was.

DR. HERNDON: That's correct.

DR. WILSON: Okay, great.

DR. ZAKS: And if I could just make a comment to the clinical outcome of these cases, the majority of the cases of bleeding in the critical organs were in fact resolved.

DR. WILSON: Okay. Good. Thank you.

Dr. Loehrer?

DR. LOEHRER: A couple of questions. The first one is kind of a softball one, but help me with the regional differences here. So 6 percent of the patients on this trial came from North America; 39 percent came from Eastern Europe. And this trial, again, is used to say, okay, how is it going to be used here in this country.

What was the access to spiral CT scans, pulmonary angiography in the Eastern European

population in terms of what equipment do they have? Because many sites don't have as much as we do. And how much -- what was the variation in terms of diagnosis and use of these materials?

A follow-up question to that is a number -- and I think Dr. Bunn mentioned this. With spiral CTs, we're going to pick up a lot of asymptomatic pulmonary emboli. We do this all the time. And particularly with the lung cancer patients, we would suspect if a baseline CT scan was done, you're going to pick up some. So how many of them had baseline studies to look for clots before they ever went on the study?

DR. ZAKS: So patients did not have baseline scans to look for clots before they went on study. It was not an entry criteria here. And if we look at the -- if I could have the pie chart again? If we look at the proportion of patients with PE who were diagnosed based on incidental findings -- thank you, slide up -- it is actually 7 percent here, if you look for those that were just scanned to look at their tumors versus

28 percent that were diagnosed due to symptomatic. So about 80 percent of the cases were in fact symptomatic from the pulmonary emboli.

Now, in terms of the regional variation, if we look at the similarity in practice as we look at some of the covariates, which I mentioned, such as central-line use, the use of bevacizumab, et cetera, North America and Western Europe seem to be similar regions in that regard, and they together account for roughly a quarter of the study population. Now, this study overall was 3200 patients, so a quarter of that is not an insignificant number of patients.

In terms of the regional variation and access to scans and the like, I'm not sure we collected that information. But I will say that the diagnosis here of the primary endpoint had to be adjudicated and confirmed. So you had blinded external people actually looking at what was the data that the investigator was using to actually claim this patient had a primary endpoint.

I'm just looking to Dr. Lawson. I don't

know if we collected anything about the statistics of the use of scan or access of scan. But obviously these patients had to have access to scans to --

DR. GURAL: Be enrolled.

DR. ZAKS: -- to be enrolled here and be evaluable.

DR. GURAL: The investigator himself, or herself, had to have access to that technology in order to be able to evaluate PE as part of the trial.

DR. LOEHRER: I just want to clarify. So the average duration of treatment with this drug was about 3 months. Is that right?

DR. ZAKS: The median was 3 and a half months, and I think there were -- if I recall correctly from the core slide, we had 932 out of roughly 1600 who were treated out to 6 months or so.

DR. LOEHRER: If you could -- I'm not sure -- it's in table -- or figure 4.11. It's the time to treatment in your briefing document. So

this is time to treatment, emergent bleeding events study. It may be also the same as your slide 310, if I -- just to help you a little bit.

DR. ZAKS: Slide up, but this might be too small for people to read.

DR. GURAL: It's definitely too small.

DR. LOEHRER: No, no, not table. It's a figure, figure 411, or I think it's your slide 310, if I remember seeing.

DR. GURAL: 310?

DR. LOEHRER: It may be the same one. I was looking, trying to compare.

DR. GURAL: Slide 310, please?

DR. ZAKS: Maybe I could speak to it in the meantime if you can -- okay. Here we go. Slide up, please?

DR. LOEHRER: So, again, in the core presentation, you make a big difference between the other low-molecular-weight heparins and the excessive bleeding, if you will, from that, a 57 percent increase bleeding complication rate.

One of the nice things about this study is

that the placebo arm basically did the same, which was really pretty good for all of them. However, in many of these other studies, the duration of the use of low-molecular-weight heparins were longer than this one. So the median duration of this one was about 3 months.

If we cut off the slide here, let's make believe at 4 months time to event, it turns out actually that the bleeding episodes actually are greater at that point in time, while you're on the drug, compared to time when you're off the drug. The placebo picks up after we stop giving drug to both arms, if you will, if I'm reading this correctly.

So my question is, again, in looking at this while you're on drug and looking at that endpoint there, it looks to me like some of the arguments about the bleeding are actually a little bit false. And then it's really the tail of the curve when you're off it that bothers me a little bit.

DR. ZAKS: I'm not sure I share that interpretation. If we look at the treating events

while on treatment or in the 30 days post-treatment, we see very similar events. The differences between the two are minute. I don't think this is a tail effect here on the curve.

DR. LOEHRER: Well, it hits me -- maybe that's wrong. I'm sorry. It seems like the placebo starts picking up after 6 months. But the question, though --

DR. ZAKS: I think that's a minute difference with a lot of competing risks.

DR. LOEHRER: Ultimately, it's there. But the concern that I have -- and I think many of us -- is that the risk of clots -- and I take care of a lot of pancreatic cancer patients. I actually disagree with you a little bit. You show that the number of VTE episodes go down with time, but that's also the fact that half of the patients have died with time also. And so the number of events go down with the number of patients. And we know in clinical practice that the longer patients live, the more they become moribund, the more blood clots they get, and they die. So I have a little bit of

concern with that, number one.

Number two, in clinical practice what will happen I believe, if we did this, is that most people aren't going to treat with 3 months of this drug while they're on one course of chemotherapy, thinking that this is going to help them. They're going to go on to another course of chemo. And they're going to say, well, we need to put this drug with this other course of chemo, and they're going to be on longer periods of time. And again, when we look at that curve, again, my concern is that this is really no different than some of the other low-molecular-weight heparins, that the bleeding episodes, the longer you're on, are going to separate, rather than a trial in which you just use it for 3 months.

DR. ZAKS: So let me address a couple of comments. First, in relation to the other low-molecular-weight heparins, this study, in and of itself as a single study, is larger than the meta-analysis of all those other studies combined. So I think the precision of our understanding of

both the benefit and the risk that we get from this study is greater. And as Dr. Bunn showed, if we compare our understanding of both the benefit and the risk to the meta-analysis, it looks like semuloparin is different.

Now, when we did the head-to-head comparisons -- I think a point here worth talking about -- the SAVE-ABDO study did not meet its endpoint of noninferiority, but it was an apples to oranges comparison because we gave semuloparin after the event of surgery, whereas we gave enoxaparin the standard of care before. So here we were trying to prevent clots after the inciting event as a patient was hospitalized. And while we didn't meet the noninferiority, clearly the efficacy is demonstrated because historically these patients would have a much higher clot burden.

When you look at the enoxaparin studies that are apples to apples comparison -- and Dr. Lawson showed them -- the relative risk we were targeting was quite high. The one study that was positive was the largest study of that group, but

unfortunately some of them didn't meet that relative risk endpoint. The meta-analysis does give us confidence that there is some improvement over enoxaparin in terms of the understanding of efficacy. So now the question is what is it and how is it going to be used, and in which patients, which is obviously the salient one. And we can only speak to the data that we have here in terms of the way that it's been studied as far as the risk over time.

I don't know if Dr. Bunn wants to add a comment here.

DR. BUNN: Well, one thing that hasn't really come out is this trial took first-line patients, but it also took second and third line. Now, it didn't take first-line people who stopped chemo, later progressed, so you'd have to assume that the second line is representative of second line.

So what would I do in my practice? In my practice, when they stop their platinum doublet and they're getting maintenance, they're not going to

get this drug. However, just like with the bone-resorbing agents, when they're in remission, I don't continue the bone resorption agents every month. I give them every 3 months. But when they progress again, and they're getting chemo again, and their tumor's growing again, I go back and give them monthly zoledronic acid or whatever. And here, in my practice, for the high-risk patients, when they recur, I would put them on. But the trial had people that had first line and people who had second line, and there was benefit in both.

DR. LOEHRER: So the implication, though -- I'm sorry. The implication, though, is that it's chemotherapy that is causing the increasing coagulation, which I don't think is necessarily true.

DR. BUNN: Well, I think it's a combination. I don't think it's purely chemotherapy. I think it's the central line and sitting around, because when you're getting chemotherapy, you're not as ambulatory, et cetera. I think it's a combination.

DR. WILSON: Okay. Let's move on. I do

want to bring up one issue that really ran by me very quickly. And that is that you put people on this trial that was getting antiangiogenic therapy?

DR. GURAL: There were a portion of the patients -- Dr. Zaks. There were a portion of patients.

DR. ZAKS: Yes. We had a small proportion of patients that were on bevacizumab.

DR. WILSON: Well, that is, according to NCCN guidelines, an accepted indication. You're randomizing them to placebo, and you're using them to justify using this in a group of folks that do not fulfill what's considered to be an accepted indication for prophylaxis. I'm a little confused by that and if you did subset analyses, excluding those people from this.

DR. ZAKS: Yes. So the proportion of patients here was very small. It's 3.4 percent of the overall population.

DR. WILSON: Right. It's a small percent, but so was your thrombosis. They may have been disproportionally represented in your patients that

had clots among the placebo. Were they?

DR. ZAKS: No, they were not. In fact, the hazard ratio here was 1.0. That was the point estimate. And the number of events here were 4 patients on each arm. So they would not have influenced the outcome of the study.

Let me ask Dr. Khorana perhaps to address your point about the NCCN guidelines.

DR. KHORANA: So to clarify the guidelines -- because I'm on the ASCO guidelines panel, and we're actually meeting in a couple weeks -- the prophylaxis recommendation for antiangiogenic treatment is restricted to thalidomide- or lenalidomide-based regimens in myeloma. That's really the extent of the recommendation. It is not recommended for bevacizumab or any of the other oral TKIs.

DR. WILSON: Okay. Thank you for that. I was simply reflecting your slide CC-59, which is a little more less specific.

Okay. FDA?

DR. PAZDUR: The issue that we have I think

is one that you've been grappling with here, and that is the heterogeneity of this population. One of the problems that we had when we initially saw this application was this broad indication of all cancer patients on chemotherapy should get this drug. And just on a brief overview of it, there were big patient groups that were missing. For example, there were no breast cancer patients. There were no prostate cancer patients. So how possibly could we have approved the drug for an indication where you have huge populations of patients, probably the ones that are most likely to get it, not receiving the drugs? And that's why we asked the sponsor to come and redefine the population.

The issue, though, that we had, is still we have a lot of unanswered questions, like what chemotherapy are we talking about here? It's kind of like, well, all chemotherapy is created equal here. And I don't know, regardless of what the slide shows here, if people will buy that from their clinical impression, that really all

chemotherapy has the same chance or similar chance of being thrombogenic here.

So the population of patients is somewhat disturbing. And the major problem that we're having is not only do you have to demonstrate a favorable risk-benefit, but you also have to define in labeling a patient population that is most likely going to benefit from this drug, the defined indication here. And this is what has been really the crux of the reason why we brought it to the committee.

For most of the other prophylactic anticoagulants, coagulation indications, whether it be hip, knee, et cetera, we're talking about a very limited period of time here. You have surgery. You're going to get this drug for a period of a couple of months, and it's well understood that these people are going to be immobile, and that's why they're being anticoagulated. But here you have a group of patients that not only is it presumably, as the sponsor would allege, the chemotherapy, but it's the underlying disease. And

you have this then heterogeneous population of first line, second line, potentially third line.

What are we dealing with? Is it truly the chemotherapy or is it the disease that we're dealing with, and is this really somewhat a constructed indication rather than being a real indication here? Remember, this drug had several other -- in advance -- or in looking at the treatment of DVTs, went head to head with enoxaparin, and did not meet its noninferiority endpoint here. So what is the relative efficacy of this drug compared to what is out there is really kind of still I think to be questioned here also.

But our major role is, from a clinical point of view, how would you really define this population? What is chemotherapy? What population are you really looking at? Is it first, second, or third line? Well, if you're going to be starting it in the second line, should you start it in the first line, continue it on? I agree with Pat in the sense that probably for most of these patients, if you do follow them, and their performance

status, et cetera, is going to be decreasing, they're going to be more better. And the likelihood of them developing deep venous thrombosis is probably going to be going up; it's not going to be going down. That doesn't really make sense to us when we discuss this amongst ourselves.

So the major issue here that we're grappling with is what is the population? How do you define how this is going to be used in a clinical context? Because here again, the purpose of -- the regulations clearly state the application should show safety and efficacy. But in addition to that, we should be able to label the drug appropriately for the patients that are being studied here. And I think the question that the group has to ask themselves, does this one single trial provide you that information, really, to label the drug?

We have 25 years plus of low-molecular-weight heparins. To say that this drug reduces deep venous thrombosis compared to a placebo is not a surprise to me. Okay? That's not

really the issue here. The issue here is how do you put this into a clinical context.

DR. WILSON: Thank you. We are running out of time, and I don't want to foreshorten any questions that are important for the sponsor. We will be having one presentation at the open public hearing, and then we will be having a discussion among ourselves.

So just due to the limited time, as I go through this list, if you could address your questions that are really necessary for the sponsor. And I think that Dr. Pazdur's comments may allow you to hone those even more because we really are running out of time.

So Dr. Neaton?

DR. NEATON: I'll come back -- I'd like to come back to Dr. Logan's point about the primary endpoint at some point, but two other areas which have not been addressed. In the slides by the presenters, they indicated that a delay or discontinuation of chemotherapy was a consequence of VTE. And so one question I had was whether or

not there is data from the trial that they could show us on whether there are differences in the treatment arms in terms of changes in chemotherapy. And related to that, I noticed that in Appendix A, where they listed the adverse events, there is a higher rate of progression of cancer on the treatment group versus placebo, and whether that is a consequence of more changes in therapy.

The second question has to do with, I realize that they didn't count primary endpoints three days after stopping therapy, and I presume that was also the case for bleeding complications. But could they verify that they counted deaths after stopping therapy and what the completeness of follow-up for survival was?

DR. GURAL: Yes. Thank you. Your question had a number of points. If we could, we'll try to address them. Let's take the neoplasm progression first.

DR. ZAKS: Okay. So we saw an imbalance in neoplasm progression, and two comments here. First, there is no real biological plausibility

here. If anything, both the preclinical and the clinical experience that Dr. Bunn described would suggest that this class would have a beneficial effect on survival.

DR. NEATON: But isn't it plausible that side effects of the treatment could lead to interruption of chemotherapy, that would lead to progression?

DR. ZAKS: Yes. So we'll get to that analysis in a minute. But just in terms of the progression, the way it was collected in the study was simply from the adverse event reporting. We did not have scans. We did not measure tumor progression here. And what we did do to verify that there are no imbalances was actually look at a time to one of these events or to death.

If we look at those curves, they're completely on top of each other. And I can tell you, furthermore, that 37 percent of the cases in which -- slide up, please -- that's the quasi PFS. It's not really progression; it's an adverse event of progression. And in fact, 37 percent of the

cases where the investigator called it a progression did not even lead to a change in chemotherapy.

DR. NEATON: What's the nature of the censoring in this analysis? I mean, you only have follow-up, for example, at one-sixth for 260 people in each group.

DR. ZAKS: Yes. So this is only to the degree that we had the follow-up. I don't think we did further analysis on censoring sensitivity --

DR. NEATON: That kind of relates to my second question. When did you stop counting?

DR. ZAKS: So let me get to that because I think that's relevant here. The reason that we stopped the analysis for survival, for overall survival at 12 months, was because that was the prespecified maximal duration of follow-up. And follow-up was to be given up to 7 months from the end of study. So up until 7 months, we have data for 95 percent and above of patients in terms of survival. And of course, between month 7 and month 12, that data drops as one would expect, down

to about 70 percent. But it's an equal distribution between the two arms.

DR. NEATON: So in terms of mortality, you have 95 percent ascertainment of it at 7 months.

DR. ZAKS: Correct.

DR. NEATON: And so why isn't that reflected more in this figure here?

DR. ZAKS: I don't have an immediate answer to you.

Scott, do you --

DR. WILSON: Let me just ask you all to please keep your responses short and specific. We're running out of time.

DR. BODDY: Alex Boddy, statistician for Sanofi. In the figure that you're seeing, this is also based on adverse event data. And that was only collected up to a month after patient discontinued treatment.

DR. NEATON: Your cancer progression outcome is only a month after stopping the therapy.

DR. BODDY: Because those are collected as adverse events, only the survival was assessed out

to one year.

DR. NEATON: Thanks.

DR. WILSON: Okay. Thank you. Dr. Kelly?

DR. KELLY: Thank you, Dr. Wilson. Two quick questions here. The first one's going back to what Dr. Freedman's talked about with clinical benefits. Just very quickly, do you have the number of patients who got IVC filters in each group, and also, surgical intervention for any bleeding episodes?

DR. ZAKS: They were balanced between the two arms. There was no significant difference. I don't think we have the analysis readily available on the slide.

DR. KELLY: Okay. The second question builds on what Dr. Pazdur said, and you may or may not answer this. Do we know how long a patient needs to be on therapy to have a clinical benefit?

DR. ZAKS: Yes. I can only speak to the way the study was designed and conducted. And so patients here continued on as long as they had chemotherapy.

DR. KELLY: So even though the majority of the VTEs were in the first 3 months, you don't know how long they had beyond that to have that clinical benefit?

DR. ZAKS: I'm not sure I understand the question. I mean, if you're asking me what would happen if I stopped the semuloparin after 3 months but continued the chemotherapy, I don't know.

DR. KELLY: All right. I mean, because the question is that you have open-ended duration of treatment. And the question is do we really know that longer duration is appropriate. You just increase the risk at that point.

DR. ZAKS: Yes. Again, the underlying assumption here is that the risk is a determinant of both cancer and the chemotherapy. And so that was the rationale for continuing in this as long as chemotherapy is given.

DR. KELLY: Thank you.

DR. WILSON: Dr. Arscott?

DR. ARSCOTT: Yes. Thank you. Since semuloparin is being presented as a preventative

treatment, I'm just wondering what the data is for clinically relevant VTE-related events and their treatment. In the patient population that actually has a clinically-relevant event and warrants full anticoagulation, or a filter, or whatever, what is the risk of that treatment? Since this is being presented as a prevention, I would think then that that would be part of the benefit of this treatment.

DR. ZAKS: Let me ask Dr. Bunn perhaps to address that.

DR. BUNN: I'm in total agreement with your sentiment. Of course, what you don't -- patients went off study if they had an event. And going off study meant that they got therapeutic anticoagulation. And as you saw in the beginning, that means therapeutic anticoagulation subcutaneous heparin for the remainder of their survival. So many of those patients, as you know, will have bleeding.

So they're getting the subcutaneous injections forever, and they're having an increased

risk of bleeding. But that was not captured as part of the study, but I think that is a clinically important observation.

DR. ARSCOTT: Thank you.

DR. WILSON: So, yes. I mean, I think it's important. That was one of the first questions we asked, what is the consequence of this. And unfortunately that data wasn't collected. However, survival up to one year was, and the two groups were not different.

Dr. Diehl?

DR. DIEHL: So this question goes to the benefit. Given the fact that overall survival was not different, the benefit then becomes how many events we prevented that impacted quality of life or its surrogate endpoints. So what I would like to be reassured is that the events that we prevented were far enough away from the patient's ultimate death that they were actually beneficial to the patient.

Put another way, for example, if a patient had a lower-extremity DVT, and then one week later

they died of progressive cancer, I wouldn't consider that of much benefit to the patient. So I'd like to be reassured that those events did not take place perimorbid.

DR. GURAL: Dr. Khorana perhaps can address that question.

DR. KHORANA: Bring up slide EF-290. So I think the question that you all are grappling with is something we've grappled with on the research side for many years now. And it's really saying, everybody talks about the high risk of VTE in patients with cancer, and sure the risk is high compared to the general population. But the risk isn't that high for most patients. So 80-90 percent of cancer patients probably don't require prophylaxis all the time. There are time periods when they start on chemotherapy, and there are certain subgroups that are very high risk. When you find those high-risk populations and you administer prophylaxis, you do get a benefit.

Here's an example from just the high-risk population from this study based on our risk score.

And if you look at just that population, and you look at score on survival, which many of you have referenced has not been significant, when you find enough events in an event-rich population, you do influence survival. In addition to that, you do reduce PE. You do reduce symptomatic DVT. And there are consequences to all of those, including hospitalization and delayed chemotherapy.

So I would submit there are clear benefits to patients, including potentially survival. It's a matter of finding the population that's most likely to benefit from this agent and from prophylaxis.

DR. WILSON: I guess I don't want to have that go by too quickly. When you look at cause-specific death due to thrombotic events, there wasn't really much difference. So that may be driven by all kinds of things other than preventing major VTEs. I think that's real problematic to show that and make a cause and effect.

DR. KHORANA: Right. But it's

also -- you're also underestimating the benefit because if you look just at VTE-related death -- you don't really know why most of our patients die, so you're underestimating the number of patients who might have died from a PE, but you don't know that for a fact. So that goes sort of both ways.

DR. WILSON: Right. But I think that we can't be making a judgment on a drug unless you have the data, that we have some assurance that the increased survival is related to your drug. I just think we just have to be very cautious about that.

Do you have a very quick statistical point about that?

DR. NEATON: I was just going to point out the earlier question. This is a totally post hoc subgroup analysis. And so the real question is, before you even show that graph, is there any evidence that this group differs from survival in any way different from the other group? And it probably doesn't. So your best estimate is what you did in the overall trial.

DR. WILSON: Yes. I mean, that slide might really bias people in a way that it shouldn't.

Dr. Vose?

DR. VOSE: I think my major question has already been addressed. But I think the issue is that we have to find is there a population where the risk-benefit ratio is adequate to be able to say that this is appropriate. And in that really high-risk population, in today's clinical practice, that might be a population where we already do use low-molecular-weight heparin, and perhaps that's a better comparison.

DR. WILSON: Thank you for that comment.

Dr. Armstrong?

DR. ARMSTRONG: This gets back a little bit to what was just presented and I think what Dr. Wilson had initially asked a question about, which is really, again, identifying the highest risk population. And looking at your slide CC-33, obviously you have the high-score patients, and then you have the patients with the two histologic tumor types. And clearly based on the numbers,

there's not overlap between the disease, the patients, and the high-risk patients.

So did you actually look at, for example, lung cancer patients who also had a high-risk score? Is that a group that gets more benefit? In other words, is there a Venn diagram overlap of patients who potentially might get greater benefit? Because I think we're all troubled by the fact that we can't really identify a population that gets enough benefit.

DR. GURAL: In fact, we did look at that.

Dr. Bunn?

DR. BUNN: Will you put up slide 211? I did show the slide, and I'll explain it again.

So in the lung and pancreas groups, you can see that in the intermediate risk score, the rate of events in the placebo arm was quite high, 10.3 in the intermediate pancreas, and 4.3 in the intermediate lung. Of course in North America, those numbers are even higher still.

To me, it's interesting that I would be asking a question that you haven't asked. And to

me, one of the narrowing that was left out was the intermediate risk in the other tumor types because there are clots there. And so I would personally favor not having this for the low risk. But one could argue whether the intermediate risk of the other types, other than lung and pancreas, should be included in the indication. But I think that certainly for lung and pancreas, these data would suggest that the intermediate score should be included in the label.

Now, just to go back to Julie's point, we don't give prophylactic treatment right now. It's not indicated. It's not in the guideline. It's not in any label. There are no approved drugs, and it's not routine use to do it. So to say that enoxaparin is available, yes, it's available, but the guidelines say don't use it. It isn't --

DR. VOSE: I was just pointing out, in clinical practice, I think that is used sometimes in the very high-risk patients; for example, pancreatic cancer patients.

DR. BUNN: Oh, right. I'm talking about

lung. It's certainly not a routine thing in lung. And, again, I do believe in evidence-based medicine. And the preponderance -- this is a large, well-conducted -- this is level 1 evidence. This is a large prospective, double-blind clinical trial, the highest level of clinical evidence that we have.

DR. ARMSTRONG: So the question I was getting at -- you show here the placebo. The question is, is there --

DR. BUNN: Yes, the benefit's the same, again, by subset analysis. The statistician can go over that. But it's the same. The reduction in risk is the same.

DR. WILSON: Let's just show one slide, because we really have to move on.

DR. EMERSON: No slide here. We're using a relative risk as our measure of efficacy. And one of the advantages of a relative risk is when you have a population that is contaminated by subjects who can't benefit because they're never going to have a VTE. The relative risk will stay constant.

And so we don't expect on the relative risk scale to see a difference in the measure as you go from a population that had 50 percent VTE risk to a population that had 10 percent VTE risk. The issue that we're trying to address is let's go to the effectiveness scale and what's the attributable risk, and that's where we'd see the difference.

Open Public Hearing

DR. WILSON: Okay. Thank you. This now concludes the questions for the presenters, and we'll now proceed with the open public hearing.

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's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you

may have with the sponsor, its product, and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

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

The FDA and this committee place great importance on the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for the open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated

with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chair. Thank you for your cooperation.

I would like to now recognize speaker number 1.

DR. NAGDA: Good morning. Thank you for the opportunity to testify on behalf of the Cancer Prevention and Treatment Fund. My name is Sonia Nagda. I'm a physician, and I received my training in public health at Harvard University. Our organization is dedicated to improving the health of adults and children, and we do that by scrutinizing scientific research. We do not accept contributions from companies that make medical products, so I have no conflicts of interest.

The data that evaluate the use of semuloparin for venous thromboprophylaxis in chemotherapy patients is based on one study of 1600 patients on the study drug. However, 36 percent of these patients did not complete 3 months on the therapy. Of these, 255 patients discontinued treatment due to adverse side effects.

Semuloparin reduced the absolute risk of DVT and fatal and non-fatal pulmonary ebolism by only 2.2 percent, compared to placebo, but there are serious side effects. There were 19 incidences of major bleeding in the semuloparin group. And of these, 5 were in a critical location, including pericardial, intracranial, splenic, and intraocular events, compared with no critical bleeds in the placebo group.

The drug was tested in patients with colon or rectal, stomach, bladder, ovarian, lung and pancreatic cancer, but was only found to reduce the risk of thromboembolism in patients with lung and pancreatic cancer. Because there were so few patients with each type of cancer, it would be necessary to include more patients to shed light on the impact that semuloparin has on the development of blood clots. Many of you have already commented on the questionable heterogeneity of the patient population in the study, and it appears that the sponsor has flung a number of errors with the hope that one would hit the target.

Patients in the study were most commonly on fluorouracil, cisplatin or carboplatin, and some were on a chemotherapy regimen of more than one agent. The sponsor just provided the analysis based on this factor and found a statistically significant reduction in the risk of thromboembolism in only one chemotherapy subgroup. Further evaluation is necessary to determine which patients, if any, would derive the most benefit from semuloparin.

The secondary outcome of this study was one-year survival, and there was no difference between the two groups, with 40 percent mortality in the semuloparin patients and 41.5 percent mortality in placebo. This high mortality rate demonstrates the severity of illness facing these patients and the importance of determining which patients are most likely to benefit, without being subjected to additional harm.

With minimal gains and efficacy over the currently accepted treatment regimen, and with risks that should not be overlooked, particularly

noting that the number needed to treat is greater than the number needed to harm in this population, we recommend that semuloparin be studied more extensively prior to approval. Making it available prior to determining whether there are some types of patients who are more likely to benefit could be harmful to many patients and helpful to few. Thank you.

Questions to the Committee and Discussion

DR. WILSON: Thank you very much.

The open public hearing portion of this meeting is now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments. We will now proceed with the questions to the committee.

Would the FDA like to frame the question for us, please?

DR. HERNDON: To briefly summarize the main results of the pivotal trial, symptomatic VTE

events were observed in 1.2 percent of patients in the semuloparin arm and 3.4 percent in the placebo arm. VTE-related death was similar in both treatment arms. There was no difference in survival at one year. Major bleeding was similar between the treatment arms, however, several patients in the semuloparin arm and no patients in the placebo arm developed major bleeding into a critical area or organ.

Given the findings of the pivotal trial, the agency asked the committee to discuss the following: Is there sufficient experience to inform the use of semuloparin for VTE prophylaxis in its previously untargeted population of patients with cancer? Should the target population considered for this use be narrower than the population studied in SAVE-ONCO?

After discussion, we have the following question for your vote. Is there sufficient demonstration of a positive benefit-to-risk assessment to recommend approval for semuloparin for thromboprophylaxis in any population or

subpopulation of patients with cancer? If yes, please define this population in your discussion after your vote.

DR. WILSON: So I think we really spent a long time going over this, and I think the presenters did a very nice job presenting the data. Just to kind of summarize from my own perspective, we see a trial here in which we are seeing a drug used in what is not considered to be now a standard clinical setting, and that is during the use of chemotherapy and only during the time that the chemotherapy is being given.

The overall trial did in fact show a very significant P value, but as we all know, the question before us is not a matter of whether or not there was a statistically significant effect, but whether or not there was a clinically meaningful effect. And in fact, for the overall trial, that really only translated into a 2 percent absolute incidence reduction in VTEs. And I cannot get my hand around whether or not this reduction really led to any overall reduction in quality of

life, other safety issues further down the line, because that data was not collected. What we do know, though, is that there was major bleeding into organs, into major organs on the treatment arm.

The problem that I'm having is that we've already now seen that the indication has been narrowed in a secondary analysis, which always makes me very uncomfortable. And, as a number of the members of the committee have pointed out, the incidence of clot probably increases over time with cancer, but the hypothesis here is that the increased incidence in clot due to chemotherapy, on top of the cancer, is what they're really targeting.

So I think that we need to discuss is there a population getting a specific chemotherapy that we feel has such a high risk that it is meaningful to use this, or have they really met the acid test. And that is, within the group they have identified, that this really has led to a clinically meaningful benefit.

So with that, raise your hands and let's

open it up.

DR. NEATON: So I think the missing data seriously compromises the inferences from this trial. And so I would not characterize it as well conducted. And I would refer to the National Academy report that Dr. Emerson referred to and the chapter on prevention of this problem, and we might be in better position. But I am not confident in the absolute risk differences.

I agree that they're going to be greater in the target population, which has been revised and chosen. But I'm not confident that that's not biased in a way that it probably -- it could be much smaller than what we are observing. Likewise, the bleeding data were similarly subjected to the same kind of missing data problems. The one outcome which was stopped, there's no difference, survival.

The other point is that I wasn't sure what to make of the meta-analysis. And I'm not sure that's a fair comparison between the results of this study and the other heparin trials because

that presumes that they were all counting events in the same way, and the same types of events. And I think in many situations, you would not kind of automatically truncated the counting of events after three days in a study as was done here.

DR. WILSON: Dr. Fojo, you had a question or a comment?

DR. FOJO: Well, I was going to make a comment with regard to what you said about clinical benefit, and the flip side of that is clinical harm. And actually I thought it was interesting. In my opinion, the elephant in the room was never addressed. And that's the fact that you have to administer this subcutaneously everyday. Actually, it was addressed by Dr. Bunn. He had a slide that said why is it bad to get clots. And he had 6 months to lifelong daily sub-Q injections. No patient likes that. Nobody likes to do that. And that's what we would have patients doing.

So we've been talking about death and about bleeding, but that's going to affect very few patients. But every single patient is going to

have the quality of their life impacted by these sub-Q injections; not only the pain, but they don't like to go out in public and the beach, and so forth and so on, with all of these things. So I think that that's not even been factored in. And, to me, it's a very important left-out consideration.

DR. WILSON: Dr. Sekeres.

DR. SEKERES: Thank you, Dr. Wilson.

You know, I'm still troubled at the definition of DVT that was used here, and I keep circling back to a clinically significant DVT. The sponsor made a very good case that there's the potential for DVTs to lead to serious outcomes in cancer patients. They even quoted a 3.5 percent risk of DVT/PE-related death, yet, we never saw that in this study. And I think part of the problem is that the same definitions and the same rate was given to a lot of different DVTs that in cancer patients may not carry the same risk or may not be viewed as being as serious in the setting of a terrible disease like cancer as they would be in

somebody undergoing hip surgery or in a medical patient who's bed-bound. And I still can't get over that.

Approximately, I would say 60 percent, the sponsor may say 75 percent of these patients had what I would consider a serious DVT or PE. So we're cutting those numbers down, and then we're comparing them to what are also clinically significant bleeding events, particularly into critical organs.

I know that's not exactly what the FDA has been asking us to focus on, but it does get to it a little bit, how high risk a patient can we define who has a life-threatening DVT, who would deserve this sort of prophylaxis. And then the overarching question is for how long would we treat them. And when I refer my patients over to vascular medicine for consultation, they always recommend about 6 months to a year of anticoagulation for patients who have even minor clots or that degree of prophylaxis. So I still can't resolve those issues.

DR. WILSON: Dr. Kelly.

DR. KELLY: Thank you. I mean, I think that I'm grappling with some of your issues, Dr. Wilson. We could go through this and find a target population that may be a high enough risk, but that's hypothesis generating. All right? And it doesn't prove that this drug will give a clinical benefit at the end.

So I guess we need some guidance from the FDA. Would I secondary trial be needed at that point to show the clinical benefit in a subpopulation?

DR. PAZDUR: Well, I think this is, can you answer and define a population from this trial? And what it sounds like is that you're having a great deal of difficulty about it. Remember, as I stated before, we have to feel adequate in approving this drug that we could label the drug. Okay? And that's the thing that we have been grappling about internally, you know, how do you define this population?

There are multiple issues that have been

brought out here. We have one trial here with a very heterogenous population. As I stated before, there are so many unanswered questions: What is chemotherapy? How long does one give this? Yes, you have some patients getting it second line, first line. Well, if you got it first line, should you get it second line, and what is the safety if you got it third line? Does this include oral chemotherapy drugs? Does it include only IV drugs? Does it include newer classes of drugs?

So many issues here that we needed help in trying to define labeling of this drug, does it make sense. All approvals have to be put into a clinical context. It is not just the P value.

DR. WILSON: Dr. Buzdar.

DR. BUZDAR: Yes. I think the thing is that even though the question which is being posed is on a subset of patient populations, the study was not designed to look at subgroup analysis and as not having enough power to address that. I think, yes, it may be very interesting hypothesis-generating information, which needs to be looked at and

defined. But I'm looking at the data, as I pointed out earlier, that if you ignore the GI bleedings, which are different, there is a fourfold increase in significant bleeding risks by giving this agent, compared to the placebo. The differences become somewhat attenuated because the GI bleeding in the placebo group was twice as much.

DR. WILSON: Dr. Wozniak?

DR. WOZNIAK: I think the biggest problem, obviously, is defining a population. I do think some people probably benefit from prophylactic anticoagulation. And then we've talked about the type of cancer, the type of chemotherapy. But there are also probably some inherent issues. Some people are just prone to clotting. I mean, you have to look at Protein S, Protein C. There are a lot of issues beyond the cancer itself that may make certain people prone to clotting and at higher risk, and I think that those need to be defined.

DR. WILSON: Dr. Arscott?

DR. ARSCOTT: Yes, thank you. To follow up with Dr. Wozniak, as a physician who, again, had

lung cancer twice, adenocarcinoma -- I'm a never smoker -- I think that we need to define the variables a little bit better. Smokers would be more inclined to clot; non-smokers not. I can tell you that as a physician, one of my biggest fears -- I had many fears going into it, but one of my big fears was having a PE, especially having two chest surgeries. I know that that increased my risk. And as a result of that, though, I was going to spinning class and drinking water, even when I wasn't feeling well, to try to reduce my risk of clotting as much as I can. So that brings in a different population. I was able to do that, but if I was somebody who was more sedentary, et cetera, maybe prophylactic anticoagulation would have been an option. I just think that there are too many variables out there right now. We need to have more data.

Also -- and I brought this up before -- I think it's important that it be defined as part of the benefit, those people who were in the placebo -- there were 27 people in the placebo

group who did go on to have significant VTE events who weren't at some type of treatment, whether that be full anticoagulation or filter or whatever, and how did that impact their quality of life? It does not sound to me like they were followed. People were -- there was an endpoint, and if they had a VTE event, that was the endpoint.

So we don't have that data. And I think that that would be important to know also, those people who did have a clinically significant VTE event, how did their treatment -- how was that impacted. So I just think that there are so many variables and so many things that need to be evaluated in this. Thank you.

DR. WILSON: Thank you.

Dr. Fojo.

DR. FOJO: To address can it be narrower, I think it will depend also on what your endpoint is, because in that last slide that was put up that you didn't like, it looked like the high-risk patients, their one-year survival was the same as the entire population. So if the endpoint was survival, then

that wouldn't make it. So then you'd have to cut back and say, so what would be the endpoint is a reduction in VTE. And then we'd probably want to know is it proximal, is it distal, is it upper extremity or not. And we'd probably want to know how long is hospitalization and so forth going to be changed.

I was thinking all along, maybe the high risk would be a population. I'm not so sure now after today's presentation and seeing some of the data. And certainly you'd have to know ahead of time what is your endpoint.

DR. WILSON: I think that Dr. Pazdur said this, and I'll say it again. I think it's no surprise that cancer patients get clots. It's no surprise that an anticoagulant will reduce those clots. And so I don't think the results of this study are anything surprising. I think it's all about whether or not we can identify a group that has a high enough risk of clots, where the risk of the drug and the discomfort associated with the drug overweighs that, and that it is worthwhile

giving that drug. And I think that in standard practices, Dr. Vose said there are -- even without NCCN guidelines, et cetera, there are patients that we all kind of have a sense have a high risk of clotting, and we are treating them with anticoagulants.

I think what this indication, though, is, is a pretty much -- even though it is somewhat limited, it's still very much of an open-ended, well, if you're getting chemotherapy and you have two different kinds of cancers or high VTE, you will get a drug. And I think that when you weigh the data, at least for me, it's not clear that the risk-benefit in that group -- and that again is a subset analysis that makes me uncomfortable -- really favors kind of changing standards of care, even though the P values and the hazard ratios do say that you do reduce VTEs. That's certainly my sense of it.

Are there any more comments or thoughts? Because if not, we can move to the voting question.

(No response.)

DR. WILSON: All right. So the voting question is, is there sufficient demonstration of a positive benefit to risk assessment to recommend approval of semuloparin for thromboprophylaxis in any population or subpopulation of patients with cancer? If yes, please define this population in your discussion after your vote.

So the vote, then, will be yes, it does have a positive risk-benefit, and therefore we recommend that it be approved, and we can discuss the subgroups if necessary. A no would be that, no, we do not think it has a positive risk-benefit in any group.

So before you -- on the mic, there will be -- I think it should light up. There is a "yes" button, a "no" button, and an "abstain" button. Yes means that you do think that there's a positive risk-benefit and recommend approval. No means that you don't, and abstain as if you don't know.

So let's go ahead and vote.

(Vote taken.)

DR. WILSON: Okay. The results are yes, 1;

no, 14; abstain, 1. And I think given that vote, it's probably unnecessary to discuss a subgroup that would be -- that should be approved for. And so I'm going to start on my right. If you would please state your name into the record, how you voted, which we know, and a very brief statement why you voted as you did. Thank you.

DR. DIEHL: Louis Diehl. I voted no. And I voted essentially because I was impressed by the post hoc analysis and the nature of the study. And also when I looked at the events that were prevented, I didn't see a clear benefit from them. And of course the toxicity was there.

DR. VOSE: Julie Vose. I also voted no. I just didn't feel that there was an adequate risk-benefit ratio in this overall study, and perhaps further studies will identify that patient population, which could be appropriate. But in this current study, I did not feel that the post hoc analysis was adequate to show that.

DR. LOGAN: Brent Logan. I voted no. Approval based on a single trial should be robust

and statistically compelling. Here we had a post hoc subgroup analysis for a single trial with a small absolute difference, where even that absolute difference had some concerns in terms of the issues with early, heavy censoring, where it's possible that that difference might be even smaller than was estimated.

DR. NEATON: Jim Neaton. I voted no because while I agree that it's kind of obvious anticoagulants should have an effect, the magnitude would depend upon the target population and how reliably it's assessed. And I did not see that it was reliably assessed here.

DR. MENEFEE: Michael Menefee, and I also voted no. Largely in part, I felt the study generated more questions than provided answers. As a clinician that sees a lot of patients with advanced malignancies in the targeted population, I just didn't have a clear answer as to how this drug is going to help that patient population. I think this study did miss an opportunity by not prolonging the length of therapy to an intolerance

or to a death and missed some of the patients that may have potentially benefitted from this treatment. And so without that information, I could not favor approval.

DR. FOJO: Tito Fojo. I also voted no, and Mike expressed some of my concerns with regard to more questions than answers. I think it doesn't reflect on the drug. This might be a really good drug. I don't know that any drug could have succeeded in this setting. It was just too tall an order. And you learn from experience, and this is one of those cases.

DR. BUZDAR: Buzdar. I voted no because I didn't think the study identified a subset of patients in which it could be appropriately used with a benefit, which would overweigh the potential risk which is caused by the therapy.

DR. WOZNIAK: Antoinette Wozniak. I actually abstained. I was going to vote no, but I decided that I really don't know who benefits. And I think there is a benefit for a defined population, and that population needs to be

defined.

DR. KELLY: Kevin Kelly. I voted no for a lot of the reasons mentioned here, but basically is we're unable to define a specific population to treat. And also when and how long to treat is also very questionable with this study.

DR. SEKERES: I'm Mikkael Sekeres. I also voted no. Cancer patients have a lot to deal with just in treating their cancer with chemotherapy. When we add adjunctive medicines to prevent potential complications, we have to be particularly careful in not also adding harm. I was not convinced that this drug prevented clinically significant clots, and I was not convinced that the bleeding that it did cause wasn't equally harmful.

DR. WILSON: Wyndham Wilson. I voted no. I felt that there was no evidence in either the overall trial or the subgroup analysis that the benefit outweighed the risk.

DR. FREEDMAN: Ralph Freedman. I voted no. I felt that the clinical benefit and the target population here remains to be adequately defined.

Also, with regard to the safety, there are a number of significant questions here and that we don't know how long administration is safe. And I do feel that the use of the VTE score is useful. Unfortunately, it wasn't available when the study was initiated, but maybe for future trials, that could be included.

DR. LOEHRER: I'm Pat Loehrer. I also voted no and for many of the same reasons already mentioned. I do want to basically applaud the company, though, for trying to address a problem that I think is clinically significant to many of our patients. And I think this didn't quite rise to the occasion, but I would hope that you would not give up on this. And I think this was, as Dr. Kelly mentioned, a hypothesis-driven trial, and I think there are some subgroups that clearly we should be studying specifically. And that would be those patients with pancreatic cancer, and I think, again, controlling for some of the other drugs. I don't think all drugs cause thrombosis, but we know that bolus 5-FU, and bevacizumab, and people with

catheters -- I think this study could be done a little bit better. And, again, I would encourage further studies.

DR. ARMSTRONG: Deborah Armstrong. I also voted no. I didn't think the findings from the study justified establishing basically anticoagulation as a standard of care in a new setting. There's clearly a need here. The fact that you needed to treat many more patients for benefit than for harm, the very high censoring to event ratio, and the absence of the survival benefit made me vote no.

DR. ZONES: I'm Jane Zones, and I voted no. I didn't think that -- I thought that there were too many unknown variables to establish a clear benefit to risk ratio, especially in one that would change standard of care.

DR. ARSCOTT: Karen Arscott. I suspected I'd be alone in my vote, but I felt when I read the question of the committee, I feel that there is a positive benefit to risk assessment in a very -- in a subpopulation of patients. I think that we have

to define that subpopulation a little bit better. Some of the variables that were not even brought up I brought up before were people who are more sedentary people who maybe are smoking, and maybe are still smoking during their treatment, who are at risk of increased clotting; people who are dehydrated; people who are not taking adequate hydration, et cetera. I think that those people weren't even included in this study, and I think that -- or at least they weren't defined. They probably were in this study.

So I think we have to define the subpopulation a little bit better. And I think that there is a subpopulation where this prophylaxis is beneficial. The thought of giving myself a subcutaneous injection everyday was not pleasant to think of, but at the same time, you know, if you want to live, you're going to do what you have to do to live. Again, that's a subpopulation who will do anything to survive.

So I think we just have to define this. So I did not want to say no to this drug altogether

because I think that this population warrants this. And I applaud the company for what they've done. Thank you.

Adjournment

DR. WILSON: I want to thank Sanofi for presenting this. I think it was a very important trial. I wish that the benefit was greater, but I do want to thank them, and also all the committee members. And the meeting's now adjourned. For the afternoon session, we'll meet here promptly at 1 o'clock. Thank you.

(Whereupon, at 12:07 p.m., the morning session was adjourned.)