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CENTER FOR DRUG EVALUATION AND RESEARCH

ANTI-INFECTIVE DRUGS

ADVISORY COMMITTEE

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P R O C E E D I N G S

8:35 AM

**Agenda Item: Call to Order - Barth Reller, M.D.,
Chair**

DR. RELLER: Good morning. I am Dr. Barth Reller, and I would like to welcome everyone to the meeting of the Anti-Infective Drugs Advisory Committee of the Food and Drug Administration for consideration of the drug drotrecogin alfa (activated) from Eli Lilly and Company.

We will open this morning's meeting with a statement by Tom Perez, our Executive Secretary.

Tom?

**Agenda Item: Meeting Statement - Thomas H. Perez,
M.P.H. Executive Secretary**

MR. PEREZ: Good morning. The following announcement addresses the issue of conflict of interest with regard to this meeting, and it is made part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda for the meeting and all financial interests reported by the Committee participants it has been determined that all interest in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting, with the following exceptions.

In accordance with 18 USC 208(b) full waivers have

been granted to Dr. Thomas Fleming and Dr. Barbara Murray. A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12830 of the Parklawn Building.

In addition, we would like to disclose for the record that Dr. Thomas Fleming and Dr. Barbara Murray and Dr. Ellen Wald have interests which do not constitute a financial interest within the meaning of 18 USC 208(a) but which could create the appearance of a conflict. The agency has determined notwithstanding these interests that the interests of the government in their participation outweigh the concern that the integrity of the agency's programs and operations may be questioned.

Therefore, Dr. Fleming, Dr. Murray and Dr. Wald may participate fully in today's discussions.

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

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

Thank you.

DR. RELLER: Today's application crosses many disciplines and consequently there are nine additional voting members and guests that will supplement the Anti-Infective Advisory Committee today.

Next we shall have introductions of all of voting members of the Committee that will hear and assess the material presented.

We will start on my far right with Dr. Eichacker. Please give your basic affiliation and name for the Committee.

Thanks.

DR. EICHACKER: My name is Peter Eichacker.

DR. RELLER: There is a little button at the bottom of the microphone. If we press that, the red light comes on. Then we are audible for all.

DR. EICHACKER: My name is Peter Eichacker. I am head of the Clinical Care Section at the Clinical Center at the NIH in Bethesda.

DR. CARCILLO: Good morning. My name is Dr. Joseph Anthony Carcillo, Jr., MD. I am Associate Director of the Pediatric Intensive Care Unit at Children's Hospital in Pittsburgh.

DR. LILLY: I am Craig Lilly. I am the Medical Director of the Intensive Care Unit at the Brugman(?)

Woman's Hospital, Harvard Medical School.

DR. SUFFREDINI: My name is Anthony Suffredini. I am a Senior Investigator in the Critical Care Medicine Department at NIH, Bethesda, Maryland.

DR. RELLER: When you done with the mike, please turn it off. Thank you.

DR. WARREN: My name is Shaw Warren. I am a member of the Infectious Disease Unit at the Massachusetts General Hospital in the Adult and Pediatric Units.

DR. MUMFORD: Bob Mumford. I am in the Infectious Diseases Division of the Department of Medicine at the University of Texas, Southwestern Medical School in Dallas.

DR. O'FALLON: Mike O'Fallon, biostatistician, Mayo Clinic.

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

DR. MURRAY: Barbara Murray, Infectious Diseases, University of Texas Medical School in Houston.

DR. WITTNER: Murray Wittner, Albert Einstein College of Medicine, Division of Tropical Medicine and Parasitology.

DR. WALD: Ellen Wald, Chief of the Division of Allergy, Immunology and Infectious Disease at the Children's Hospital, Pittsburgh.

DR. RELLER: Barth Reller, Division of Infectious

Diseases and Director of Clinical Microbiology, Duke University Medical Center.

MR. PEREZ: Tom Perez, Executive Secretary for this Committee.

DR. EBERT: Steven Ebert, Infectious Disease Pharmacist, Meritor(?) Hospital and University of Wisconsin, Madison.

DR. RAMIREZ; Julio Ramirez, Chief, Division of Infectious Diseases at the University of Louisville, Kentucky.

DR. CHRISTIE-SAMUEL: I am Celia Christie, Professor and Chair in Pediatrics and consultant in infectious diseases, epidemiology and public health, University of the West Indies, Kingston, Jamaica.

DR. CHESNEY: Joan Chesney, Infectious Disease, Pediatric Infectious Disease, University of Tennessee Health Science Center in Memphis.

DR. CROSS: Alan Cross, Division of Infectious Disease, University of Maryland, Medical School, Baltimore, Maryland.

DR. ARCHER: Gordon Archer, Chair of the Division of Infectious Diseases of the Medical College of Virginia in Richmond, Virginia.

DR. LEGGETT: Jim Leggett, Infectious Diseases, Providence Portland Medical Center, and the Oregon Health

and Sciences University, Portland, Oregon.

DR. FORSYTH: I am Linda Forsyth, Center for Biologics, FDA.

DR. LINDBLAD: Robert Lindblad, Center for Biologics, FDA.

DR. JOHNSON; Gibbes Johnson, CBER, FDA.

DR. SIEGEL: Jay Siegel. I direct the Office of Therapeutics at CBER, FDA.

DR. RELLER: Thank you very much. We will now have Dr. Gibbes Johnson, Chair of the FDA Review Team with opening comments.

Agenda Item: Opening Comments: Gibbes Johnson, Ph.D., Chair, FDA Review Team

DR. JOHNSON: Good morning. My name is Gibbes Johnson, and I would like to provide some brief introductory information on the drug product and the FDA review process for this biologics license application or BLA.

The sponsor of this BLA is Eli Lilly and Company and Xigris is the brand name for the drug product. The international non-proprietary and the United States approved name for the active pharmaceutical ingredient is drotrecogin alfa (activated). The common name for the active pharmaceutical ingredient is recombinant human activated protein C.

This biologics license application was assigned

submission tracking number 125029, and this slide contains the action dates involved in the review of this BLA.

The application was received on January 26, and granted priority review status. The application was filed as acceptable on March 12. A major amendment to the BLA was received on May 23. This major amendment contained additional clinical data and extended the first action due date by 3 months.

Three distinct facilities are involved in the manufacture of Xigris and pre-approval inspections of these facilities have been performed. Lonza Biologicals, Incorporated is the contract manufacturer for the bulk drug substance and was inspected from late May to early June.

DSM Catalytica Pharmaceuticals is the contract manufacturer for the final drug product and as inspected in August.

Eli Lilly Corporate Center performed certain release testing and all stability testing as well as having quality assurance oversight over the two contract manufacturers.

This facility was inspected in August. The agency will take action on this application on or prior to October 26.

The purpose of this slide is to recognize the FDA individuals responsible for the review of this BLA and to

mention that the review process involves multiple disciplines. These disciplines include chemistry, manufacturing and controls or CMC, clinical biostatistics, pharmacology and toxicology. In addition, there are bioresearch monitoring facilities and inspections of these facilities.

Also, the regulatory project managers play an important role in coordinating the activities of the review committee.

Now, I would like to provide some general introductory information regarding the manufacturing of Xigris and recombinant human activated protein C.

It is produced by recombinant DNA technology in a human cell line, purified by a series of chromatographic and filtration procedures, analyzed for identity, potency and purity and the drug product is supplied as a sterile lyophilized powder containing recombinant human activated protein C, sucrose, sodium chloride and sodium citrate.

Now, recombinant human activated protein C is a glycosylated serine protease and activities include anti-coagulant via cleavage and inactivation of clotting factors 5A and 8A. APC, also, exhibits anti-inflammatory activities as well as pro-fibrinolytic activities.

At this time I will turn it over to the sponsor who will start their part of the presentation.

DR. RELLER: Thank you, Dr. Johnson.

I would like to call on Dr. Holger Schilske to introduce the presentation of Eli Lilly and Company.

Agenda Item: Eli Lilly and Company Presentations

DR. SCHILSKE: Mr. Chairman, ladies and gentlemen, good morning. My name is Holger Schilske. I am the team leader for the product development team, the Xigris product development team at Eli Lilly and Company.

On behalf of Lilly, I would like to thank you for the opportunity to discuss drotrecogin alfa (activated) today.

The proposed trade name for drotrecogin alfa (activated) is Xigris.

The next slide, please?

The indication for which we are currently seeking approval is for the treatment of adult and pediatric patients with sepsis associated with acute organ dysfunction which is by definition severe sepsis. Treatment with drotrecogin alfa (activated) reduces mortality in patients with severe sepsis.

The efficacy and safety profile of this new life-saving therapy will be extensively highlighted in subsequent presentations today. The contents of this application meet all expectations contained in applicable FDA and ICH guidelines and it was designed and conducted consistent with

agreement and advisement from the FDA.

We strongly believe the development of Xigris represents a revolutionary breakthrough in the treatment of severe sepsis, a devastating disease with an extremely high mortality.

Xigris is the first compound in a long row of failed ones that could clearly demonstrate that it significantly reduces mortality.

The next slide, please?

The next slide actually highlights the significant burden which the disease state of severe sepsis puts on patients and society. The annual incidence of severe sepsis in the United States is approximately 750,000 cases per year with a mortality rate of 28 to 50 percent despite the advances in modern medicine.

Also, the socioeconomic burden with regard to the costs of the treatment of severe sepsis is high, totaling almost \$17 billion per year. The annual incidence rate, also, of severe sepsis is increasing due to our aging population and other various factors.

The next slide, please?

As presented on this slide, the incidence rate of severe sepsis even in comparison to other very significant diseases is very high, with the incidence rate of severe sepsis equality the incidence rate of congestive heart

failure and breast cancer combined, and the number of patients dying from acute myocardial infarction and severe sepsis is roughly the same.

Next slide, please?

By breaking down the annual numbers on incidence rate and mortality, it is fair to say that in the United States on average 600 patients die every day with severe sepsis. Xigris has been shown to reduce the 28-day, all-cause relative risk of mortality by 19.4 percent. That means that one out of five patients who would have died will be saved.

The next slide, please?

This slide illustrates the structure of drotrecogin Alfa (Activated). Xigris, as you already heard this morning is a recombinant homologue of plasma human activated protein C.

The protein sequence of drotrecogin alfa (activated) is identical to that of human plasma activated protein C but differs in the carbohydrate portion of the molecule.

Human protein C was cloned by Lilly scientists in the early 1980s. The molecule shows a highly complex structure and requires four different types of post-translational modifications for its full biological activity.

Biochemical characterization, pharmacology experiments and preclinical toxicology studies were conducted during the 1980s and early 1990s. The clinical evaluation of Xigris then began shortly after the initial IND was filed in 1995.

Next slide, please?

Today we will demonstrate that the data submitted in the biologics licensing application for Xigris meet or exceed the proof for efficacy and safety.

We will provide data to you that support Xigris's ability to save lives of patients suffering from severe sepsis. Our presentation will encompass a number of scientific and regulatory matters, and we will follow the outlined agenda.

First, Dr. Steven Opal, professor of medicine, Chief, Infectious Disease Division, Brown School of Medicine will discuss the scientific background of sepsis disease state.

Following him will be presentations by two Lilly scientists. Dr. William Macias, Medical Director of the Xigris Product Team will present the clinical trial results in adults and ongoing trials. He will be followed by Dr. Jeff Helterbrand, Senior Regulatory Scientist of the Xigris Product Team who will review the formal benefit risk assessment.

Dr. Macias will then conclude with an overview of the pediatric trial data and overall study conclusions.

We look forward to a full discussion of the issues raised. Dr. Macias will facilitate Lilly's response during the discussion period.

Also, we have a number of key scientific staff and external experts available here today to respond to your questions.

The next slide, please?

We, in particular wish to thank the following experts for working with us and for being here today to assist with your deliberations, Dr. Gordon Bernard, Professor of Medicine, Pulmonary Medicine Division, Vanderbilt University Medical Center, Dr. Brett Giroir, Chief Medical Officer, Children's Medical Center, Dallas, Associate Dean for Clinical Affairs, University of Texas, Southwestern Medical Center, Dr. Mitchell Levy, Associate Professor of Medicine, Brown University School of Medicine, Medical Director, Intensive Care Unit, Rhode Island Hospital, Dr. Steve Opal as already mentioned and Dr. Michael Seneff, Medical Director, George Washington University Medical Center, Intensive Care Unit.

We ask for your active consideration to recommend approval of drotrecogin alfa (activated) for the treatment of patients with severe sepsis. We strongly believe the

documentation provided will support such action and we look forward to a mutually productive session.

We, also, would like to ask you to hold your questions, please until the end of our presentation.

I now have the pleasure of introducing Dr. Steve Opal for the scientific disease state overview.

DR. OPAL: Thanks, Dr. Schilske, and good morning.

Sepsis and severe sepsis is described as a clinical syndrome characterized by a host systemic and inflammatory as well as procoagulant response to microbial pathogens, and it goes by the acronym SIRS for systemic inflammatory response syndrome.

An intense host response may lead to organ dysfunction, and this is now designated as severe sepsis. The mortality rate for severe sepsis remains high despite appropriate antimicrobials and supportive care and as such improved therapies for this disease are a major unmet medical need.

The current thinking as to the pathophysiology of sepsis is related on this slide, and it is now viewed that a network of integrated host-derived inflammatory mediators actually induce severe sepsis, and these mediators are initially induced because of an infectious process resulting in the systemic release of a number of microbial products into the circulation, and these pathogen-associated pattern

molecules such as endotoxin and lipoproteins and other elements are recognized by the innate immune response and both a cellular and humoral response is induced which includes such elements as the pro-inflammatory cytokine such as TNF, IL1 and IL6, bradykinin complement activation, phospholipid activation, oxidant stress is generated along with neutrophil proteases. There is activation and coagulation of the system and there is activation of platelets, and all these elements combine to induce a diffuse endovascular injury in the host and result in a coagulopathy of sepsis and these combine to induce organ dysfunction and if left unchecked may potentially lead to the death of the patient.

There have been numerous attempts over the last 15 to 20 years to alter the outcome in sepsis by interventions which were designed to interfere with the pathophysiology of sepsis, and I will just show a few of these that I think are illustrative, the anti-endotoxin, monoclonal antibodies such as HA-1A and E5 and a variety of anti-TNF strategies and inhibitors of interleukin 1 have all been attempted in the past, and in each of these studies either large Phase II or Phase III trials designed to improve the survival of patients, the initial studies were unsuccessful, but in each case a subgroup was identified in each one of these studies often by post hoc analysis that suggested there might be a

subpopulation within this septic population that may benefit from these agents and in each case a confirmatory trial was performed, and in each case the confirmatory study was unable to confirm the hypothesis that there was a subgroup of patients that might benefit from these agents, whether it was HA-1A going after gram-negative bacteremia or E5 and patients who had sepsis but did not have shock or the TNF inhibitor which tried to go after patients with severe sepsis without refractory shock or patients who had a predicted risk of mortality of greater than 24 percent using an APACHE II type system, and in each one of these circumstances the subgroup that was identified was not shown to be significantly benefitted in subsequent confirmatory trials, and I think these studies, as well as a number of other studies have taught us that there are some hazards in trying to do subgroup analysis in sepsis trials and, also, that we needed a new strategy to go after if we are going to improve the outcome of these patients, and within the last 5 to 10 years there has been a great deal of interest in the endogenous anticoagulants as a potential treatment strategy for sepsis, and the reason for this is that there is an increasing level of evidence, both experimentally and clinically using improved methods of detection of coagulation activation that shows us that activation of the coagulation system occurs very early in the septic process

and is associated with a number of events including intravascular trauma generation and fibrin deposition and paired fibrinolysis, the depletion of key regulatory elements of the coagulation system, such as the protein C pathway in antithrombin, decreased capacity to activate protein C in the circulation and the evidence that the systemic inflammation has an interaction between the coagulation pathways and the inflammatory pathways involving neutrophils, other white cells and the endothelium.

Also, it has become apparent that activation of the coagulation system is largely independent of the type of infecting microorganism, and so, the data seen here which is from the Phase III trial have been shown in other studies as well and that is that if one looks at evidence of coagulation activation using very sensitive assays, such as a D-dimer which is a specific fibrin degradation product virtually 100 percent of patients who meet the criteria for severe sepsis will have evidence of coagulation activation, and this is true whether you have a gram-negative infection or a gram-positive infection or a fungal infection or sepsis without an identified microorganism. They virtually all have evidence of coagulation activation by D-dimer measurement.

It is, also, seen that a vast majority of patients had depletion in their protein C pathway and their protein C levels are inappropriately low in the majority of patients,

and again, this is independent of the type of infecting microorganism as the cause of sepsis.

Prothrombin time is a very simple global assessment of coagulation, is abnormal in the vast majority of patients and the results are as compelling as is interleukin-6 as a global measure of pro-inflammatory cytokine generation that both coagulation and inflammation is activated simultaneously and in an interactive fashion in patients with sepsis and this is independent of the class of microbial pathogen.

Now, the mechanism of action of activated protein C is actually complex and multifactorial. It is certainly an endogenous anticoagulant but has other important properties, and I will just go through this figure to try to highlight these.

First, the coagulation system in sepsis is primarily activated via the tissue factor pathway through up regulation by pro-inflammatory cytokines of monocyte and endothelial cell tissue factor expression, and this results in activation of the coagulation system with the generation of thrombin within the circulation, and thrombin has many injurious effects within the microcirculation. It promotes fibrin deposition and platelet deposition resulting in an intravascular fibrin clot.

Thrombin has, also, been shown to react with

specific receptors, thrombin receptors known as the PARs receptors or protease activated receptors and can directly activate cells such as platelets and white cells through the action of this receptor and through the presence in intravascular thrombin.

Thrombin has another property and that is that thrombin can not only act as a pro-coagulant but also, can potentially act as an anticoagulant when thrombin becomes bound to an integral cell membrane protein found in endothelium known as thrombomodulin and thrombomodulin and thrombin complex then has the capacity to convert circulating protein C into activated protein C, and this is a critical step in that protein C is zymogen and is an inactive precursor of the active moiety which is activated protein C, and this is actually mediated by thrombin itself in combination with thrombomodulin.

Activated protein C in combination with protein S will then feed back and inhibit the coagulation system by degrading factors 5 and 8A which are acceleration factors in the coagulation system.

So, there is a negative feedback loop here by which thrombin activation begets an inhibitor of thrombin activation and that is designed to regulate coagulation.

Unfortunately in septic patients this system is disrupted in that the protein C levels rapidly are consumed

and this is due to decreased synthesis as well as increased utilization. Also, pro-inflammatory cytokines inhibit the synthesis of thrombomodulin by endothelial cells, and so the ability to peripherally convert activated protein C is abnormal.

Additionally neutrophil proteases, elastase and other proteases will cleave thrombomodulin as well as another receptor, the endothelial protein C receptor from the surface of endothelial cells further compromising the system and preventing the peripheral conversion of protein C to activated protein C where activated protein C can then go back and inhibit the coagulation system.

Now, it, also, turns out that activated protein C has at least two other properties of potential value in septic physiology, one of which is that activated protein C is a relatively important and significant inhibitor of PAI-1 or plasminogen activated inhibitor which is a molecule which inhibits the fibrolytic system, and so, activated protein C inhibits the inhibitor fibrinolysis, therefore, allows fibrinolysis to occur and allows plasmin to degrade intravascular fibrin clots which is a potentially desirable attribute in septic patients.

Additionally, as has been recently shown activated protein C, also, has anti-inflammatory properties and these properties include the actual binding and translocation and

alteration of gene transcription frequencies of neutrophils as well as other white cells, monocytes and the effect has been shown to attenuate the pro-inflammatory cytokine generation, decrease surface adhesion expression and, also up regulate anti-apoptotic genes particularly in endothelial cells in such a way to protect the endothelium from injury and further injury found in systemic inflammatory states.

So, activated protein C as an anti-thrombotic is a profibrinolytic and is an anti-inflammatory molecule that, also, has anti-apoptotic effects.

If I could go to the next slide, please?

Okay, just briefly the preclinical evidence to support the use of activated protein C, I will just summarize this one slide. There is a wealth of literature in this topic and a number of different animal models, but I will just show you one of the original studies by Fletcher Taylor's group in 1987, where they showed using their lethal *E. coli* baboon model that the administration of activated protein C would reduce mortality in this system.

They, also, wanted to show if you use a sublethal dose of *E. coli* the administration of an antibody that inhibits the generation of activated protein C, the endogenous activated protein C converts a sublethal dose to a lethal infection, and if one then administers exogenous activated protein C in those animals in which the endogenous

system has been turned off that can prevent this increase in lethality.

Just a comment about what is available in the literature with respect to the use of activated protein C as opposed to heparin as a treatment for DIC; this is a study performed in Japan and published last year in abstract form in *Blood*, and this group of investigators actually randomized patients who had DIC to either activated protein C, and I should point out this is plasma-derived activated protein C versus heparin at moderate doses of heparin and what was found was that the 30-day, all-cause mortality was 20.4 percent in those patients randomized to APC and 40 percent in those patients randomized to heparin. This is a small study. It was statistically significant, but it points out or at least indicates that it is possible that some of the other properties about activated protein C independent of its antithrombotic effects may be important in survival benefit in patients with sepsis.

So, in summary the therapeutic rationale for activated protein C in patients with severe sepsis is as follows: The basic pathophysiology of sepsis is now quite clear that the infection, the systemic inflammatory response and the procoagulant response is highly integrated in patients with severe sepsis, and via multiple mechanism of action activated protein C may disrupt this linkage between

inflammation and coagulation and this may result in improved survival both experimentally and in clinical studies.

The baboon E. coli sepsis model indicates a critical role for activated protein C in survival activated protein C as opposed to protein C itself is the preferred treatment strategy because patients may be unable to adequately convert protein C to activated protein C in vivo in the face of severe sepsis.

So, thank you.

I will now turn the podium over to Dr. William Macias who will describe the clinical studies with drotrecogin alfa (activated).

DR. MACIAS: Thank you very much, Dr. Opal.

Mr. Chairman, members of the Advisory Panel, my colleagues at the FDA, my name is Bill Macias. I am a nephrologist and intensivist, and I am the Medical Director for the Xigris Product Development Team at Eli Lilly and Company, and I have the pleasure of presenting for you or reviewing for you the data supporting the efficacy and safety of drotrecogin alfa (activated) as therapy for patients with severe sepsis.

The objectives of my presentation are to provide the rationale for the proposed indication statement, to review the data supporting the recommended dose and dose duration for drotrecogin alfa (activated) and to review the

primary efficacy and safety data from the pivotal Phase III study that demonstrates the favorable benefit/risk profile of the compound.

In addition, I would like to provide a very brief update on our ongoing clinical studies as well as review our experience in the pediatric patient population.

As Dr. Schilske reviewed for you the proposed indication statement for drotrecogin alfa (activated) would read as follows. Drotrecogin alfa (activated) is indicated for the treatment of adult and pediatric patients with sepsis associated with acute organ dysfunction with severe sepsis.

Treatment with drotrecogin alfa (activated) reduces mortality in patients with severe sepsis. Drotrecogin alfa (activated) would be recommended as adjunctive therapy to best standard of care.

The definitions of sepsis and severe sepsis contained in the indications statement are derived from the 1991, SCCM/ACCP consensus conference definitions for sepsis and severe sepsis.

Efficacy in adults with severe sepsis is based on data from a single pivotal Phase III study with supporting data from a single Phase II study.

Use in pediatric patients with severe sepsis is supported by data from open-label, safety and

pharmacokinetic studies conducted in pediatric patients age 38 weeks' gestation to 18 years of age. However, efficacy must be extrapolated from well-controlled study in adults.

The inclusion of the mortality reduction statement in the indications statement is felt to be important as the benefit associated with drotrecogin alfa (activated) is the improvement in survival, and we would intend that drotrecogin alfa (activated) be used in patients who are assessed as being at risk of dying from severe sepsis by the treating physician.

The Phase II study EVAA was initiated in 1996. This study was a randomized double-blind placebo-controlled study of drotrecogin alfa (activated) in patients with severe sepsis. The primary objectives of the study were to assess the safety of drotrecogin alfa (activated) as a function of infusion rate and infusion duration, to assess the impact of drotrecogin alfa (activated) on coagulation abnormalities, primarily on the level of D-dimers and to assess the pharmacokinetics of drotrecogin alfa (activated).

In addition one of the intents of the Phase II study was to determine the dose for Phase III testing, and we had prospectively determined that that dose would be based upon the infusion rate and infusion duration that produced the maximum decline in D-dimer.

The study was conducted in two stages. Stage 1

explored an infusion duration of 48 hours, an infusion rate that ranged between 12 and 30 micrograms per kilogram per hour.

Stage 2 explored infusion durations of 96 hours and infusion rates of 12, 18 and 24 micrograms per kilogram per hour.

As mentioned the primary pharmacodynamic marker for this study was the effect of drotrecogin alfa (activated) on D-dimer levels.

This slide displays the median percent change in D-dimer from baseline to end of infusion with all patients grouped by the treatment infusion rate to which they were assigned.

A statistically significant monotonic dose response was present with the largest declines in D-dimer being most evident in patients receiving the 24 microgram and 30 microgram per kilogram per hour infusion rates.

Infusion rates of 12 and 18 micrograms per kilogram per hour were not associated with sizeable declines in D-dimer levels.

A similar observation was, also, seen when we looked at serial IL-6 levels. IL-6 was used as a surrogate measure for systemic inflammation. Again, a monotonic dose response was present with the largest decline in IL-6 being most evident in patients receiving the 30-microgram per

kilogram per hour infusion rate.

There were no safety concerns noted in the Phase II study. In patients with severe sepsis drotrecogin alfa (activated) displayed linear pharmacokinetics, and there was no accumulation of the drug for infusion durations up to 96 hours.

The decline in D-dimer and IL-6 levels was most evident at infusion rates greater than 18 micrograms per kilogram per hour, and the maximum decline in D-dimer was most evident at the end of a 96-hour infusion. Therefore, the 24 micrograms per kilogram per hour infusion rate for 96 hours was recommended for Phase III testing.

The Phase III study was started in 1998. This study was a randomized double-blind placebo-controlled study conducted in adult patients with severe sepsis. There were 164 investigative sites in 11 countries. The dose investigated was the single dose identified in the Phase II study. Both drotrecogin alfa (activated) or placebo were administered for 96 hours. The primary objective was to determine the effect of drotrecogin alfa (activated) on 28-day all-cause mortality, and the secondary objectives included an assessment of the safety and analysis of the effect of drotrecogin alfa (activated) on organ function as well as an assessment of the pharmacokinetics and pharmacodynamics of the drug.

The population studied had severe sepsis defined as the presence of known or suspected infection, evidence of systemic response to that infection and one or more sepsis-induced organ dysfunctions.

This slide displays the study design. Patients had to meet all inclusion and no exclusion criteria within a 24-hour time period. From the moment all entry criteria were met an additional 24-hour period was allowed to obtain consent, randomly assign the patient and initiate the study drug infusion.

Study drug was administered for 96 hours. Routine patient care was not dictated by the protocol, and 28-day all-cause mortality was assessed for all patients exposed to study drug for any length of time.

The first patient was enrolled in the study in July 1998. The protocol was amended once very early in the course of the study. The first patient was enrolled under the amended protocol in June 1999.

The first interim analysis conducted by an independent data and safety monitoring board was conducted in October 1999. The efficacy stopping rules were based on the method of O'Brien and Fleming. The recommendation at that time by the DSMB was to continue the trial without modification of the protocol.

The second interim analysis was conducted in June

2000. At that time the recommendation from the DSMB was to stop the trial for highly statistically significant results.

The last patient enrolled in the study completed the study in July 2000. At study completion 1728 patients had been randomly assigned to either drotrecogin alfa (activated) treatment group or the placebo treatment group.

Of those patients randomized to drotrecogin alfa (activated) 21 patients did not receive treatment, and of those patients randomized to placebo 17 patients did not receive treatment. The most common reason for not receiving treatment is that the patient developed an exclusion criteria after informed consent was obtained or the patient died prior to the start of the study drug infusion.

In total 850 patients assigned to the drotrecogin alfa (activated) group completed the protocol and 840 patients assigned to the placebo group completed the protocol.

The site of infection as assessed by the investigator was similar between treatment groups. The majority of patients had the lung identified as the site of infection with approximately 20 percent of patients having the abdomen identified as the primary site of infection.

Urinary tract infections were identified in approximately 10 percent of the population. The types of infecting organisms were, also similar between treatment

groups. Approximately 25 percent of patients had gram-positive infections; 22 to 23 percent had gram negative. Pure fungal infections were present in 2 to 3 percent of the population and approximately 30 percent of the population had no identifiable microorganism, a finding very consistent with prior sepsis studies.

Almost all patients had laboratory evidence of a coagulopathy. This slide shows on the ordinate above the percent of patients with abnormally high values and on the ordinate below the abscissa the percent of patients with abnormally low values. Almost all patients had elevated D-dimer and thrombin, anti-thrombin levels.

Approximately 70 percent, 75 percent of patients had elevation in the prothrombin fragment F1.2 indicating ongoing thrombin generation.

Approximately 80 percent of the patients had a reduced protein C, protein S and anti-thrombin level indicating the consumption of endogenous anticoagulants.

This slide shows a similar analysis for other measures of coagulation and systemic inflammation. Approximately 40 percent of the patients had elevated PAI-1 levels indicating impaired fibrinolysis.

As Dr. Opal mentioned all patients had elevated IL-6 levels indicating a state of global inflammation. Almost all patients had elevated prothrombin times.

Approximately 60 percent of patients had elevated APTTs and only about 30 percent of patients had abnormally low platelet counts.

Taken together the inclusion criteria for the EVAD study defined a population with severe sepsis in which the majority of patients had documented infection. All patients had evidence of a systemic response to that infection that was characterized not only by an inflammatory response but a pro-coagulant response with evidence of thrombin generation, fibrin deposition and impaired fibrinolysis.

Again, as Dr. Opal showed you, the systemic response to infection is really independent of the infecting organism. The most common types of sepsis-induced organ dysfunction were respiratory and cardiovascular dysfunction, and this slide displays the 28-day all-cause mortality for both treatment groups.

The placebo mortality was 30.8 percent. The drotrecogin alfa (activated) mortality was 24.7 percent. Based on the primary analytical plan this resulted in a 19.4 percent relative reduction in the risk of death in favor of Xigris, a highly statistically significant finding with a two-side P value of 0.005.

The Kaplan-Myer(?) curve shows that drotrecogin alfa (activated) improves survival compared to placebo. An absolute difference in the survival curves is evident within

days following the start of the infusion and continues to increase throughout the entire 28-day study period.

A 20 percent relative reduction in the risk of death is evident throughout the entire 28-day study period.

This slide provides a variety of sensitivity analyses that demonstrate that a highly statistically significant reduction in mortality is evident regardless of the way the clinical trial data are analyzed.

The first row shows the relative risk reduction and the P value for the primary analysis. The second row shows the results of a non-stratified analysis as performed. The third row shows the results of patients are analyzed as treated as opposed to as randomly assigned, and there were three patients that received all or part of the wrong therapy, and finally the fourth row shows the analysis for all randomized patients including the 38 patients who did not receive study drug.

In each instance a very consistent relative risk reduction was observed that was highly statistically significant.

As I mentioned there was one amendment to the protocol. The amendment occurred very early in the course of the study. To analyze the potential effect of that amendment on outcome we looked at the cumulative mortality rates for patients enrolled at sites that participated both

under the original and the amended versions of the protocol.

This graphs shows the cumulative mortality rate for the placebo population and the cumulative mortality rate for the drotrecogin alfa (activated) population.

This is approximately 1460 of the 1690 patients. The first vertical line shows the point at which the first patient was enrolled under the amended version of the protocol and the second vertical line shows the point in time where the last patient was enrolled under the original version of the protocol.

A treatment benefit was clearly evident prior to the introduction of the amendment. The placebo mortality rate gradually drifted down over the course of the study as did the mortality rate for the drotrecogin alfa (activated) population.

Based on this analysis and other analyses we don't believe that the amendment had a substantial impact on the overall outcome of the study.

This graph displays the relative risk and the 95 percent confidence interval for a variety of subgroups defined by patient demographics.

On the left side is the subgroup of interest and on the right side is the number of patients within the subgroup and the mortality rates for either the drotrecogin alfa (activated) group or the placebo group.

For subgroups defined by gender age cut at either 50 years of age or 65 years of age and for origin, Caucasian or non-Caucasian uniformly lower mortality was observed with drotrecogin alfa (activated) compared to placebo.

Lower mortality with drotrecogin alfa (activated) was, also, observed for patients enrolled in Europe, North America and for the remaining countries grouped together as other.

Investigators in the United States enrolled the largest number of patients of any individual country. The administration of drotrecogin alfa (activated) was, also, associated with an improvement in cardiovascular function as evidenced by a reduction in time averaged CV-SOFA scores and an increase in the number of vasopressor free days compared to placebo patients. There were, also, fewer deaths in the drotrecogin alfa (activated) group from septic shock.

The administration of drotrecogin alfa (activated) also improved respiratory function, again as evidenced by a reduction in time-averaged respiratory SOFA scores and an increase in ventilator-free days compared to placebo-treated patients, and there were fewer deaths from respiratory failure in the drotrecogin alfa (activated) group.

A comparison of 28-day survivors between treatment groups indicated that drotrecogin alfa (activated) patients had similar patient location and functional status as

compared to placebo-treated patients.

The only adverse drug reaction associated with drotrecogin alfa (activated) was an increase in bleeding and this graph displays the percent of patients in each treatment group that experienced a bleeding event reported as a serious adverse event either during the study drug infusion period or during the 28-day study period.

Over the course of the 28-day study period 13 more patients of the drotrecogin alfa (activated) experienced a serious adverse event that was of a bleeding nature.

We analyzed the types of serious bleeding events either by the type of event or by whether the event was considered to be procedure related or non-procedure related. The difference in bleeding events between the two treatment groups resulted predominantly from procedure-related bleeding events. The types of non-procedure related or the incidence of non-procedure related or if you will spontaneous bleeding events was actually similar between the two treatment groups.

An analysis of the remaining safety data indicated no other safety concerns. There was a similar incidence of serious thrombotic events in both treatment groups with approximately 3 percent of placebo patients experiencing a thrombotic event reported as a serious adverse event versus 2 percent of patients in the drotrecogin alfa (activated)

group.

There was a similar incidence of post-baseline infections. There was a very low incidence of anti-APC antibody formation and when detected the level was low and non-neutralizing, and there were not other safety concerns identified based on analysis of other adverse events, other serious adverse events and analysis of organ function or analysis of the central laboratory data.

Since completion of the pivotal Phase III study we have initiated a number of other clinical studies of drotrecogin alfa (activated) in patients with severe sepsis. Protocol EVBC is a treatment use protocol sometimes referred to as a compassionate use protocol and studies EBVE, EBVF and EVBG are open-label studies being conducted worldwide.

Both protocols employ very similar inclusion and exclusion criteria as utilized in the pivotal Phase III study. In the compassionate use protocol EVBC approximately 185 patients have received drotrecogin alfa (activated). The current 28-day all-cause mortality rate is 21 percent although it is important to note that not all patients have completed the 28-day follow-up period.

Approximately 3.2 percent of patients have experienced a serious bleeding event during the study drug infusion period.

Five hundred and eighty patients have received

drotrecogin alfa (activated) under our open label studies. The current 28-day all-cause mortality rate is 19 percent. Again, the same caveat applies. Not all patients have completed the 28-day study period, and the percent of patients experiencing a serious adverse event, a bleeding event reported as a serious adverse event during the study drug infusion period is 2.1 percent. Both values are somewhat similar to what we observed in the pivotal Phase III trial.

We have looked very carefully at all of the intracranial hemorrhage events that have occurred in our ongoing studies through an adjudication process that employs two external independent neuroradiologists and an external independent neurologist who review in a blinded fashion all of the events that have occurred.

Our numbers will differ a little bit from Dr. Lindblad's because some of the intracranial hemorrhages that have been reported to date have been adjudicated as not being intracranial hemorrhages.

However, there were three patients in the ongoing trials who experienced a cerebral hemorrhage that was fatal during the infusion period. One patient experienced hemorrhagic infarct that was fatal during the post-infusion period. This event occurred on day 14 while the patient was receiving heparin for dialysis.

There have been a number of non-fatal intracranial hemorrhages which are predominantly hemorrhagic infarct, so, is stroke with hemorrhagic transformation and in these three cases these are small petechial hemorrhages, and there have been three small subarachnoid hemorrhages reported.

For those patients experiencing a cerebral hemorrhage during the study drug infusion period these events always occur in the setting of severe thrombocytopenia usually with platelet counts less than 30,000.

To assess the benefit/risk for patients with severe thrombocytopenia we went back to the pivotal Phase III study, the EVAD study and we looked at the mortality rates for patient populations defined by those having a platelet count of less than 50,000 at baseline, a platelet count of less than 50,000 at some time during the study drug infusion period or a platelet count of less than 30,000 either at baseline or during the study drug infusion period, and there were 40 patients who had a platelet count of less than 50,000 at baseline. Although the numbers are small the mortality rate for the placebo group was 63 percent and for the drotrecogin alfa (activated) group 25 percent.

For patients who had a minimum platelet count during the study drug infusion period of less than 50,000 mortality rate was 54 percent versus 24 percent and there a

total of 113 patients in this subgroup, and finally, for the population that had a minimum platelet count of less than 30,000 either at baseline or during the study drug infusion period the mortality rate for the placebo group was 84 percent and for the drotrecogin alfa (activated) group was 33 percent. So even in the setting of severe thrombocytopenia there may still be a favorable benefit/risk profile for drotrecogin alfa (activated) given the fairly dismal prognosis for patients with severe consumptive coagulopathy and severe thrombocytopenia.

In conclusion drotrecogin alfa (activated) administered to patients with severe sepsis substantially reduces 28-day, all-cause mortality. The administration of drotrecogin alfa (activated) also improves cardiovascular and respiratory function which may explain in part the improved survival associated with its use.

There is an increased risk of serious bleeding events although it is infrequent, and many of the events seem to be related to vessel trauma or occur in the setting of severe coagulopathy and taken together these data support the very favorable benefit/risk profile for drotrecogin alfa (activated) as a therapy for patients with severe sepsis.

I would like to now turn over the podium to Dr. Helterbrand who will review for you a formal benefit/risk assessment of drotrecogin alfa (activated) as therapy for

patients with severe sepsis.

DR. HELTERBRAND: Good morning. My name is Jeff Helterbrand, and I am the Senior Statistical Scientist on the Xigris Product Development Team.

A formal evidence-based benefit/risk assessment of Xigris in the treatment of patients with severe sepsis was conducted using the pivotal Phase III trial results.

We will begin this presentation with an assessment of the benefit/risk profile for Xigris for the overall population of patients enrolled in the study. Then we will discuss what the trial results suggest regarding potential differential effects across subgroups, both in terms of bleeding risk and in terms of the Xigris survival benefit.

This benefit/risk analysis will show that Xigris is associated with a positive benefit/risk profile across the diverse population of patients enrolled in the study.

In the remainder of the presentation we will take the opportunity to specifically address six questions that have been posed by the agency to the Advisory Committee that are related to subgroups, namely, those questions related to patients without laboratory evidence of DIC, low-dose heparin exposure and less severe disease patients.

In the benefit/risk assessment each patient's outcome can be classified into one of three outcome categories. The first and best outcome is the patient

survived 28 days and did not experience a serious bleeding event.

The higher percentage of Xigris patients compared to placebo patients experienced this optimal outcome. The second outcome is the patient survived the 28 days but did experience a non-fatal serious bleeding event in that time window. There were 18 Xigris and 8 placebo patients in this category.

The third outcome is that the patient died. In commonly applied benefit/risk assessment models each of these three possible outcomes are seeing the value from the patient's perspective with the greatest value being assigned to the optimal outcome and the least value being assigned to the worst outcome. In this model one must determine what value to assign to the middle outcome relative to the other two outcomes.

Intuitively this value should be assigned based on the number of additional serious bleeding events in survivors one would be willing to accept in order to save one additional life.

As this value for the middle outcome approaches zero, the one is essentially equating a non-fatal serious bleeding event to death. Alternatively as this value approaches one, then one is following the philosophy that the preservation of life is of greater importance than

virtually any non-fatal risk.

This figure applies the benefit/risk model to the overall Phase III trial results for Xigris. Due to the magnitude of improvement in survival associated with Xigris and the relatively smaller increased risk of non-fatal serious bleeds the key message is that regardless of how one assesses the number of additional serious bleeding events in survivors one would be willing to accept to save an additional life the pivotal Phase III trial results demonstrate a highly favorable benefit/risk profile associated with Xigris.

Next we turn to subgroup analyses. Before proceeding it is important to reiterate the often-cited caveats associated with interpreting subgroup analyses. First, the pivotal Phase III trial as with most trials was sized to detect a treatment benefit for the entire population only and not for subgroups, and as you know, no trial can ensure definitive statistical evidence of a benefit in all subgroups.

Additionally when one is trying to interpret the results of individual subgroup analyses they must be interpreted in the context of the multiplicity of analyses that have been performed. Analyses from over 70 subgroups are presented in the Lilly briefing document and in this presentation, and with this in mind it is really important

that we point out that it is not Lilly's intention to conclude greater efficacy in selected subgroups based solely on exploratory subgroup analyses.

There are some fundamental differences between the Lilly briefing document and the agency briefing document in the manner in which the consistency across subgroups was assessed, and these differences may lead to some confusion among readers. So, I will take a few moments here to specifically describe Lilly's approach.

In the briefing document and in the biologics license application we relied on two commonly applied measures for subgroup results namely relative risk and its close cousin odds ratios.

As stated in one of the mostly widely referenced books on categorical data analysis the odds ratio scale is the most generally accepted scale to perform interaction analyses across subgroups.

The agency briefing document does focus on a different risk scale by comparing absolute risk reductions across subgroups. Lilly's analytic approach for subgroup analyses follows commonly accepted methods. We focus on within subgroup relative risk confidence intervals and on interaction tests that are based on odds ratios.

However, it is important to emphasize that these approaches do not overcome the fact that subgroup analyses

are exploratory in nature and not confirmatory. However, these approaches do assess the statistical evidence supporting any hypothesis that may be conjectured based on exploratory subgroup analyses.

With respect to bleeding since there were so few serious bleeding events in the study to begin with, the ability to detect differential effects across subgroups is limited. Indeed, when we actually include all serious bleeding events during the 28-day study period and include non-procedure related and procedure related events there is still limited ability to detect a differential effect with respect to serious bleeding risk, and indeed no clinically relevant differential effects were observed. Indeed based on these analyses what we have here is that there was no evidence of an exceptionally higher increased risk of bleeding associated with treatment in a particular subgroup.

In order to have more discriminatory power we actually, also, did a similar analysis on all treatment emergent bleeding events. However, again, no clinically relevant differential effects were observed.

Thus as much as the pivotal trial results can suggest from a statistical perspective the increased relative risk of bleeding with treatment is consistent across subgroups.

Turning to survival extensive subgroup mortality

analyses were, also, conducted. This slide from the briefing document displays the mortality results for subgroups defined based on patient demographics, recent surgery status and site and type of infection.

There is a considerable amount of information on this slide. However, for each subgroup there are two key points to look for. First, one should note whether the relative risk point estimate for the subgroup lies to the left of the vertical unity line indicating that lower mortality was observed with Xigris compared to placebo within that subgroup.

The second point to look for is whether the relative risk 95 percent confidence interval for the subgroup contains the point estimate for the overall trial indicating that subgroup result consistent with the overall trial results.

Dr. Macias already reviewed the uniformly lower mortality observed with Xigris compared to placebo across all subgroups defined based on patient demographics. In addition, lower mortality was observed with Xigris for patients who did and did not have a surgery prior to the start of study drug administration and for the subgroup of patients with lung, intra-abdominal and quote, unquote, other sites of infection.

Similar mortality rates were observed in the two

treatment groups for the subgroup of patients who had urinary tract classified as their presumed primary site of infection by the investigator.

In addition uniformly lower mortality was observed with Xigris regardless of the type of bacterial infection. As illustrated by their 95 percent intervals all summary results presented on this figure were consistent with the overall trial.

The following two slides recreated from the briefing document display mortality results based on subgroups defined by clinical measures of disease severity. As you know, the clinical diagnosis of a patient's condition in the decision to treat the patient is typically based on multiple measures of disease severity, and therefore it is important to consider how multiple measures describe a patient's condition and how these measures actually show evidence supporting a beneficial effect with Xigris across these measures.

With respect to APACHE II scores lower mortality was observed with Xigris compared to placebo for patients in the second, third, and fourth APACHE II quartiles. The mortality rate for treatment was higher than for placebo in patients in the first APACHE II quartile. However, as noted by the broad width of the 95th percent relative risk confidence interval containing the point estimate for the

overall trial it does meet the consistency criteria.

We will discuss this observation in further detail when we specifically address a couple of the agency's questions to the Advisory Committee in a few moments.

Importantly uniformly lower mortality with Xigris as compared to placebo is observed across all subgroups defined by the various measures of cardiovascular organ function collected in the trial and by the various measures of respiratory organ dysfunction measured in this trial.

Furthermore lower mortality was observed with Xigris compared to placebo for all subgroups defined by measures of hematologic, renal, metabolic, hepatic or based on the number of organ failures present at baseline.

As illustrated by their confidence intervals all subgroup results based on clinical measures of disease severity that were presented on this figure and on the previous figure were consistent with the results of the overall trial.

The final subgroup figure reproduced from the briefing document displays the mortality results for subgroups defined based on biochemical measures of disease severity.

Notice that lower mortality was observed with Xigris compared to placebo across all these subgroups defined by these measures.

There are three key points, however, that can be made from this graphic. First, in the secondary objectives of the trial protocol there was only one subgroup for which there was a priori conjecture that a differential effect on mortality may be observed, specifically a greater treatment effect was hypothesized for protein C deficient patients compared to non-protein C deficient patients.

In final analysis a survival benefit was evident in both subgroups. Second, in the context of the agency's questions regarding DIC note that a beneficial effect with Xigris is observed in patients with normal protein C levels, normal prothrombin times, normal APTT levels in those patients with platelet counts above the lower limit of normal and for patients with normal anti-thrombin levels.

This implies that a survival benefit with Xigris is present in patients who generally would not be classified as having a clinical diagnosis of DIC, and finally, the only subgroup of all 70 subgroups assessed with a relative risk observation inconsistent with the overall trial results was the first IL-6 quartile where we saw much lower mortality with Xigris than for placebo.

This subgroup includes those patients with the lowest baseline IL-6 levels, patients, therefore with less severe disease as assessed by this marker.

Thus, to summarize our overall mortality subgroup

findings, lower mortality was observed with Xigris compared to placebo for nearly all or 68 of the 70 subgroups assessed, the lone exceptions being the first APACHE II quartile and the relatively small subgroup of patients who had urinary tract infection classified as their presumed primary site of infection by the investigator.

Importantly, a consistent treatment effect with Xigris was observed for nearly all or 69 of the 70 subgroups assessed. A lower relative risk estimate in favor of Xigris was observed for those patients in the first IL-6 quartile, that is patients with the least inflammation by this marker and therefore the least disease severity where a 53 percent reduction in relative risk of death was observed with Xigris compared to placebo.

Thus, from a statistical perspective we conclude that a consistent treatment effect on the relative risk of bleeding and on the relative risk of death is observed with Xigris across subgroups as can be assessed by the trial results.

When this is accounted for in a formal benefit/risk analysis Xigris is associated with a favorable benefit/risk profile across the diverse population of patients that were enrolled in the pivotal Phase III study, that is from a population viewpoint for this devastating disease the demonstrated life-saving capability of Xigris

outweighs the risks associated with its use.

Now, this completes the formal benefit/risk assessment, and we will turn directly to addressing six questions that were posed by the agency to the Advisory Committee that are related to subgroups.

Due to the limited time of this core presentation we will be happy to address any of these questions in further detail in the question and answer session.

Next slide, please?

The agency has posed questions No. 4 and No. 5 to the Committee based on the subgroup results in patients in whom DIC status at baseline was absent or unknown, and it is important to clarify a few key points regarding this analysis

Here we display the clinical trial definition of non-overt DIC used in the study. This definition is based on laboratory markers and does not take into account clinical signs of DIC.

As shown in the table accompanying Question No. 4, there were 115 patients who were classified as having their DIC status at baseline as absent or unknown. A total of 113 of these 115 patients did not have biochemical data available at baseline to assess their status. Thus, the subgroup was really defined based on the absence of data and not based on the absence of a clinical condition.

So, when we only assess those patients who did have laboratory data available we find that 99.9 percent of the patients in the trial met the clinical trial definition of non-overt DIC.

A review of data from another recent sepsis trial for an anti-inflammatory agent with similar inclusion criteria actually had similar results. Thus, as Dr. Opal and Dr. Macias alluded to earlier the inclusion criteria employed in this study, namely infection, inflammatory response and associated organ dysfunction by themselves essentially defines a population with sepsis-associated coagulopathy.

Next, turning to heparin the agency has posed Question Nos. 6 and 7 regarding low-dose heparin exposure, and we have a few remarks related to these questions.

First, regarding bleeding risk similar rates of serious bleeding were observed in Xigris patients who did receive heparin and Xigris patients who did not receive heparin, and there no treatment by heparin interaction with respect to bleeding events.

Second, regarding mortality we note that uniformly lower mortality was observed with Xigris compared to placebo and all subgroups defined by either baseline or concomitant heparin exposure with relative risk reductions in excess of 10 percent in all cases.

A further point to make is that analyses based on subgroups defined based on concomitant heparin exposure as opposed to based on a pure baseline covariate are severely biased, and this statement is true for analyses of any concomitant medication where many patients are exposed to the concomitant medication for the first time after the start of study drug infusion, and indeed in this trial many patients moved from the no heparin group to the heparin group with their first post-baseline exposure, and this type of bias is widely discussed in the statistical literature.

Next slide, please?

Therefore to perform statistically valid analyses we adopted two approaches. The first approach and maybe the best approach from a purist perspective was to define our heparin subgroups based on baseline heparin exposure only.

When we look at the trial results from this perspective there is no treatment by heparin interaction and actually when we do non-randomized comparisons of heparin and non-heparin patients within the two treatment groups again there is no evidence that low-dose heparin affects mortality in either of the two treatment groups.

The second approach which incorporates post-baseline heparin exposure in an unbiased manner is to use a Cox regression model with heparin exposure expressed as a time-dependent covariate when this approach is used, again,

there is no statistical evidence to support a treatment by heparin interaction and furthermore there is no statistical evidence that low-dose heparin affects mortality in either of the two treatment groups.

Therefore we conclude that any conjectures that may be made regarding the effects of low-dose heparin based on exploratory subgroup analyses are speculations and are not compelling supportive from the statistical evidence perspective.

The agency has posed questions No. 2 and No. 3 to the Committee regarding the treatment of Xigris in patients with relatively less severe disease.

Importantly in Question No. 3, the agency has challenged the Committee to advise whether the indication for Xigris should be limited to a subset of the population enrolled in the pivotal Phase III trial.

Here we review the evidence supporting the beneficial effect with Xigris in patients with relatively less severe disease, and we have three key points for the Committee to consider. First from a statistical perspective the observed variation in relative risk estimates observed across subgroups is in harmony with random chance alone if treatment were uniformly beneficial at a constant 20 percent relative risk reduction across all subgroups.

As was discussed in Lilly's briefing document due

to the multiplicity of analyses performed we would have expected high mortality for the effective treatment arm for five of the 70 subgroups assessed, and as we discussed already we saw that for two subgroups.

Second, a survival benefit with Xigris is evident in less severe patients almost uniformly across the totality of measures of disease severity that were collected in the trial, and third, a survival benefit with Xigris is evident in patients with less disease severity within the first APACHE II quartile subgroup itself, and my last two slides will discuss these last two points.

This figure displays the relative risk in 95 percent confidence intervals for the lesser disease severity subgroups that were presented earlier.

For example, the following subgroups are included: The first APACHE II quartile, those patients with a single organ dysfunction, those patients with no evidence of shock at baseline, patients not on mechanical ventilation, those patients with less hepatic organ dysfunction as measured by SOFA, patients with normal activated partial thromboplastin times and normal prothrombin times, patients with less respiratory organ dysfunction and again the patients with the lowest IL-6 levels indicating the least inflammation, patients in the first IL-6 quartile.

In total 21 subgroups defining patients with

relatively less severe disease are presented on this graphic. Lower mortality is observed with Xigris compared to placebo for 20 of the 21 subgroups clearly demonstrating that survival benefit with Xigris is evident in less severe disease patients enrolled in the pivotal Phase III study.

Additionally for approximately half or 12 of the 21 subgroups we actually saw larger relative risk reductions within the subgroup itself than was observed for the overall trial, and this observation supports our consistency conclusion.

In line with the ICHE 9 guidelines when one observes an unusual result we explored results within the first APACHE II quartile subgroup itself and the survival benefit is evident in less severe disease patients within this subgroup.

In patients with fewer than three organ failures a 20 percent relative risk reduction was observed with Xigris compared to placebo. This relative risk reduction is identical to what was observed in the overall trial.

It is important to note that approximately 75 percent of the patients that make up the first APACHE II quartile had fewer than three organ failures at baseline. In patients with three or more organ failures at baseline higher mortality was observed with treatment compared to placebo, and this apparently drove the result for the entire

subgroup as a whole.

Not that Xigris patients with three or more organ failures had higher mortality than Xigris patients with fewer than three organ failures as one would expect. However in the placebo group we see similar mortality rates for patients with three or more organ failures compared to patients with fewer than three organ failures, an apparent anomaly.

It is, also, noted that within the first APACHE II quartile similar beneficial effects are evident in patients with low IL-6 levels, normal prothrombin times and normal APTT levels within the first APACHE II quartile, and we would be happy to share this data with the Committee during the question and answer session.

Thus, with regard to disease severity we conclude that a survival benefit with Xigris is clearly evident in patients with less severe disease enrolled in the pivotal Phase III trial as assessed by the multiple measures of disease severity that can be used to assess the patient's condition.

In simple terms lower mortality is observed with Xigris in nearly all subgroups and in the one subgroup where we do not see lower mortality the subgroup itself is internally inconsistent with the less effect and less severe patient hypothesis.

Therefore based on many well-founded scientific principles the results of this trial support granting an indication for this life-saving treatment that includes all patients who meet the inclusion criteria studied in the pivotal Phase III trial.

I am now going to return the podium to Dr. Macias who will provide additional clinical perspectives related to the treatment by disease severity analyses.

DR. MACIAS: Thank you, Dr. Helterbrand. Before I review the pediatric data, I would like to make just a few comments about the treatment by disease severity analyses and those comments really relate to the treatment by APACHE observation, and we have looked at this observation quite extensively and have really had a difficult time if you will operationalizing the observation.

As Dr. Helterbrand has reviewed for you, the observation itself does not really reconcile with the treatment by disease of the rest of the treatment by disease severity analyses. Particularly it doesn't reconcile with the observation that in patients with the lowest IL-6 levels there is a clear treatment benefit indicating that patients with less inflammation do benefit from a drug that has anti-inflammatory properties.

In addition, it doesn't reconcile with the analysis by normal PT, normal PTT and normal platelet count

indicating that patients that do not have abnormalities in the global measures of coagulation do benefit from a drug that has anticoagulant properties.

To further complicate the observation, the APACHE II data collected in the EVAD trial were not collected and the score was not calculated according to the published methodology. It was never our intent to use the APACHE score in the EVAD trial to predict mortality. It was simply used to assess the parity of baseline between the two treatment groups, and finally, the APACHE II score itself is rarely used in the making of individual patient treatment decisions.

In fact, to my knowledge there is no outcome prediction model that has ever been validated for the use of individual patient treatment decisions. However, what physicians do look at --

You can go to the next slide, please?

What physicians do look at is the number of failed organs that are present at baseline, whether or not the patient has cardiovascular dysfunction and if present what is the extent of that dysfunction and whether or not the patient has respiratory dysfunction, and again if present what is the extent of that respiratory dysfunction.

This slide shows us the treatment by number of organ failure analysis and regardless of the number of organ

failures present at baseline and treatment benefit, regardless of the number of organ failures present at baseline lower mortality is observed with the drotrecogin alfa (activated) group compared to placebo.

The interaction P value is .93, and despite the finding that there is no treatment by number of organ failure, there is no interaction, there is a tendency for individuals to focus on the point estimate for the relative risk that is observed in patients with single organ failure.

To explore that a bit further we separated that out into the population of patients who had single organ respiratory failure and single organ cardiovascular failure, the two most common types of organ dysfunction in patients with severe sepsis. These two subgroups constituted 85 percent of all patients with single organ failure and in this analysis, the point estimates are actually quite similar to what was observed in the overall trial.

In addition although this is a subgroup of a subgroup, the number of patients with single organ respiratory failure is actually quite similar to the total number of patients with four organ failures at baseline and is actually much larger than the number of patients that have five organ failures at baseline.

Physicians will, also, look and try to assess the severity of cardiovascular dysfunction at baseline. In the

EVAD trial physicians were asked to assess cardiovascular dysfunction as defined in the inclusion criteria either within the 48-hour period, immediately preceding the administration of study drug or within the 6-hour period immediately preceding study drug and that assessment was a yes or a no.

Graded assessment of cardiovascular dysfunction at baseline was performed using the cardiovascular SOFA score and physicians were asked to record the worst SOFA score within the 24-hour period immediately preceding the administration of study drug, and in each instance lower mortality is observed with drotrecogin alfa (activated) compared to placebo.

We, also, generated two additional subgroups, an any shock, yes and an any shock, no, and the subgroup that is any shock, no is the population of patients that had no evidence of cardiovascular dysfunction within 48 hours of drug, a SOFA score of no greater than zero or one with 24 hours of drug and no evidence of cardiovascular dysfunction within 6 hours of drug, and when you look at the point estimates for any shock, yes, and any shock, no, they are actually quite similar to what you see in the overall population.

This slide shows us the graded scale for cardiovascular function at baseline. Again, this is the

worst SOFA score obtained within the 24-hour period immediately preceding study drug with zero being the complete absence of cardiovascular dysfunction and four being the requirement for very high-dose vasopressor.

What you see is when you look at the population of patients and it has no or only mild cardiovascular dysfunction within the 24-hour period immediately preceding drug there is a clear treatment benefit.

These two slides demonstrate as we have looked at these data that there is no treatment by baseline cardiovascular status interaction related to the effect of drotrecogin alfa (activated).

This slide shows us the respiratory SOFA score, again, graded 0 to 4, 0 being complete absence of respiratory dysfunction, 4 being the worst respiratory dysfunction with a severe decline in PF ratio and the requirement for mechanical ventilation.

Again, when we look at the population of patients with no or only mild respiratory dysfunction, a treatment benefit is evident although the numbers are a bit small.

Again, as we look at these data that there is a treatment by respiratory status interaction related to the effect of drotrecogin alfa (activated), and finally when we look at the baseline characteristics for the population of patients that comprise the first APACHE quartile, what we

see is that this population of patients is actually critically by almost every other measure of disease severity.

Sixty percent of the population have two or more organ failure. Seventy percent have respiratory failure. Sixty percent require mechanical ventilation. Fifty-six percent are in shock. Almost 50 percent require high-dose vasopressors, and 65 percent are severely protein C deficient.

Seventy percent of the patients in the first APACHE quartile have two or more organ failures and/or require the administration of high-dose vasopressors to support blood pressure.

To sum up the subgroup conclusions, the EVAD study tested one primary hypothesis, and the results of the study show that drotrecogin alfa (activated) significantly reduces mortality in the population of patients defined by the inclusion and exclusion criteria.

As Dr. Helterbrand has pointed out caution should be exercised in interpreting individual subgroup analyses, and as we look at the data in its totality we find no clear evidence to support a differential effect of drotrecogin alfa (activated) based on disease severity.

Moving on to the clinical experience with pediatric patients as most of you are aware the majority of

drugs used by pediatric intensivists are not approved for use in the pediatric population. Our intent in our pediatric development program was to provide guidance to pediatric intensivists on the use of drotrecogin alfa (activated) on the assumption that if it were approved for use in the treatment of adults it would be used in pediatric patients with severe sepsis.

The development program was based on ICH guidelines and the Code of Federal Regulations and was developed in collaboration with our colleagues at the FDA.

The studies employ open label safety and pharmacokinetic studies, and therefore efficacy must be extrapolated from the adult trial according to the Code of Federal Regulations which reads, "Where the course of the disease and the effects of the drug are sufficiently similar in adult and pediatric patients FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic results.

Approximately 180 pediatric patients have received drotrecogin alfa (activated) either in our study EVAO which is an open label PK, PD and safety study, in our compassionate use programs, EVAS or EVBC or in the ongoing open-label studies, EVBE, EVBF and EVBG.

EVAO was the primary pediatric study which we will discuss now. Eighty-three patients were enrolled in this study. Approximately 50 percent of the population was male; 67, 68 percent were Caucasian, and the primary site of infection was blood in 35 percent of the patients and lung in 20 percent of the patients

For comparison we provide the similar baseline characteristics for the adult population in EVAD. The patient age range enrolled in the EVAO study was from 38 weeks gestation to 18 years of age.

This slide shows abnormalities in baseline markers of coagulation, protein C, D dimer and anti-thrombin, and again for comparison similar findings of values from the adult trial are, also, provided.

Almost all patients had evidence of elevated D-dimer, abnormally reduced protein C and abnormally reduced anti-thrombin levels indicating that the systemic response to infection in the pediatric population is actually quite similar to the systemic response that you see in the adult population.

If time permits during the question and answer period we can provide some additional data on the profile of organ dysfunctions in the pediatric patient population.

This slide shows us on the ordinate clearance, weight-adjusted clearance and on the abscissa the age range

from the youngest patient enrolled in the pediatric program to the oldest patient enrolled in the adult program, so, from age 5 days through age 99 years, showing that weight-adjusted clearance does not change with increasing age indicating that at least by age no dose adjustment is necessary with the administration of drotrecogin alfa (activated).

This slide displays for us the pharmacodynamic analysis. This column contains the analysis for the pediatric population and again, for comparison the similar analysis of the adult population now divided by the treated group and the placebo group.

As prospectively defined in the protocol, the primary pharmacodynamic marker that we would look at in the pediatric trial to compare the similarity of drug effect to the adult population was D-dimer. The percent decrease in median D-dimer was 26 percent, a value very similar to what we saw in the drotrecogin alfa (activated) treated adults and for comparison placebo-treated adults actually had an increase in D-dimer over the course of the study drug infusion period as opposed to decreases in D-dimer noted both in the pediatric population treated with drotrecogin alfa (activated) and in the adult population, also, treated with drotrecogin alfa (activated).

The administration of drotrecogin alfa (activated)

to pediatric patients with severe sepsis was, also associated with an increase in protein C levels and an increase in anti-thrombin levels and these values for comparison are provided for both the drotrecogin alfa (activated) and placebo groups from the pivotal EVAD trial.

The safety data obtained in the study is discussed in the briefing document, but briefly turning to bleeding events reported as serious adverse events during the study drug infusion period two patients out of the 83 or 2.4 percent of patients experienced a bleeding event reported as a serious adverse event. Throughout the entire study period four patients experienced a similar event for a total percent of 4.8 percent, and during the study drug infusion this percentage is actually similar to what we observed in the adult trial for adult patients administered drotrecogin alfa (activated).

Looking at all the pediatric patients enrolled in all of the trials, a total of 182 patients, the current percent of patients experiencing a bleeding event reported as a serious adverse event during the study drug infusion period is 2.2 percent, again, a finding very similar to what we see in the adult trial.

In summary, the pediatric patients are similar to adult patients based on the use of similar inclusion criteria and the almost universal presence of coagulopathy.

The effect of drotrecogin alfa (activated) is similar in adult and pediatric patients based upon the finding of similar pharmacokinetics, a similar pharmacodynamic effect of drotrecogin alfa (activated) on D-dimer and a similar safety profile.

The results of the pediatric study support drotrecogin alfa (activated) use in pediatric patients with severe sepsis. However, they require the extrapolation of efficacy from the well-controlled study in adult patients.

The overall conclusion to our presentation is that drotrecogin alfa (activated) reduces mortality in patients with severe sepsis and is associated with a favorable benefit/risk profile in patients with severe sepsis.

The 6.1 percent absolute reduction in mortality translates into a number needed to treat to save an additional life of 16 and this number compares favorably to the number needed to treat to save an additional life with streptokinase over placebo in the ISIS II trial or the number needed to treat to achieve the additional benefit of TPA over streptokinase in the GUSTO(?) trial.

As we have presented these data, we believe these data strongly support the approval of drotrecogin alfa (activated) for the proposed indications statement.

Thank you very much.

DR. RELLER: Thank you, Dr. Macias and colleagues

from Eli Lilly for the company's presentation which is now open to questions from the Committee members.

Dr. Chesney?

DR. CHESNEY: I had three questions. The first is, maybe I can give all three, and then the response. Were the APACHE scores determined when the patient first presented or were they determined at the time the infusion was started, and the second on Page 27 which is the intracranial hemorrhage summary, the top slide, I wondered why there were only 185 patients in the treatment use group instead of the 850, and the third on Page 22, I wondered with the bottom slide if you could just explain how that cumulative mortality graph works? I am sorry, I don't understand it very well.

DR. MACIAS: Okay, I am a little bit of a loss because I don't have the briefing document to look at the two to answer your second two questions. However, and maybe somebody could bring me the briefing document very quickly, but to answer your first question the APACHE score was calculated on data obtained -- thank you very much. I am sorry, this one and this one, okay. The APACHE II score was calculated based on data obtained within the 24-hour period immediately preceding the administration of study drug. If the patient were in the hospital for less than 24 hours prior to the administration of drug, in other words, they

were enrolled in the emergency room, then the 24-hour period was truncated, and data collection for the APACHE II score was stopped at the time study drug was administered.

It was not collected for the first 24-hour period immediately following entry to the ICU.

To answer your second question which relates to how the cumulative mortality rate is, this is the 28-day cumulative 28-day all-cause mortality for each of the days throughout the entire 2-year study period, and then to address your third question which is the ICH which is Slide 53, we have two ongoing studies.

One is what I termed here as just the open label. It is really three studies being conducted globally, but they all use the same inclusion/exclusion criteria. Five hundred and eighty patients have been enrolled in that study to date, and there have been two cerebral hemorrhages that have occurred during the study drug infusion period.

In addition there are 185 patients that have been enrolled in the treatment use protocol which is what we call, you know, otherwise called the compassionate use program and there has been one patient who had a cerebral hemorrhage during the infusion and one patient who suffered a hemorrhagic infarct on day 14, again, while receiving heparin during an intermittent dialysis procedure.

DR. SUFFREDINI: I had three questions. Can you

comment on the use of adjunctive steroids, stress dose steroids in the trial; was that controlled for, and was that data collected?

DR. MACIAS: Patient specific treatment protocols were not dictated by the protocol. So, it was not controlled for. However, approximately 30 to 35 percent of patients did receive some type of steroid, either at baseline or during the study drug infusion period. We did not record the dose of the drug being administered. We only have the fact that they received steroid and the type of steroid. There was no influence of the use or non-use of steroids on the outcome of the trial.

DR. SUFFREDINI: Can you comment on the issue of blinding in terms of the infusion of the, if your activated protein C will alter the activated partial thromboplastin time? If this was monitored during the infusion to decide whether the rate was too fast or too little, how did you achieve blinding in the study in terms of the providers' care of the patient?

DR. MACIAS: Activated protein C does influence the APTT assay depending upon the particular assay being employed and the reagents being employed. So, the effect is actually quite variable from site to site. In addition, the decay of APC in plasma is really quite rapid and begins to decay within minutes following the collection of the sample.

So, by the time the sample gets to the hospital laboratory and actually gets run the influence is really quite variable, and you would not be able to look to see whether or not the patient was receiving drug based upon a local laboratory APTT measurement.

DR. SUFFREDINI: So, it would be unlikely that a provider in terms of routine monitoring of the PTT in that 4-day infusion period would be knowledgeable whether or not the patient was getting the drug?

DR. MACIAS: Absolutely. That statement is correct.

DR. SUFFREDINI: A last question, if I may, I am curious as to I guess the rationale in terms of the amended protocol, and I wonder if you could comment on the significant changes that went into the amended protocol in terms of the types of patients that were being involved, what the incentive was, what the determination from the trial sponsors was that made those changes; why did they occur and why weren't they initiated at the beginning of the protocol?

DR. MACIAS: With respect to the type of patients being enrolled, and I think Dr. Forsyth will review some of the other objectives of the amendment, but predominantly with respect to what we were trying to achieve with respect to patient population the major attempt of the amendment was to further clarify for investigators that they should not

enroll patients in the study who had a high probability of dying from their underlying non-sepsis related disease within the 28-day study period.

That exclusion criteria was contained with the original protocol. However, as we monitored in a blinded fashion the sepsis histories we were beginning to see that patients with significant underlying non-sepsis-related disease where the patient would be assumed not to be able to survive 28 days were being enrolled in the study. That was the intent of the amendment was to remind physicians that we are, I won't say saddled with, but the primary end point is 28-day all-cause mortality, and that patients dying from non-sepsis-related disease are generating noise.

DR. SUFFREDINI: But in the event that one did not do that, if they were evenly distributed across the study, would that have sort of in a sense washed itself out in the final mix?

DR. MACIAS: It takes away from your power. You have to increase sample size to adjust for it. In addition when I showed you the slide to try to assess the impact of the amendment on the overall outcome of the trial we felt that the best way to do that was to try to control for the side effect and to look at sites that participated under the original amendment and participated under the amended version of the protocol, and when we look at that analysis

we really don't see that big of an impact, if really much of an impact at all on the outcome of the trial.

DR. RELLER: That series of questions and reply by Dr. Macias was from Dr. Anthony Suffredini.

Dr. Wald?

DR. WALD: Did you use mortality rates before and after the amendment was introduced?

DR. MACIAS: Yes, we did.

DR. WALD; And what did they show?

DR. MACIAS: Could you bring the slide up for me, please with mortality rates for all patients under the original and the amendment and, also, under the for sites enrolling under the original and the amended protocol, and you can bring the slide up for me, please?

This is the relative risk for all. This is now looking at the entire population of 1690 patients. This is the relative risk for patients enrolled under the original protocol .94, the relative risk for patients enrolled under the amended protocol. The interaction P value is .08, and then as we tried to explore this we looked at trying to control for the side effect. We looked at sites that participated under both the original and the amended versions of the protocol. The original relative risk for patients under the original was .87, and under the amended .77; the interaction P value is .5.

DR. WALD: Did you look specifically at the relative mortality rates in the two groups, the treated and the placebo group?

DR. MACIAS: Yes, the placebo mortality remains relatively constant over the course of the trial and the mortality rate is not there, but the mortality rate for the drotrecogin alfa (activated) population under the original enrollment in the original version is approximately 29 percent and under the amended version is approximately 24 percent. I am looking at Jeff for -- this just shows me the relative. I think it is about 24 percent, 23 percent.

DR. WALD: Was there ever any question about legitimacy of combining the two?

DR. MACIAS: We have looked very extensively at whether or not we felt that the amendment truly influenced outcome, and when we controlled for the site effect almost all the influence of the original versus the amendment went away. So, for example, can I see the slide with greater than 25, greater than 20, greater than 15 patients per site?

You can bring this up, please?

So, when we tried to control for the site, a site effect, we looked at sites that enrolled at least 25 patients, at least 20, 15, at least 10 and at least 5, and when you do that as you move down the interaction P values you don't see anything that is statistically significant,

and as you look at the relative risks they begin to even out.

There is clearly as the trial progressed, I think physicians enrolled, I don't want to say better quality patients but more discriminating patients, patients that had a higher probability of dying from their severe sepsis and not from their underlying non-sepsis-related disease.

DR. RELLER: Dr. Peter Eichacker had a question from the NIH Critical Care Section.

DR. EICHACKER: You know, Bill, first a clarification because I am still confused. Was the infusion of the drug monitored with PTTs?

DR. MACIAS: No.

DR. EICHACKER: During the trial?

DR. MACIAS: No, it was not. There was no monitoring required for study drug administration.

DR. EICHACKER: Although during the Phase II study 50 percent of patients who received that dose of drug required a change in drug. I believe the --

DR. MACIAS: The way the study was done in Phase II, it was done with bedside monitoring of whole blood APTT, and the reason we used whole blood APTT is if you actually spent time to separate the plasma and sent it to the lab the effect of the APC would be gone.

So, during the Phase II study as we dose escalated

we used a bedside monitor in whole blood to look at the APTT and the assay was obtained within 2 minutes of the sample being drawn. That is how the Phase II study was done, and then when we went to Phase III there was no monitoring.

DR. EICHACKER: All right, along those lines then, also, I am confused in the uncontrolled data that we were given talking about the incidence of intracerebral hemorrhage in the uncontrolled studies. I am seeing a number of 13 over 520 whereas the number that you showed was much smaller. Now, are these the same uncontrolled studies?

DR. MACIAS: For clarity, the number that Dr. Lindblad will report is the 13 events that have been reported to the agency as serious adverse events by the number, his 580 that he had at the time that he made his slides, the smaller number. The current numbers that I show you in my slide are the updated figures as of September 30. To look at all the intracranial hemorrhages that have occurred in the ongoing studies we put in place an external adjudication committee, and as the committee has adjudicated the intracranial hemorrhages 3 out of the 13 were adjudicated as not being intracranial hemorrhages.

So, the current number that we have is 10 as of September 30, and then we just gave you the total number of patients that had been exposed to study drug on that date. That is where our number came from. That is why it is a

little bit different than Bob's.

DR. EICHACKER: One last question, and that has to do with the drug preparation and the change in the drug preparation. First of all, when was that instituted over the time of the study, and what was the change in the drug?

DR. MACIAS: It was instituted approximately at the same time as the amendment, and the change in the drug was just, and I will actually ask Ralph Riggins if he can just provide the crisp clean answer; otherwise, I will have to get clarity to my answer.

DR. RIGGINS(?): Yes, the process change in the manufacturing process for the drug was simply creating a new master cell bank from existing working cell bank by expanding the single cell isolate and then a minor adjustment in the way the drug substance is frozen after purification.

DR. MACIAS: And I think out of interest, could I see the BDS2, BDS2-plus slide by greater than four patients per site, greater than four and three? This goes back to the issue that we have just addressed when we tried to take care of the site effect.

Can you bring the slide up for me, please?

We did basically the same thing we did when we were trying to address the original amendment and that is to get the best idea of whether there was an influence of the

amendment or the change. We looked at sites that enrolled both under the original and the amendment or dosed patients with BDS2 which is the material used early and BDS2-plus, the material used late, and if you look at sites dosed at least four patients of each and very similar mortality rates and this is the corresponding placebo rate, four and three, again very similar mortality rates, the corresponding placebo rate and then greater or equal to three at both sites.

When you start to go below that and start putting sites that did one patient, then you begin to see differences in sorting that out at the time of the amendment. It was really quite difficult.

Slide off, please?

DR. RELER: Dr. Rotello?

DR. ROTELLO: As related to heparin, when you look at the two placebo groups on those receiving low-dose heparin and not receiving low-dose heparin there seems to be some mortality effect afforded by heparin alone. Have you substratified that population at all, and do you have any information on patients receiving full-dose heparin?

DR. MACIAS: Full-dose heparin was excluded from the protocol. Basically you either had prophylactic dose or below by the protocol, and I will as Dr. Helterbrand to address your question about whether heparin works in the

placebo group.

DR. HELTERBRAND: Could I have slide 334, please?

To specifically address your question we did, indeed, look within the placebo group and looked at patients who did get low-dose heparin and those patients who did not get low-dose heparin.

Slide on, please?

Now, again, we have to remind everybody that this is a non-randomized comparison in the sense that patients in the placebo group were not randomly assigned to receive low-dose heparin or not receive low-dose heparin. So, there could be a patient selection bias, but nonetheless, it is interesting to look at.

As I referred to in the core presentation we did a Cox regression analysis looking at baseline, either looking at the analysis when the heparin groups were defined either by baseline exposure or using a time-dependent covariate in a Cox regression model.

When we look at baseline heparin exposure only and do no stratification for any measure of disease severity you see a relative rate of death of .94. That means just a 6 percent relative reduction observed, and it is clearly not statistically significant. It is very broad confidence interval, and the P value is very high there.

If we adjust for one measure of disease severity

such as APACHE II quartile again there is very little evidence to suggest that heparin is having any effect on mortality in the placebo group.

In addition, if we actually do take the approach of, also, including patients in the heparin group who get heparin post-baseline using a Cox regression model, again, what you see here is no evidence that low-dose heparin has any effect on mortality in the placebo group.

DR. RELER: Dr. Mumford?

DR. MUMFORD: How much overlap was there in the patients in the first APACHE II quartile and the patients in the lowest IL-6 quartile? They are being described as if they are both indicators of relatively mild illness, but do they in fact represent the same patients?

DR. MACIAS: Jeff, could you provide the answer to that? The first APACHE quartile does contain a lot of the patients in the lowest IL-6 quartile. I don't have the specific number.

DR. HELTERBRAND: I am going to look at 347 to attempt to answer your question.

Slide on, please?

This is one of the analyses that we said we would be happy to share with you later on where we look within the first APACHE II quartile and look at patients below the median IL-6 level and above the median IL-6 level. So, as

you can see there, there are 433 patients that made up the first APACHE II quartile, and if I do the math correctly here I come up with 258 patients who had IL-6 levels below the median level, and as you can see, again, in people with IL-6 levels within the first APACHE quartile we see a relative risk reduction, again of 20 percent consistent with the overall trial results.

DR. RELLER: Dr. Warren?

DR. WARREN; Since there was a change in the way the drug was made do you have a release test that you use in house of some sort and is there, also, some sort of a, can you go back into the baboons or something to assure yourself that there had been no change in the drug function?

DR. MACIAS: There is extensive in vitro testing on the pharmaceutical product indicating no difference between the two compounds.

DR. WARREN: Can you describe what those, are they all hematological testing or --

DR. MACIAS: I will ask Ralph Riggins, could you please provide the answer to this?

DR. RIGGINS: Yes, we have done extensive not only physical-chemical but structural analysis in addition to coagulation-based activity assays and by all measures there is no difference between the preparations, and there is really no difference in the preparation of the drug other

than the minor changes that I mentioned.

DR. RELLER: Dr. Cross?

DR. CROSS: I am still trying to get a handle on the impact of the change in exclusion criteria, on the patient population. What I would like to know is was there any difference in terms of the relative distribution of patients who developed sepsis outside or at least inside the hospital after a few days versus those who may have been hospitalized for a longer period of time. Perhaps one measure of that may be how many days the patient was in the hospital before receiving the treatment.

DR. MACIAS: Could you bring up on the monitor down here for me the profile for original versus amendment?

I believe as the, and that doesn't include the data that I need. I believe as the protocol progressed more patients came from home as opposed to being transferred from an outside institution or coming from a nursing home.

I don't think we have the analysis of that number of patients developing in-hospital, if you will, nosocomial sepsis versus non-nosocomial sepsis.

Yes, you can bring the slide up for me, please?

This is the slide that I was referring to. As you move through the study there is a little bit higher percentage of the patients that came from home, kind of a similar percent that came from another acute care facility,

but then as you move through the study a little bit less that came from the skilled nursing facility, and then you looked at the population of patients without disabilities.

So, there were some changes as the protocol progressed.

Slide off, please?

DR. CROSS: But when you say, "Came from home," is that within a certain period of time? I am trying to --

DR. MACIAS: Oh, immediately prior to hospitalization.

DR. CROSS: Right. For example, as you excluded, for example, immunocompromised patients I would imagine you would have fewer patients who may be seen let us say in a tertiary care facility who are there for a while who then after a week or two then develop sepsis.

DR. MACIAS: Yes.

DR. CROSS: I would imagine a consequence of that amendment is that you would have fewer of those patients.

DR. MACIAS: It was clearly, that hospital location was where the patient came from at the time that they came into the hospital. So, theoretically they could have been at another institution a week earlier, been discharged to home and then popped into that hospital.

DR. RELLER: Dr. Christie-Samuel?

DR. CHRISTIE-SAMUEL: Did you look at the

treatment effect stratified by APACHE score and age?

DR. MACIAS: By APACHE score and coupled by age?

DR. CHRISTIE-SAMUEL: Younger patients.

DR. MACIAS: Jeff, obviously the APACHE includes an age component. I don't think we did an analysis of APACHE II by age separately.

DR. HELTERBRAND: I guess I have a number of responses I could make. First of all, as we have shown with age there is really no interaction in terms of treatment effect by age on the relative risk of death. We did do a multivariate analysis that includes age and APACHE score as well as various other measures to try to take into account the multiplicity of clinical and biochemical measures that we collected in this trial in order to assess, you know, if we do all take all those variables into account what happens when you put them in a multivariate model, and it did include age, and it did include APACHE II scores, and what we came up with was a constant 40 percent increase in the survival with Xigris compared to placebo.

So, only in the multivariate sense have we done it, and it came out to a result of no interaction in the multivariate model.

DR. RELLER: Dr. Ramirez?

DR. RAMIREZ: Yes, two questions. I would like to go back to the amendment. According to the data that we

have before the protocol was amended we have a difference in mortality of 2 percent; with the placebo 30 percent mortality and with the study drug 28 percent mortality, and after the amendment was performed we have placebo 31 percent mortality and the study drug 22 percent mortality and this decreased mortality rate of 7 percent before the amendment and 29 percent after the amendment. This is extremely significant.

I would like to re-ask the question. Is the only explanation that we have for this difference in mortality before the amendment and after the amendment the explanation of the enrollment site? Were there any other possible explanations?

DR. MACIAS: I think it is actually a combination of things. I think there clearly is over the course of the entire trial an improvement in the enrollment of discriminating patients, patients in whom the effect of the drug would be more evident because of the exclusion of patients likely to die from underlying non-sepsis-related diseases, and I think that occurs throughout the entire 2-year study period, but there clearly is an effect of site, and when you try to control for that effect of site and you look at only sites that participated under the original and participated under the amendment there is not a significant interaction.

DR. RAMIREZ: And the second question, during the amendment protocol there was an exclusion criteria, the exclusion criteria No. 17, and the presence of the first sepsis-induced organ failure of greater than 24. That was prior to the start of window two, and the question is in the first protocol there was any time for the beginning of organ failure or during the first part of the protocol the patient can be enrolled regardless of the time of initiation of organ failure?

DR. MACIAS: Under the original protocol no. The answer to that is no. There was not a restriction. At the time you met all inclusion and no exclusion criteria there was not a limit to the duration of that organ failure. However the vast majority of patients were enrolled within 24 hours of organ failure because it is the organ failure, the development of the organ failure that is basically allowing you to meet the inclusion criteria.

In other words, the patient gets infected first, then has SIRS(?) and then the organ failure allows you to complete that. When we did a fairly extensive analysis of treatment by duration of organ failure there is no difference, and maybe we could pull that up very quickly, the mortality by duration of organ failure, and there was no interaction present, and if we don't have it is not necessary to pull it up real quick.

DR. RAMIREZ: This exclusion criteria 17 was at the time when we see this great advantage of the drug. It would be fair to say that we are defining in the natural history of severe sepsis that the finding in the population that early onset severe sepsis because we are saying that a patient should be included within 24 hours of the first organ failure because in my mind you have a patient in intensive care unit. You have 6, 7, 10 days of organ failure and an average period of 7 days in some studies, but we are saying here that the person that developed the respiratory insufficiency or cardiovascular insufficiency more than 24 hours is already too late to be enrolled in the study. This was part of the criteria, and I am trying to see if the second part with such a great benefit is because we are looking in the natural history of the disease at patients with early progression, early severe sepsis even though the severity is there, this is in the natural history early severe sepsis because this is important when we look at indication because severe sepsis, often severe sepsis would imply well, I can have organ dysfunction for any number of days, but this protocol is telling me that you need to have only 24 hours.

DR. MACIAS: Could I have the slide with the schematic of the study design from the core presentation, and I think your point is actually a very extremely

important point, but I would like to, if you can bring the slide up, please?

This is the window in which the patient had to meet all inclusion and no exclusion criteria and they had to do that within a 24-hour period.

At the moment in time within this window that the patient met all inclusion and no exclusion criteria, the organ failure could be no older, as you say, not present for longer than 24 hours but from this point to the start of study drug an additional 24-hour period was allowed to obtain informed consent, randomly assign the patient and initiate study drug. So, the maximum duration of organ failure could be 48 hours. However, approximately 75 percent of the patients received study drug within 24 hours of the onset of first sepsis-induced organ failure.

When we looked at treatment by duration of organ failure over that 48-hour period there was no interaction. In other words patients enrolled with organ failure greater than 24 hours had similar benefit than patients enrolled with less than 24 hours with an organ dysfunction, and we could provide those, Jeff, if you have those exact numbers.

DR. HELTERBRAND: Right, roughly, as Dr. Macias pointed out, roughly one-quarter of the patients had organ failure for longer than 24 hours before they started using study drug.

DR. RAMIREZ: But longer than 24 hours but less than 48 hours?

DR. MACIAS: Yes.

DR. HELTERBRAND: The majority were less than 48 hours. That is correct and in the group that had longer than 24 hours a 30 percent relative risk reduction with Xigris was observed.

DR. MACIAS: I think it is an extremely important point that we were not enrolling patients in the trial who had organ failure for 5 and 6 and 7 days prior to the administration of study drug.

DR. RELLER: Dr. Archer?

DR. ARCHER: More than one-half of the patients' infections was lung. How was pneumonia differentiated from ARDS?

DR. MACIAS: Pneumonia was defined in the protocol by chest x-ray consistent with pneumonia and the presence of purulent sputum and that was the guideline that we gave the investigators in the protocol and in the case report form. There was no further differentiation.

DR. RELLER: Dr. O'Fallon?

DR. O'FALLON: I think there will be many statistical questions. Let me ask one?

DR. MACIAS: Should I switch places with the statistician?

DR. O'FALLON: We can find out. We have heard in the last half hour or so I suppose two or three dozen references to the fact that there were no statistically significant interactions. Those are kind of useless statements unless we have some sort of a power statement regarding how likely it was that you could have detected such interactions, and those of us who do this kind of thing for our livelihood know that that likelihood is almost certainly very, very small.

So, any answer about power of the interaction effects would be useful at different times here.

DR. MACIAS: Are you asking for an answer? Because then I can turn it over to Dr. Helterbrand.

DR. O'FALLON: I have implied there are many of them. So, if he gives me one answer, I will have to know which one of the statements it applies to.

DR. HELTERBRAND: To speak to Dr. O'Fallon's question, indeed interaction analyses are typically lower powered because you are going into subjects and some of the subjects that we are talking about here today are 100 patients, a 200-patient subgroup, sometimes up to 400 patients and again they will have limited power, and that is why it was important for us to really look at it from a couple of perspectives, looking at it both in terms of interaction test and kind of follow the concepts of the

exploratory data analysis by looking at the 95 percent confidence intervals and saying, "Do the confidence intervals contain the point estimate of the overall trial?" Again, those are, also, somewhat underpowered types of analyses, but that is why we took multiple approaches that are generally accepted in statistical literature to try to assess evidence of differential effects across subgroups.

DR. RELLER: Dr. Fleming?

DR. FLEMING: Many issues to discuss here, and time won't allow, but I would like to ask just two questions at this point that relate to the amendments and certainly strongly endorse Dr. O'Fallon's comment that he just made.

What is very apparent when you look at the amendment is that your thoughts about the motivation were fully justified, i.e., you were targeting the intention of excluding those patients with non-sepsis-related disease because if these people had a high rate of risk of death and treatment couldn't affect them it would dilute your odds ratio.

This is exactly what we see. I don't need to see a test for interaction to know whether it is significant or not significant. It is very apparent that after the amendment the estimate of the treatment effect is much larger. The overall death rates are much less. So, you did, in fact accomplish exactly what your intention was. My

question was the first of my two questions then is if, in fact, you are excluding these patients that won't in fact likely benefit has your label, how has your label accounted for this?

DR. MACIAS: I think there are two points to it. One is as a point of clarity, we didn't exclude patients with underlying non-sepsis-related diseases. What we excluded or who we excluded were patients with non-sepsis-related diseases in whom the investigator would assess the patient as being at high likelihood of dying within the 28-day study period.

That was what we excluded.

DR. FLEMING: Is your label accordingly excluding such patients? I don't see that it is. The second question, can you assure us at the time that this amendment was made that no one from within Lilly had access to the code and let me go a bit further to say that it is not just that you amended the eligibility, you, also, amended your primary end point. So, if in fact someone from within Lilly had the code could you clarify who that was and could you clarify who was doing the ethically necessary safety monitoring because this code, this amendment was not done until about 8 months after the initiation of the trial. So, I am assuming ethically somebody should have been monitoring the two intervention groups for relative safety.

Did anybody within Lilly have access to that code?

DR. MACIAS: With respect to monitoring safety we monitored safety in a blinded fashion. However, the pharmaco-vigilance group at Lilly had the option to unblind individual patients who experienced a serious adverse event throughout the course of the study, and that group is separate from our group, but they had the option to unblind individual patients.

DR. FLEMING: So, am I to understand then that there was not an independent, non-Lilly assessment of relative safety issues during the first 8 months of this trial?

DR. MACIAS: No, there was. Jeff, do you want to answer very quickly, and then I will --

DR. HELTERBRAND: I mean for that particular question I think it is true that the monitoring was going on by Lilly, and then once we had the interim analyses, of course, our Data Safety Monitoring Board did review all the efficacy and the safety data both at the first interim and at the second interim analysis.

DR. FLEMING: At least I would like to call to the FDA's attention two issues that to me are major concerns. One is that it is apparent that Lilly was assuming the responsibility as opposed to an external committee for early safety monitoring and secondly, there was access to this

code within Lilly, and we had a change in the primary end point during, well into the course of the study.

DR. HELTERBRAND: Actually I would like to speak to that because I think it might make sense to understand the organizational structure of how this trial was conducted, and it was conducted in a manner to optimize the integrity of the resulting data and the inferences that could be drawn.

Can I please have Slide 354?

This is a schematic. There are really three key points to make to Dr. Fleming's point. First, patient treatment assignments were provided pharmacists at the investigative site by Covance(?) which was a contract research organization via central randomization center and treatment assignments were retained by Covance during the trial, and it is important to point out that data management was performed at Lilly without access to patient treatment assignments. We did not have that access.

However, as Dr. Macias has pointed out, for regulatory safety reporting purposes we actually, our pharmaco-vigilance group did have the opportunity to unblind patients if there was a study drug related death, study drug related as assessed by the investigator or a study drug related unexpected event and there were approximately 10 unblindings of this trial. However, it is important to

reiterate that Lilly did not have access to patient treatment assignments during the conduct of the study.

So, what we actually did is we did our data management without access to patient treatment codes, built the data sets without treatment assignments and then shipped them to an external statistical services organization, Pat O'Meara(?) and Associates who then married the data up with the actual treatment assignments that were contained at the external contract research organization. Dr. O'Meara then produced the prospectively defined analyses based on our interim analyses and then once he prepared the interim analysis report he provided them to our independent external Data Safety Monitoring Board.

If I could have the next slide, please?

That included the following individuals, Dr. Opal, who presented to you this morning was our Chairman. Dr. Abraham, Dr. Lowery, Dr. Wittus was our statistician involved in our Data Safety Monitoring Board. They reviewed both the safety data and the efficacy data and followed the O'Brien-Fleming methods in terms of for trial stopping rules, and so, just a point of clarification, Lilly did not have treatment assignments during the conduct of this trial, only when it was necessary for regulatory reporting purposes did our pharmaco-vigilance group have the opportunity to call Covance, get unblinded and that occurred approximately

10 times.

DR. SIEGEL: I would like to address that question, also, from a somewhat other angle.

We, as you know, our concerned especially when a company is dealing with preparing data reports for data monitoring which is a typical practice about those potential biases and one way is to look at whether the decisions that were made might have reflected such biases.

In that regard, regarding the MT(?) criteria if you could look at the FDA slide in the bottom right hand corner of Page 7 we divided the patients who had been treated pre-amendment to those who fell in a group that was now being excluded, the patients you expressed concern about who had a high risk of mortality based on the physician's assessment independent of sepsis.

If you look at that group with the new criteria excluded the first line in that table, the relative risk in that group is .8 similar to the overall study population in favor of treatment.

If you look at patients treated to that point in time in the other, in the complementary group, those who would have been eligible even under the final criteria there is little evidence of a drug effect.

So, in fact, their change in eligibility was excluding the group that provided the most evidence of drug

effect to date. That, also, has some bearing as to whether one would want to exclude those patients in the labeling even though they were ultimately excluded in the entry criteria. The little data are present and obviously the numbers are small, suggesting that there isn't a differential effect there and further suggest that it wasn't out of knowing bias that that change was made.

A little bit different in terms of the study sites that were excluded. Interestingly the study sites that were small that were excluded were not showing a very good drug effect as it turned out. That is why when you see the analysis of same sites you don't see the differences in the first and second half that you do when you include those sites. However, by any way we can look at it, there is little to suggest that those sites were excluded other than for valid reasons.

They were, in fact, enrolling at a much lower rate than other studies. The third issue you mentioned is end point changes, and I think the fundamental end point didn't change. There was some change in how protein C, I guess would be, levels would be included into the end point and whether that was primary or secondary and my recollection although maybe the company can answer this, I think the data have been analyzed both ways, and I don't think it made a profound difference in the final analysis or even much of a

difference at all.

DR. MACIAS: No, it did not. The change in the amendment with respect to the primary analysis, we kept the primary analysis which was 28-day all-cause mortality for all treated patients, so patients exposed to drug for any length of time. The original stratifications were age, APACHE and quote, unquote, presence of shock within 6 hours.

We modified the shock to change it to baseline protein C level and so the final analysis was an analysis stratified by age, APACHE, protein C, but we did provide in the final study report submitted to the agency the analysis that was the original prospectively defined analysis of age, APACHE and shock status. It made no difference.

DR. RELLER: Question from Dr. Murray.

DR. MURRAY: Sort of two questions. One is a follow-up on the previous question relating to the proposed labeling by Lilly. Would the proposal be that people with organ failure more than 48 hours not be administered the drug since that is how it was studied and then the second question which is totally unrelated but is more for curiosity, if you have any longer-term follow-up to the 28 days to see if people that did survive that had not gone back home were back to a more functional status?

DR. MACIAS: To answer the first question, from a restriction standpoint we would not propose that we would

restrict it 48 hours, but the label would reflect the fact that patients were enrolled in the study within 48 hours of the onset of their organ dysfunction.

The reason for that is I don't think we believe that if a patient has organ dysfunction for 47 hours he would be eligible and for 50 hours he would be ineligible which is I think very different than TPA and stroke where if you have a stroke syndrome for 3 hours you might benefit and when you have stroke syndrome for 6 hours you don't benefit. So, I think there would be a reflection, we would recommend reflection of the duration of organ failure in the clinical trial section of the label but not a restriction for the reasons I have expressed.

With respect to follow-up beyond 28 days, we have currently initiated the follow-up protocol to EVAD. So, it will follow up all survivors in the EVAD protocol up through I think for some patients a minimum of 1 year but for patients enrolled early follow-up will be longer.

It will assess eventual hospital disposition for all hospitalized patients on day 28 along with survival status.

DR. RELLER: Dr. Suffredini?

DR. SUFFREDINI: In terms of other aspects of the study that were changed the placebo was changed. Can you comment on why that would be the case?

DR. MACIAS: Very early in the course of the study we were made aware that since activated protein C is a protein that if you perturb the solution too much you would get foaming, and the original placebo was saline. So, immediately following the start of the study sites were instructed to wrap all bags, the bag and the tubing so they could not visually see whether or not the solution foamed or didn't foam, and then at the amendment we elected to institute albumin, low-dose albumin to provide the same foaming just to improve the blind.

DR. SUFFREDINI: And they were considered to be comparable in terms of their foaming, the duration of foaming or were they still wrapped?

DR. MACIAS: We left them wrapped, but the duration of the, the amount of albumin contained within the saline produced the same amount of foaming as the other solution, but we still continued to wrap except in France where albumin was not allowed to be used as the placebo.

DR. SUFFREDINI: I guess there are at least four factors that changed between Part A and Part B of the study and in terms of the change in the DNR rate in the treatment group that diminished significantly but that wasn't shared by the placebo group which certainly may have a significant effect in terms of the 28-day mortality.

Can you comment on that?