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Gastrointestinal Drugs Advisory Committee

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C O N T E N T S

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Debra Silberg, M.D., Ph.D.

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P R O C E E D I N G S

Call to Order

DR. CHANG: It is 8 o'clock. I am Lin Chang. I am the Acting Chair of the GI Drug Advisory Committee, so good morning to everyone and thank you for joining us.

I want to just make a few statements and then we are going to introduce the Committee.

For topics such as those that are being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the Chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the Advisory Committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious

to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

I would like to remind everyone present to please silence your cell phones and other electronic devices if you have not done so already.

The Committee is reminded to please refrain from discussing the meeting topic during the breaks or lunch. Thank you.

Introduction of Committee

We will first start introducing the committee. Maybe, Dr. Silberg, can you introduce yourself?

DR. SILBERG: I am Dr. Silberg. I am the industry representative. I work for AstraZeneca and I am a gastroenterologist.

DR. BARANSKI: I am Dr. Ed Baranski. I am a general surgeon from Gettysburg, Pennsylvania.

DR. FOGEL: I am Dr. Ron Fogel, gastroenterologist.

DR. NEATON: Jim Neaton, Professor of Biostatistics, University of Minnesota.

DR. BLUM: Dick Blum. I am a clinical

pharmacologist and internist, Long Island, New York.

DR. SMITH: Roy Smith, hematologist, University of Pittsburgh, Pittsburgh, Pennsylvania.

DR. FURBERG: Curt Furberg, Public Health Sciences, Wake Forest, University.

DR. SKLAR: Jill Sklar, consumer representative.

DR. RAUFMAN: Jean-Pierre Raufman, Chief of Gastroenterology, University of Maryland.

DR. CULLEN: Joseph Cullen, Professor of Surgery, University of Iowa.

DR. KHUC: Kristine Khuc, Designated Federal Official.

DR. KANE: Susie Kane, gastroenterologist, Mayo Clinic, Rochester.

DR. SHIH: Weichung Shih, Department of Biostatistics, University of Medicine and Dentistry of New Jersey.

DR. EPSTEIN: Michael Epstein, clinical gastroenterologist, Annapolis.

DR. HASLER: Bill Hasler, Division of Gastroenterology, University of Michigan.

DR. GAO: Wen-Yi Gao, Medical Officer, Division of

GI, CDER, FDA.

DR. MARKS: Zana Marks, Division of GI, Medical Officer, and I am a clinical gastroenterologist.

DR. RAJPAL: Anil Rajpal, Medical Officer, Acting Team Leader, GI.

DR. HE: Ruyi He, Acting Deputy Director, Division of GI.

DR. BEITZ: I am Julie Beitz, Director, Office of Drug Evaluation III in the Office of New Drugs, CDER.

Conflict of Interest Statement

DR. KHUC: The Food and Drug Administration is convening today's meeting of the Gastrointestinal Drugs Advisory Committee of the Center for Drug Evaluation and Research under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and temporary voting members of the Committee are special government employees or regular employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with Federal ethics and conflict of

interest laws covered by, but not limited to, those found in 18 U.S.C. Section 208 and Section 712 of the Federal Food, Drug, and Cosmetic Act are being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with the Federal ethics and conflict of interest laws.

Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular Federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the Federal Food, Drug, and Cosmetic Act, Congress has authorized FDA to grant waivers to special government employees and regular Federal employees with potential financial conflicts when necessary to afford the Committee essential expertise.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including

those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, cooperative research and development agreements, teaching, speaking, writing, patents and royalties, and primary employment.

For today's agenda, the Committee will discuss the recommendations regarding the safety and efficacy of New Drug Application 21-761, Sanvar (vapreotide acetate) by Debiovision, Inc., for the proposed indication as an adjunctive therapy to endoscopic intervention for the control of acute esophageal bleeding as a result of portal hypertension.

This is a particular matters meeting during which specific matters related to Debiovision's Sanvar will be discussed.

Based on the agenda for today's meeting and all the financial interests reported by the Committee members and temporary voting members, no conflict of interest waivers have been issued in connection to this meeting.

With respect to FDA's invited industry

representative, we would like to disclose that Dr. Debra Silberg is participating in this meeting as a non-voting industry representative, acting on behalf of all regulated industry. Dr. Silberg's role at this meeting is to represent industry in general and not any particular company. Dr. Silberg is employed by AstraZeneca.

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

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

At this time I would also like mention that the press contact is Ms. Kim Rawlings. Ms. Rawlings, if you are here, please stand. Thank you.

DR. CHANG: Thank you.

We will now proceed with the FDA opening remarks. Dr. He.

Opening Remarks

DR. HE: Good morning. Welcome to the GI Drugs Advisory Committee meeting.

[Slide.]

My name is Ruyi He. I am Acting Deputy Director in the Division of Gastroenterology Products. Today, we are talking about Sanvar NDA 21-761.

[Slide.]

The purpose of today's meeting is to discuss the efficacy and the safety of Sanvar for the proposed indication--that is, adjunctive therapy to endoscopic intervention for the control of acute esophageal bleeding as a result of portal hypertension.

[Slide.]

At first, let me give you some brief regulatory history about these NDA submissions. In February 2004, an NDA was submitted with three studies; Egypt study, Hong Kong study, and a French study.

The Egypt study was a small, single center, Phase 2 study. The Hong Kong study was a bigger study and enrolled more than 130 patients. However, it was a negative study and the data indicate that there was no difference

between the treatment arm and the placebo arm.

The third study, the French study. was the only positive study, but it was not robust.

In December 2004, we took approvable action and asked the sponsor to provide additional efficacy data to support the proposed indication.

[Slide.]

In the current submission, the sponsor did provide two additional studies, Study 301 and Study 06.

Study 06 was an active study. The data indicate that there was no difference between the treatment group and the placebo per original protocol. The sponsor did additional analysis and statistical analysis plan was amended one year after the end of the study. We consider such additional analysis as an exploratory purpose only.

Study 301 was a single arm, open-label study with historical control.

[Slide.]

We have efficacy concerns about Study 301. We have a concern about the open-label, single-arm study design that has the potential to introduce bias. We have a concern about validitating of historical comparison. We have a

concern about contribution of band ligation to the efficacy.

As we point out in the background package, the majority of the patients in Study 301 were treated by banding ligation. In contrast, the majority of patients in the historical control study were treated by sclerotherapy.

This table summarizes the results of banding ligation versus sclerotherapy for control of initial bleeding, re-bleeding, blood transfusion, and the mortality.

The study clearly indicates that the banding ligation had significant benefit over sclerotherapy for control of initial bleeding, 97 percent versus 76 percent. There was a more than 20 percent benefit by banding ligation alone.

The study also indicate that banding ligation had significantly less re-bleeding rate and less blood transfusion than sclerotherapy did.

In addition, the study indicated that banding ligation had amortality benefit over sclerotherapy, 19 percent versus 35 percent.

[Slide.]

Therefore, the question is, does the Study 301 qualify as one of two adequate and well-controlled studies

to support the efficacy of Sanvar?

Somatostatin and octreotide are not approved for this indication, but used off-label in the United States.

A review article published in Cochrane Database of Systematic Reviews early this year on the topic of those drugs for acute esophageal bleeding, this review article summarized a total of 21 clinical trials that include both double-blind and open-label studies.

This table summarizes the findings from 82 randomized, double-blind clinical trials. The data indicate that the drugs did not reduce mortality, 18 percent versus 19 percent, and did not reduce re-bleeding rate either, 19 percent versus 24 percent.

Although the drug did increase control of initial bleeding, about 14 percent, the article concluded that the need for blood transfusion corresponded to 1/2 unit of blood saved per patient. It is doubtful whether this effect is worthwhile.

[Slide.]

During today's meeting, there are several presentations from both sponsor and FDA. Please think about those three questions during presentations and the

discussion.

The first question is an efficacy question. Does the NDA provide substantial evidence of efficacy for the proposed indication?

The second question is a safety question. Do you have significant safety concerns for Sanvar used for the control of acute esophageal bleeding?

The third question is a very important question. Based on currently available data, do the potential benefits outweigh the potential risks of Sanvar for the control of acute esophageal bleeding?

We will pose those questions again in the afternoon. We are looking for a vigorous discussion.

Now, I turn the podium to our chairman. Thank you very much.

DR. CHANG: Now, we will proceed with the sponsor's presentation. The sponsor asks that questions be held to the end of their presentations.

Presentations from Sponsor

Introduction

[Slide.]

DR. PETRELLA: Thank you, Dr. Chang.

[Slide.]

Madame Chair, members of the Advisory Committee, representatives from FDA, colleagues, ladies and gentlemen. Good morning. My name is Marco Petrella and I am the Director of Clinical Affairs and New Product Development for Debiovision in Montreal.

We are here today to present the efficacy and safety data in support of our New Drug Application with our product Sanvar (vapreotide acetate).

[Slide.]

We are pleased to have with us Professor Roberto Groszmann, an internationally-recognized leader in the field of portal hypertension from Yale School of Medicine. Dr. Groszmann will discuss important aspects of the pathophysiology and clinical management of esophageal variceal bleeding and address the unmet medical need that exists for this serious and life-threatening condition in the United States.

I will then return to present efficacy data from clinical trials that evaluated treatment with vapreotide for the control of bleeding due to portal hypertension in cirrhotic patients.

Dr. Kamel Besseghir, CEO of our sister-company in Switzerland, will present our analysis of the vapreotide safety data.

Next, Dr. Naga Chalasani, during his presentation of benefit-risk, will discuss clinical benefits with vapreotide following careful consideration of this product's overall efficacy and safety profile.

At the end of the presentations, I will conclude with a few remarks that summarize our main arguments.

[Slide.]

The indication that we are seeking from the agency for Sanvar is as adjunctive therapy to endoscopic intervention for the control of acute esophageal bleeding as a result of portal hypertension.

[Slide.]

The esophageal variceal bleeding, or EVB, is a rare or orphan disease. Because of this, Sanvar has been granted orphan drug status by the FDA. As will be shown, EVB is a serious and life-threatening complication of portal hypertension in patients with liver cirrhosis.

This condition requires emergency medical intervention and although considerable advances have been

realized in therapy, morbidity and mortality remain remarkably high. In the United States, there is no vasoactive agent approved for this indication, and, as will be explained later, drugs from this class are used off-label by clinicians to treat patients in accordance with the current standard of care for EVB.

Vapreotide is a cyclic octapeptide analog of human somatostatin with improved metabolic stability. Its pharmacological properties are similar to those of somatostatin, but with a longer duration of action.

[Slide.]

Before briefly discussing our vapreotide clinical trials, I would like to take a moment to review the major regulatory milestones that we believe were important for decisions regarding the clinical development and registration of our compound.

As you can see, Debiovision initially submitted a New Drug Application for vapreotide in 2004. This submission was based primarily on VAP-14, our pivotal Phase 3 study which, as we will show, provides persuasive evidence of the efficacy of vapreotide.

Data from VAP-07, a small, single-center pilot

study, was included as supportive evidence of efficacy while data from a third study, designated as VAP-02, was provided for the analysis of safety only.

A third trial, VAP-06, was ongoing in Eastern Europe. Near the end of the review period, FDA requested results from VAP-06 which at that time were not yet available. FDA then issued an approvable letter at the end of the review, requesting additional evidence of efficacy while making reference to the just completed VAP-06 trial.

As we will discuss in our efficacy presentations, the results of VAP-06 were compromised by a major protocol amendment, and it was determined by FDA that these results would not resolve the outstanding clinical deficiency.

As placebo-controlled trials were no longer an option for ethical reasons, Debiovision ultimately proposed a multi-center, open-label, historical-controlled trial to be conducted in the United States in order to provide the additional evidence of efficacy that was requested by FDA.

This new trial, referred to as VAP-301, was accepted by FDA under a Special Protocol Assessment, or SPA. A summary of these regulatory agreements will be presented in the next two slides.

Finally, the complete response to the approvable letter which included the results from VAP-301 was submitted by Debiovision in September 2008.

[Slide.]

It was agreed with FDA that the original 2004 vapreotide NDA would be based on data from three studies as follows:

VAP-14, as the efficacy study, with supportive evidence of efficacy from VAP-07 and additional safety data from VAP-02. And, as stated in the agency's 2004 approvable letter, a request was made to provide additional evidence of efficacy.

[Slide.]

Under the SPA assigned to VAP-301, it was agreed with FDA that the study design of VAP-301 was acceptable to address the request for additional efficacy data. In addition, the agency's 2006 SPA letter acknowledged that VAP-301 would be statistically constrained by study design.

Also, it was agreed with FDA that the primary objective of the VAP-301 study was to demonstrate a "clinical efficacy signal" that would be evaluated for clinical significance. This will be explained later in our

presentation.

[Slide.]

Five studies were conducted to investigate the efficacy and safety of vapreotide for the treatment of EVB in cirrhotic patients. Each of these trials will be discussed in greater detail.

It is important to note that the design of these studies reflects current practice for the treatment of EVB in accordance with the recommendations of international consensus guidelines.

The primary endpoint used in all trials was control of bleeding with survival over five days. This will simply be referred to as control of bleeding from now on.

An important aspect of the treatment regimen involved early administration with vapreotide prior to the initiation of the endoscopic intervention. The dose of vapreotide used in all trials was identical and consisted of an initial 50 microgram IV bolus followed immediately by a continuous infusion at a rate of 50 micrograms per hour for five days. The planned daily dose of vapreotide was 1.2 mg.

[Slide.]

The following table outlines our five EVB clinical

trials.

The first trial listed, VAP-02, was a Phase 3, placebo-controlled study conducted in Hong Kong. It was prematurely terminated because of very slow patient enrollment and major protocol non-compliance.

VAP-06, the study referred to earlier that incurred a major protocol amendment was a multi-center placebo-controlled trial conducted in Romania and Bulgaria. Because of serious procedural flaws, both VAP-06 and VAP-02 are uninterpretable studies and their results will only be used for the analysis of safety.

VAP-07 was a small Phase 2 pilot study conducted at a single center in Egypt and was not powered to show statistically significant differences between vapreotide and placebo.

VAP-14, conducted at 22 centers in France, is our pivotal study. It is an adequate and well-controlled study for demonstration of the clinical efficacy of vapreotide for the treatment of EVB.

This study published by Cales and collaborators in the New England Journal of Medicine has become a reference for the field where it served to establish and entrench the

current standard of care for EVB with vasoactive drugs because of its compelling results.

VAP-301 is the Phase 3 open-label study that was accepted by FDA under a Special Protocol Assessment. This trial was completed in June 2008 and enrolled patients at 15 centers in the United States.

[Slide.]

Our goal for the Sanvar Advisory Committee hearing today is to present the body of evidence provided by the VAP-14 and VAP-301 studies that establishes the efficacy of vapreotide for the proposed indication.

In VAP-14, a statistically persuasive result for the primary endpoint, control of bleeding over five days, was achieved. This result was confirmed by positive treatment outcomes with vapreotide for secondary endpoints that include control of bleeding at the time of endoscopy and the requirement for fewer units of blood transfused during the first five days following the index hemorrhage.

Furthermore, VAP-301 successfully achieved its objective as stated in the SPA and has demonstrated a clinical efficacy signal that confirms the results of VAP-14.

Consistent treatment effects with vapreotide were also observed in clinically-important patient subgroups from both VAP-14 and VAP-301. These results show the relevance of VAP-14 in the contemporary U.S. clinical setting for treatment of EVB.

[Slide.]

For the primary analysis of safety, five EVB studies encompassing 469 patients showed that vapreotide was well tolerated in this orphan drug indication with frequency and nature of adverse events and serious adverse events comparable to that observed in the placebo group.

The most commonly reported treatment-emergent adverse events were pyrexia and upper GI bleeds.

Similarly, a review of safety data from a larger data set consisting of 728 patients across nine studies which also includes different diseases involving higher drug exposures demonstrates that the risks associated with the use of vapreotide in EVB are minimal.

[Slide.]

In conclusion, the results from our clinical trials have demonstrated the efficacy and favorable safety profile of vapreotide for the treatment of EVB in

association with endoscopic intervention.

Finally, in consideration of the serious and life-threatening nature associated with this orphan indication, the approval of vapreotide will help to satisfy an important unmet medical need for an effective vasoactive drug in the United States.

[Slide.]

I would like to invite Dr. Roberto Groszmann who will discuss the medical need that exists in the treatment of EVB.

Dr. Groszmann.

Esophageal Variceal Bleeding

an Unmet Medical Need

DR. GROSZMANN: Thank you, Dr. Petrella.

[Slide.]

I am Professor of Medicine at Yale University School of Medicine.

I am here because of my interest in complications of cirrhosis and portal hypertension. I have been working in this area for more than 30 years. I chair the Steering Committee of the 301 VAP study.

I am going to be using the pointer, so I apologize

for the members of the Committee who have their back here.

[Slide.]

Cirrhosis of the liver is a multi-system disease. Practically, when the patient develops cirrhosis, all systems are affected. The main complication is the development of hepatocellular carcinoma, ascites, accumulation of fluid in the abdomen.

There are always methodological complications. Anemia, leukopenia and thrombocytopenia are particularly seen in all patients with cirrhosis and portal hypertension.

[Slide.]

Finally, the subject for discussion today is variceal bleeding. This is an acute complication, highly lethal for these patients.

[Slide.]

We have approximately half a million patients with cirrhosis in United States, and the most common causes are hepatitis C, alcohol, and nonalcoholic steatohepatitis, a complication of obesity.

Varices are present in more or less 60 percent of patients with cirrhosis. There is an normal rate of bleeding of 5 to 15 percent. We estimate that approximately

30,000 patients in the United States are projected to bleed from varices this year.

[Slide.]

This is a life-threatening complication of cirrhosis and portal hypertension. When you see a patient bleeding from varices, you will never forget about it. It is a dramatic complication of chronic liver disease.

In cirrhotic patients, more than 85 percent of upper GI bleeds are due to variceal bleeding. So when a patient presents to emergency room bleeding, having upper an GI bleed, you have to assume that a patient is bleeding from varices. Any cause of chronic liver disease can lead to portal hypertension.

The collateral veins in the lower part of the esophagus dilate due to the increased pressure in the portal system and that pressure causes these veins to balloon outward, and the vessels may rupture and bleed.

[Slide.]

I am going just to spend a few minutes on the pathophysiology of this entity, because it is important to understand the treatment.

The normal liver with cirrhosis, the nodules

compress the capillaries of the liver called sinusoids, and impair the blood flow, the portal blood flow, into the liver and increase pressure in the portal vein.

There with that, there is another phenomenon that develops. There is a hyperdynamic splanchnic circulation and increased the blood flow enters into the portal system that aggravates portal hypertension. The reason I am emphasizing this phenomenon is because all drugs that we are using today to treat portal hypertension are based in reducing this hyperdynamic state, a mechanism for reducing portal pressure.

[Slide.]

You see here the collaterals that are coming from the portal vein, and they are feeding the varices, the esophageal varices. When the varix ruptures and bleeds, it bleeds at high pressure. This is seen through an endoscope, and you can see the stream of blood that looks like an interior bleed. This is a very, very--a situation that requires very rapid action by the physicians.

[Slide.]

The goal of treatment is to stop bleeding as soon as possible, restore blood volume to prevent shock and

death. The risk of re-bleeding is the highest in the first five days following the control of the initial hemorrhage.

The mortality rate, although improved in the last 10 or 15 years, still there is a level of 20 percent. It is higher than the mortality from acute MI, acute myocardial infarction. Patients die as a consequence of multi-system failures; liver failure, sepsis, exsanguination, et cetera.

[Slide.]

When the patient comes to the emergency room, the patient is bleeding from varices, the physician comes right away when cirrhotic is bleeding, having upper GI bleeding, and early drug administration is mandatory.

These drugs, the way they work, they are splanchnic arterial vasoconstrictors. So they will use the portal venous inflow and, by that mechanism, reduce portal pressure. At the same time they are portal collateral constrictors. They constrict the collaterals that are feeding the varices.

So, while the patient is seen in the emergency room, these medicines can be administered, and that facilitates the work of the endoscopy team that have to apply banding or sclerotherapy while the patient still is on

drug.

Failure to control bleeding usually leads to rescue therapy with procedures such as TIPS, transjugular intrahepatic portosystemic shunt, performed by the cardiologist or the surgeon.

[Slide.]

Now, how do the drugs that we are talking about work? Well, as I said before, they reduce the blood flow entering into the portal system and, by that mechanism, they reduce portal pressure. But there is collateral similar to these collaterals that goes from the splenic vein to the renal vein and, in experimental cirrhosis, in these collaterals, the flow can be measured with flowmeter so we can quantitate the effect of drugs.

There are two studies, one with vapreotide and the other with octreotide, that show that the infusion of these drugs for use as reduction in the blood flow in these collaterals of around 25 percent.

[Slide.]

This is a challenge to conduct clinical trials in this area. I have been involved in three clinical trials in all the years that I have been working in this area, and it

is getting more and more difficult because there is more constraints about taking care of these patients because patients come late to the tertiary center.

The scarcity of patients, difficult to obtain consecutive flow of patients and adherence to protocol are routine. An emergency life-threatening condition requires quick decisions by the physician and sometimes the physician doesn't have really time to dedicate to comply with the protocol, the research protocol.

[Slide.]

This is a meta-analysis of somatostatin or somatostatin analogs, octreotide or vapreotide, comparing endoscopic therapy versus endoscopic therapy plus drug, effective drug. You can see that the meta-analysis shows very favorable results to these combination. In response to what was shown by the FDA representative, there is another meta-analysis that includes all drugs used, not only somatostatin and somatostatin analogs, and shows even a more favorable effect of combination of drug plus endoscopic therapy.

[Slide.]

This is accepted as a critical first step to

control bleeding. It is very careful. It is absolutely necessary to control or ameliorate bleeding by time of endoscopy. It helps tremendously in performing endoscopic procedure. These drugs reduce the rate of re-bleeding, fewer blood transfusions, controlled bleeding over the initial five days.

There are guidelines in practically every country in the world including the United States that support that octreotide should be used for off-label use here in the United States or natural somatostatin, terlipressin or vapreotide wherever available.

[Slide.]

So, in summary, the vasoactive drug plus endoscopic treatment is the standard of care for acute esophageal variceal bleeding everywhere you go, I mean even here in the United States.

Octreotide is currently used off-label for more than 90 percent of the physicians. Without an FDA drug approved for this indication, there are no consistent instructions for use, no structured ongoing safety surveillance.

In my personal view, I would like to have a drug

to treat these patients that is supported by the FDA. At this time, we are probably the only industrialized country in the world that doesn't have a drug for this indication approved by the Food and Drug Administration.

[Slide.]

Now, Dr. Marco Petrella will continue.

Efficacy

DR. PETRELLA: Thank you, Dr. Groszmann.

[Slide.]

Our review of the clinical efficacy of vapreotide for the proposed indication will cover the following topics:

The study design and endpoint description for all trials, efficacy data from the indicated studies, and summary arguments for the body of evidence that we believe establishes the efficacy of vapreotide in EVB.

[Slide.]

The goal of our clinical development program was to evaluate early administration of vapreotide in association with endoscopic intervention for the control of bleeding over five days. It is important to note that treatment with vapreotide in these trials was initiated early, prior to initiation of therapeutic endoscopy.

As will be shown in greater detail on the next slide, the primary endpoint used, control of bleeding over five days, is in fact a composite endpoint consisting of control of initial bleeding, or primary hemostasis, and revention of early re-bleeding, also referred as secondary hemostasis, and survival.

[Slide.]

This diagram outlines the various components of the primary endpoint that was uniformly evaluated in our clinical trials. Note that this endpoint, control of bleeding over five days, is in accordance with international consensus conference recommendations. The abbreviation Tendo that appears throughout our presentation refers to the time at the end of therapeutic endoscopy.

As illustrated here, for a patient to be considered a treatment success for the primary endpoint, prespecified targets for several clinical parameters which include systolic blood pressure, heart rate, hematocrit, and blood transfusions need to be satisfied during each of the three time intervals illustrated.

The first two windows extending from 0 to 6 hours, and from 6 to 48 hours after the end of therapeutic

endoscopy, are used to assess control of initial bleeding. Prevention of early re-bleeding is assessed from 48 to 120 hours post-endoscopy.

[Slide.]

The inclusion criteria specified for our studies are conventional for this disease indication and are consistent with the target population.

[Slide.]

Similarly, the exclusion criteria are also standard for therapeutic trials in EVB.

[Slide.]

An identical dose regimen with blinded study medication or open-label vapreotide in the case of the VAP-301 study was utilized. This consisted of an initial bolus injection followed by an IV infusion for up to five days after completion of the therapeutic endoscopy. The planned daily dose of vapreotide was 1.2 mg.

[Slide.]

As you will note, the protocol-defined ITT population for our studies is a modification of the conventional ITT population, and only includes patients in which a diagnosis of bleeding related to portal hypertension

could be confirmed at the time of diagnostic endoscopy.

Study drug was promptly discontinued if bleeding was found to be unrelated to portal hypertension. In this case, patients were excluded from the ITT analysis population and were followed for safety up to Day 42.

[Slide.]

VAP-07, VAP-06, and VAP-02, the three EVB trials briefly mentioned in my introduction, will now be discussed further.

[Slide.]

VAP-07 was designed as a Phase 2 pilot study and included a patient population with different disease etiology than patients from the pivotal VAP-14 study. It was not powered to demonstrate a significant difference between the vapreotide and placebo treatment groups.

[Slide.]

Control of bleeding over five days, in VAP-07, was achieved in 71 percent of vapreotide-treated patients compared to 59 percent of patients in the placebo group. Although not statistically significant, the magnitude of the treatment effect observed here is similar to that with the VAP-14 results as we shall see.

[Slide.]

As originally planned, VAP-06 was a multi-center, placebo-controlled trial conducted in Romania and Bulgaria. The implementation of a major protocol amendment to address shortages of blood for transfusion changed the trial's primary endpoint and resulted in significantly different patient treatment practices pre- and post-amendment that compromised the results of this study. Consequently, VAP-06 is uninterpretable.

[Slide.]

VAP-02 is also a multi-center, placebo-controlled study and was conducted in Hong Kong. Serious issues regarding slow patient recruitment and major protocol non-compliance, regretfully, necessitated premature termination of this study.

VAP-02 is also an uninterpretable study. In discussions with FDA, it was agreed that the results from VAP-02 would be used for the analysis of safety only. Results from both VAP-06 and VAP-02 are provided in the sponsor's briefing document.

[Slide.]

Efficacy results from VAP-14, our pivotal study,

will now be presented.

[Slide.]

VAP-14 was a multi-center, placebo-controlled trial conducted in France. In total, 227 patients were randomized at 22 study centers. After the protocol-specified exclusion of 31 patients for which upper GI bleeding was not related to portal hypertension, the vapreotide and placebo group ITT populations each contains 98 evaluable patients.

[Slide.]

Overall, the baseline characteristics of the vapreotide and placebo-treated patients in this study were quite similar with the exception that there was a higher proportion of male subjects in the placebo group.

[Slide.]

The next several slides will examine key efficacy results from VAP-14. As shown here, vapreotide was found to be superior to placebo for control of bleeding over five days, the primary endpoint.

[Slide.]

In addition, the outcomes for several secondary endpoints including control of bleeding at the time of

endoscopy, control of bleeding six hours after the start of drug infusion, and the number of blood units transfused during the first five days after the index hemorrhage were all significantly better with vapreotide.

Importantly, these findings corroborate the statistically persuasive result for the primary endpoint outcome achieved with vapreotide in this study.

[Slide.]

This Kaplan-Meier curve from VAP-14 shows the progression over time for control of bleeding with vapreotide compared to placebo. It is important to note that vapreotide's therapeutic effect manifests early, attaining a maximum within six hours of the start of the drug infusion which is then consistently maintained for the remainder of the five-day treatment period.

[Slide.]

As shown in this table, a consistent treatment effect with vapreotide for control of bleeding over five days is observed across study centers. The FDA's briefing document states that there is a center effect in VAP-14. However, a thorough analysis of the data conducted by independent experts and which was also previously discussed

with the agency, show in fact that there is no center effect in this study. As indicated, the statistical test for heterogeneity across centers was not significant.

[Slide.]

Finally, let me draw your attention to two slides that demonstrate the consistent effect produced with vapreotide in clinically important patient subgroups and also in regard to the outcomes for multiple endpoints.

First, regarding patient subgroups, here we see a trend favoring treatment with vapreotide in all subgroups.

I would like to draw your attention to the center of this slide, where it is shown that vapreotide delivers a consistent drug effect when used either with band ligation or with sclerotherapy.

[Slide.]

On to multiple endpoints. Here, we see that vapreotide again yields statistically significant outcomes for a diverse array of clinical events.

The difference in deaths at Day 42 between treatment groups, although not statistically significant, nevertheless points to a trend for improved survival with treatment with vapreotide.

Note the result on this slide for control of bleeding at the time of endoscopy. This is a particularly important finding, because it is indicative of vapreotide's native pharmacological effect that was exerted prior to the initiation of therapeutic endoscopy. This result, as will be explained by Dr. Chalasani, has relevance as it demonstrates that treatment with vapreotide can facilitate an unobstructed visual field which can be important in the conduct of the endoscopic procedure.

[Slide.]

In summary, VAP-14, our pivotal study, provides clear evidence of the efficacy of vapreotide for the treatment of EVB in conjunction with endoscopic intervention.

This is based on results that show superiority of vapreotide over placebo for control of bleeding over five days and also statistically significant outcomes for secondary endpoints demonstrating improved control of bleeding at the time of endoscopy and reduced requirement for blood transfusions during Days 1 to 5.

The publication of the VAP-14 results in the New England Journal of Medicine by Cales and collaborators is

also viewed as an important milestone. This study is recognized as a reference by the field where it has served to establish the current standard of care with early administration of vasoactive drugs for the treatment of EVB.

Accordingly, following publication of VAP-14, and also as advocated by international consensus conference guidelines and clinical investigators, it became unethical to include a placebo-control arm in therapeutic trials for EVB since the standard of care was already well established and globally well entrenched at that time.

[Slide.]

VAP-301 will now be discussed.

[Slide.]

Also recall from my introduction that VAP-301 is the most recent prospective clinical trial conducted by Debiovision. A placebo-controlled design for this study was obviously not possible for the reasons that I have just mentioned.

Moreover, a dose-response study was also not deemed to be a viable option. The design of such a study would require prior knowledge of the shape and slope of the dose-response curve with vapreotide which has not been

determined from non-clinical models of portal hypertension in early clinical studies.

More importantly, clinical investigators had already accepted the 50 microgram per hour dose level that was determined to be safe and effective on the basis of the published results from VAP-14.

The use of a potentially ineffective lower dose of vapreotide was also seen as unethical as it could potentially place patients at risk for uncontrolled bleeding.

Also, investigation of the uncertain incremental clinical benefit associated with higher doses of vapreotide was also not seen as a priority by independent clinical investigators who strongly advised that efforts should be deployed instead to conduct a more clinically relevant study with vapreotide in view of the important unmet medical need in the treatment of EVB.

Also, as indicated on this slide, a comparative study of vapreotide with an active control--that is, another vasoactive agent--could also not be done because there is no FDA-approved comparator drug in this indication. Therefore, because of these study design limitations, VAP-301

represents the best study option that could be performed.

[Slide.]

Because of the non-traditional design of VAP-301, Debiovision sought, and was granted, an SPA so that the design agreements made would not later be questioned on the study's lack of statistical rigor.

FDA's SPA process reduces to writing arguments on the design of clinical trials intended to form the basis of an efficacy claim. Per its own guidance document, FDA will not agree to an SPA for a clinical study whose data cannot form the basis of efficacy.

[Slide.]

In the course of issuing the SPA, FDA affirmatively stated that:

1. A single-arm study is acceptable.

2. That there is no need to demonstrate a statistically robust result; that is, the results of the trial would be judged on their clinical rather than statistical significance.

3. Vapreotide is appropriately designed to resolve the deficiency noted in the 2004 approvable letter. Acknowledging the statistical limitations of the VAP-301

study design, FDA agreed up front that under the circumstances we faced, that this design was appropriate and sufficient to confirm the results of VAP-14.

[Slide.]

Our understanding was that in order for VAP-301 to be considered a successful trial, the clinical efficacy signal referred to a moment ago would need to yield a rate for control of bleeding that would be consistent with the primary outcome from the pivotal study VAP-14.

With a rate of 77 percent, we believe that this objective has been met, leading us to conclude that the results of VAP-301 are indeed consistent with those of VAP-14.

[Slide.]

VAP-01 is an open-label, multi-center, historical-controlled study. VAP-301 is a contemporary study that reflects current treatment practices for EVB. This trial is also believed to be one of the larger prospective clinical trials conducted in the United States.

[Slide.]

103 patients were enrolled in VAP-301 between August 2006 and May 2008. The ITT population for this trial

encompasses 70 patients after the protocol-specified exclusion of 31 patients in which the upper GI bleeding was not related to portal hypertension and two more patients in which the endoscopy could not be performed.

[Slide.]

For this and subsequent slides that show results from VAP-301, these will be presented alongside their respective findings from VAP-14 for ease of comparison.

On this slide are the baseline and demographic characteristics for the VAP-301 ITT population, which, as we can see, are similar to those for the ITT patients in VAP-14.

[Slide.]

In VAP-14, alcohol-related disease was the predominant cause of cirrhosis. Patients from VAP-301 presented with more viral hepatitis and complex disease etiology.

[Slide.]

In both VAP-301 and VAP-14, patients had experienced similar numbers of previous bleeding episodes related to portal hypertension at the time of admission. Also, endoscopic findings indicate a similar distribution of

small and larger varices in both patient populations.

[Slide.]

The data on this slide corroborate findings from published studies that show band ligation has now largely superseded sclerotherapy as the preferred type of endoscopic treatment modality. In VAP-301, 86 percent of patients compared to 31 percent in VAP-14 were treated with band ligation.

[Slide.]

The data that will be presented on the next slides will show that the clinical efficacy in VAP-301 is consistent with the results from VAP-14. Positive outcomes for secondary endpoints favoring treatment with vapreotide were consistently demonstrated. Also, consistent results in patient subgroups between both studies show the relevance of VAP-14.

[Slide.]

In VAP-301, 77 percent of patients in the ITT population attained the primary endpoint compared to 66 percent and 50 percent of vapreotide- and placebo-treated patients, respectively, from VAP-14.

[Slide.]

Recall the Kaplan-Meier curve for control of bleeding in VAP-14. As we superimpose a similar analysis of VAP-301, we can see that the results between both study populations are indeed consistent.

[Slide.]

A consistent clinical efficacy signal with vapreotide was observed between VAP-301 and VAP-14 for control of bleeding at the time of endoscopy and control of bleeding over five days according to the stratification by the Child-Pugh class. Fewer patients with Child-Pugh Class C in both trials, compared to those with Class A or Class B, achieved the primary endpoint.

[Slide.]

As this slide illustrates, the outcome from the primary endpoint in patients that received band ligation in VAP-301 is consistent with that for the subgroup of patients from VAP-14 that were also treated with vapreotide in association with band ligation.

[Slide.]

In both VAP-301 and VAP-14, when examining patients for whom alcoholism was the sole cause of liver cirrhosis, treatment with vapreotide produced consistent

outcomes in this patient subgroup. This was also observed in those patients with both alcoholism and viral hepatitis.

[Slide.]

In conclusion, the body of evidence provided from VAP-14 and VAP-301 establishes the efficacy of vapreotide in conjunction with endoscopic intervention for the treatment of EVB. This conclusion is based on the following:

A statistically persuasive result for VAP-14 in the context of this serious and life-threatening condition for which there exists an important unmet medical need.

Confirmation of the results of VAP-14 by VAP-301.

Consistent treatment outcomes with vapreotide in VAP-301 and VAP-14 across clinically important patient subgroups which show the relevance of VAP-14 for the treatment of EVB in the United States.

[Slide.]

Dr. Kamel Besseghir will now review the vapreotide safety data. Thank you.

Safety

DR. BESSEGHIR: Thank you, Dr. Petrella. Good morning. My name is Kamel Besseghir. I am the CEO of Debiopharm, the sister-company of Debiovision Switzerland.

[Slide.]

I would like to share with you the clinical safety data for vapreotide for the EVB indication.

[Slide.]

I will discuss first the clinical exposure to vapreotide and the safety datasets, which includes studies in EVB and in other indications. Then, I will review the adverse events and serious adverse events that have been observed specifically in the esophageal variceal bleeding population, which I will call EVB population.

We will move on then to discuss specific adverse events that may represent safety signals. We will also mention two cases of significant, unintentional and intentional overdose that bring additional clinical tolerance information before summarizing the safety results.

[Slide.]

The treatment duration in the vapreotide studies ranged from five days to six months, and the daily dose that the patients were receiving varied from 0.3 mg per day to 1.5 mg per day. The exposure was highest in the oncology indications both for the doses and for the duration of exposure.

[Slide.]

These nine vapreotide trials collected detailed safety data. These trials were in EVB and other four indications. These included 728 receiving vapreotide and 536 patients receiving placebo.

In the EVB indication, there are 469 patients who received vapreotide and 347 who received placebo. The vapreotide group is larger than the control group because it includes the 103 patients from VAP-301, which did not have a placebo arm.

This point has to be kept in mind for the interpretation of the safety data, as the adverse events reported for vapreotide-treated patients are over-represented because of the absence of a control arm in 301.

[Slide.]

My presentation will now focus on safety in the patient population of interest, that is, EVB. In these EVB studies, you see that over the 42-day study period, approximately three-quarters of patients had an adverse event. About one-third had a serious adverse event. 10 percent discontinued the treatment due to adverse events, and 17 percent of patients died. These rates were all

similar to placebo.

[Slide.]

This slide lists the most common adverse events, experienced by over 5 percent of the patients in the EVB studies. The list of frequent adverse events includes pyrexia and headache as well as gastrointestinal and other disorders that are common in this population, such as upper GI hemorrhage and hepatic encephalopathy.

As is common in clinical trials, all untoward effects are recorded as adverse event regardless of relationship to the underlying disease. Note that infections and infestations include all types of infections, especially those appearing despite preventive antibiotherapy. The vapreotide and placebo rates, as you see, are very similar.

[Slide.]

Now, I will review the adverse events that are commonly reported in the somatostatin drug class. For the metabolic, GI and hepatobiliary disorders shown on this slide, you will note that these events were experienced by similar percentages of vapreotide and placebo patients.

Within cardiac events, we noted that while

bradycardia was reported for one patient in the placebo arm, which represent 0.3 percent rounded here to one of the patients. In the vapreotide arm, it was reported for five percent, which represent 1 percent of patients. We will discuss the bradycardia adverse event in a moment.

[Slide.]

In terms of adverse events classified as serious events, the incidence of these events were comparable in the vapreotide and placebo groups. Not surprisingly, GI and hepatobiliary disorders were the most common observed adverse events.

[Slide.]

We had three cases of accidental overdose, all occurring in the phase study VAP-02. Two were with vapreotide. One patient received the entire 5-day dose over six hours. As you can see, this patient experienced minor transient symptoms. In both cases, the patients recovered without sequelae. The third overdose case in that study involved placebo, and this overdose case was one of the major reasons for us to stop the study VAP-02.

[Slide.]

Let us now turn to specific adverse events that

have been identified as possible signals. The first is thrombocytopenia. Four of the EVB studies included measurements of baseline and end-of-treatment platelet counts. There was a higher number of thrombocytopenia in the vapreotide group compared to placebo in the placebo-controlled EVB series. A comparable rate for vapreotide was observed in VAP-301.

To explore whether this may be a drug-related effect, we looked at the rate of thrombocytopenia in a non-EVB placebo-controlled study, the study in which vapreotide was tested in the prevention of complications of pancreatic surgery. Here, a similar number of cases were observed with vapreotide and placebo.

[Slide.]

The data are presented graphically here for platelet counts in EVB studies and in pancreatic surgery. The shaded area indicates the normal range of platelets. As already known, cirrhotic patients represented here, present in general with thrombocytopenia as discussed earlier by Professor Groszmann.

In the controlled studies, the same slight decrease in thrombocytes was observed in both placebo and

vapreotide arms. The patients included into the pancreatic surgery had normal thrombocytes at entry that actually tended to increase with time during the seven days of treatment both for vapreotide and placebo-treated patients.

This does suggest that underlying disease rather than vapreotide is the cause of thrombocytopenia. The pancreatic surgery study involved a higher exposure to vapreotide; that is, the mean dosage in patients was 1.2 mg/day for seven days as compared to the five days in the EVB studies.

When we look at the actual change in platelet counts in these studies, both the vapreotide and the placebo arms showed a small decrease in mean platelet counts compared to baseline values. One potential reason for the observed decrease could be the fluid resuscitation that occurs during the initial treatment of patients with variceal bleeding.

[Slide.]

Now, let's have a look at the cases that occurred during drug infusion the first five days. Five occurred in vapreotide in the study VAP-06. In that study, there was no baseline measurement and evaluation of platelets, meaning

that these cases may not have met the definition of thrombocytopenia, and all of these occurred in one single site. None of these events, by the way, led to drug discontinuation and none were serious.

[Slide.]

The remaining case that occurred during drug infusion occurred in VAP-301 in a patient who had at baseline renal failure, pneumonia, urinary infection and borderline low platelets. The patient completed the 5-day infusion.

[Slide.]

Another event that was highlighted is disseminated intravascular coagulation. We had one case in the placebo-controlled studies reported during a re-hospitalization during the follow-up period, and we had two cases in VAP-301, of which one occurred during the infusion of the study drug.

[Slide.]

As with thrombocytopenia, disseminated intravascular coagulation is known to occur in about 30 percent of patients with advanced liver disease and overt or latent DIC has been reported in more than 45 percent of

patients with variceal bleeding.

Presented here are the details of the patient in 301 who presented DIC during vapreotide infusion. As you see, the patient presented both liver and renal failure at entry and also coagulopathy at entry. His status worsened with additional sepsis, and this ending by death.

[Slide.]

If we look at renal failure, this occurred in three vapreotide-treated patients and four placebo patients in the placebo-controlled trials. There were 10 reports in the VAP-301 study, five being observed during vapreotide infusion. We will analyze these reports in the next slides.

[Slide.]

The details of the patients who experienced renal failure during the infusion of study drug are summarized here. As you can see, four out of five patients entered into the study with elevated creatinine or baseline renal failure. Two recovered after vapreotide infusion. One died at Day 5 in renal and liver failure and DIC, and one at Day 28 of respiratory failure. The last patient presented transient renal insufficiency confounded with spontaneous bacterial peritonitis, and that patient recovered at Day 5.

[Slide.]

Let's look at the cases of bradycardia. The numbers of this adverse event was the same in the placebo-controlled study, had one case in each arm. When we look at the specific vapreotide cases, one patient developed, in 301, mild bradycardia during infusion out of the three patients.

Vapreotide was not discontinued, the patient fully recovered without treatment. Two other moderate and one severe case were confounded with other nondrug-related potential causes. The FDA has categorized in its document another patient as having bradycardia. In fact, that bradycardia event was not precipitating cardiac arrest in this patient with multi-organ failure. This case will be discussed later in the presentation.

[Slide.]

Now, let's review the deaths that occurred in the EVB studies. In the placebo-controlled studies, and counting all together 301--that is the non-controlled study and the controlled studies--we observed 15 percent deaths in the vapreotide group and 16 percent in the placebo group.

The higher death rate is observed in the single-

arm 301 study, and although this mortality rate is higher than in other studies, it remains within the range of 18 to 26 percent reported in other recent EVB trials.

When you look at when the deaths occurred in these studies, you can see that deaths during the 5-day treatment period occurred at similar rates in 301 versus the other studies. However, there was a higher death rate in Days 6 to 42 in VAP-301.

[Slide.]

If you look at the cause of death during the treatment period, Study Days 1 to 5, you can see that the causes of death in VAP-301 are similar to those of the placebo-controlled studies except for the higher rate of infection/multi-organ failure--that, is 3.9 percent rounded to 4.0, versus 0 percent. These deaths due to infection or multi-organ failure were considered related to the underlying disease and can be discussed individually if considered of interest.

[Slide.]

The cause of death after the drug-treatment period, Study Days 6 to 42, shows the incidence of deaths due to infection and multi-organ failure were again higher

in VAP-301 compared to the placebo-controlled studies, as was worsening of liver disease.

[Slide.]

In FDA's briefing package, some of the causes of death were attributed differently than the investigators did. The cases where there are discrepancies outlined on this slide. Note that the three cases that the FDA has attributed to bradycardia occurred as pre-terminal clinical events or as part of the patient's cardiac arrest.

The case labeled thrombocytopenia by the FDA was a patient who had continued uncontrolled hemorrhage, required vasopressors to support blood pressure, had renal failure with a serum creatinine of 6.2 mg/dL, required ventilatory support, had ventricular tachycardia and bacterial sepsis, and these all prior to enrollment.

The case with pulmonary embolism involved a patient with a left pleural effusion that abruptly desaturated while receiving oxygen. The treating physicians considered mucus plugging versus pulmonary embolism, but no diagnostic studies or postmortem examinations were performed to make that diagnosis.

The final case was admitted for thrombocytopenia,

hypotension, and coagulopathy. After enrollment the patient experienced hemodynamic instability requiring vasopressors. He developed then severe lactic acidosis and septic shock. His plasma ammonia was 419 micromole/liter. Support was withdrawn and the patient expired. The treating physician suspected severe systemic inflammatory reaction. However, diagnostic criteria for this can be discussed.

[Slide.]

Supplementing the safety data from the EVB trials are data from vapreotide studies in other indications, which are shown here. These studies included patients with pancreatic cancer, acromegaly, carcinoid tumors, and Crohn's disease. As you can see, in the larger database, adverse events, serious adverse events, and deaths are similar in the vapreotide and placebo groups.

[Slide.]

In summary, the safety profile of vapreotide has been established in the indicated population through the four placebo-controlled trials plus VAP-301, and is supported by studies in other indications.

In EVB studies, the profile of adverse events and serious adverse events are similar to placebo. We looked

more closely at the serious adverse events that could be considered safety signals--that is, those serious adverse events, although in small absolute numbers, that were observed more frequently with vapreotide.

They were evaluated by taking into account both the critical medical condition and the confounding polymedications of the patients, and also by analyzing the data obtained in other indications in which vapreotide was evaluated.

This analysis strongly suggests that none of the possible safety signals could be attributed to vapreotide, although it is not possible to completely rule out the causality of vapreotide in some of the adverse events discussed. Overall, vapreotide has clearly a favorable safety profile especially in view of this medical indication.

Now, I will turn to Dr. Chalasani who will discuss the benefit-risk assessment.

Benefit-Risk

DR. CHALASANI: Good morning, Dr. Chang, members of the Advisory Committee, members of the agency, ladies and gentlemen. I am a clinician. I take care of patients with

cirrhosis and am also a clinical investigator. I have participated in many studies in portal hypertension for the past 15 years of so.

In the spirit of full disclosure, I participated as an investigator in VAP-301 study and currently, I am also serving as an external consultant to Debiovision.

[Slide.]

As was pointed out by Dr. Groszmann, variceal bleeding is dramatic and quite catastrophic given when it happens. Over the last two decades, there have been numerous improvements, the survival has improved, but still it remains around 20 to 25 percent.

Patients with cirrhosis are quite fragile and, when they present with variceal bleeding, it remains quite critical to control the bleeding without which our patients can deteriorate quite rapidly into multi-organ failure and high fatality rate.

[Slide.]

There have been many practice guidelines including the one that I quoted here from 2007. Both the American Association of Study for Liver Diseases, as well as the College of Gastroenterology, two large organizations

strongly endorse early pharmacological therapy when patients with suspected variceal bleeding present to the emergency room, and the treatment should be continued for 3 to 5 days in addition to the evidence Level A.

The clinical rationale is before endoscopy, which is effective, it improves control of bleeding, and it certainly helps endoscopists in performing their procedure offering treatment, and also, as was shown, reduces the number of blood transfusions.

One of the authors of these practice guidelines, Dr. Grace, is in the sponsor box if any specific questions about the Guidelines were to arise.

[Slide.]

As was pointed out by the sponsor, the VAP-14 study publication appears to have an impact in how we take care of patients with variceal bleeding. Clearly, more clinicians are using vasoactive drugs and the regimen that is used currently in clinical practice, which is 50-microgram bolus, when patients hit the emergency room, and continuing the infusion at 50-micrograms per hour is what was published in the VAP-14 study.

So, clinicians have accepted that this is the

right way to treat patients with variceal bleeding, but there is no approved medication for treating variceal bleeding, therefore they resort to the off-label use of octreotide, which is very well entrenched. As Dr. Groszmann has pointed out, more than 90 percent of the patients, our clinicians are using octreotide currently.

[Slide.]

If you wonder, the control of bleeding over the first five days is it a valid surrogate, the answer is yes. When a patient with variceal bleeding presents, as I said earlier, control of bleeding is very critical.

If you achieve hemodynamic stability, you lower the risk of deterioration in terms of multi-organ failure and death, as well as liver decompensation.

The first five days after a patient presents with variceal bleeding is the interval that has the highest risk of re-bleeding. That may explain why the duration of vasoactive drugs is up to 3 to 5 days. Moreover, the early control, control of bleeding for first five days generally reflects the survival benefit at Day 42.

Day 42 is the typical way you assess the mortality in acute variceal bleeding, not only at five days, but any

other interval you look at, for example, bleeding control at endoscopy, bleeding control at 24 hours, 48 hours, generally reflects a survival benefit at Day 42.

[Slide.]

As was pointed out before, lack of an approved vasoactive drug to treat acute variceal bleeding is an important unmet clinical need.

[Slide.]

It is highly desirable to have a product that is approved, which has been proven safe and effective and has been investigated for an intended indication. It offers a comprehensive labeling to provide standardized and accurate guidance for patient selection, dosing, and administration. Moreover, it offers structured ongoing safety surveillance if there are any safety signals.

[Slide.]

What are the benefits of vapreotide for esophageal variceal bleeding? We have heard that it has better control of bleeding over first five days. It has higher control of bleeding at the time of endoscopy. As an endoscopist, I find this to be an important benefit.

Many on the panel are clinical

gastroenterologists, and you realize over the course of the last decade the number of times we go to do bleeders in the night, at nighttime has significantly gone down, at least that is in part due to the vasoactive drugs being given in the emergency room prior to we get called in.

Vapreotide reduces the number of transfusions needed. More importantly, it has been investigated and has been scrutinized for the intended indication.

It can be administered easily to patients with suspected variceal bleeding. In the emergency rooms, it doesn't have to be tertiary care. It can be a community hospital. It doesn't require any special monitoring, or it can be given on the floors, as well, unlike the earlier vasopressor, which requires intensive care units and close monitoring.

[Slide.]

If you are wondering, the VAP-14 findings, are they clinically significant, I find them to be clinically significant. For example, the absolute difference of 12 percent of active bleeding at the time of endoscopy is a clinically important benefit.

Similarly, 16 percent higher control over first

five days is also found to be clinically significant. The transfusion requirement was lower in VAP-14 almost by a unit, which is not a trivial benefit, which is certainly in my opinion, an important benefit.

[Slide.]

The vapreotide has a favorable risk profile. As was shown, it is safe in both cirrhotic and non-cirrhotic patients. It is well tolerated. Adverse events and serious adverse events are comparable to placebo-administered patients.

The agency in this document has highlighted thrombocytopenia, renal dysfunction, and DIC as possibly related to vapreotide. As somebody who has taken care of a lot of patients with cirrhosis, I would like to point out that these events are quite common in patients with decompensated cirrhosis whether they are hospitalized patients admitted for decompensated cirrhosis, whether they are hospitalized for variceal bleeding, whether or not they receive any vasoactive compounds.

This is the manifestation of deteriorating liver condition and also concomitant complications.

I would like to point out the agency has

attributed some of the deaths to these discrete events. When patients with variceal bleeding do not respond to your treatment, continue to bleed, they really are very sick and they have multi-organ failure, they are heavily transfused, they receive a lot of different concomitant medications. It has been my experience that attributing cause of death to one event is quite difficult.

For example, VAP-301 study, subject 604, it was raised that the cause of death may be thrombocytopenia, however, this patient was recruited from my site. I was the principal investigator. This patient presented with hypotension, renal failure, acidosis, really was very sick, and deteriorated. Along the way he developed thrombocytopenia, which is not uncommon.

I find it difficult to attribute the cause of death of that patient to thrombocytopenia. I believe it is the multi-organ failure and uncontrolled hemorrhage was more accurate attribution.

[Slide.]

The 6-week mortality in VAP-301 was 26 percent. It was numerically higher than was noted in VAP-14, however, contemporary cohort showed that 25 to 26 percent, 6-week

mortality is very relevant and accepted range for patients with acute variceal bleeding.

This is an abstract that was just presented at the EASL meeting just within the last month or two from Barcelona where they collected 210 patients with variceal bleeding in a prospective fashion, the 6-week mortality was identical to that of what was noted in VAP-301.

All these patients also received vasoactive medications.

[Slide.]

To summarize, lack of an approved vasoactive drug in this country is an important clinical unmet need when we take care of patients with variceal bleeding.

Because of proven efficacy, lack of serious side effects and excellent tolerability, moreover recognizing how difficult it is to conduct clinical trials in patients with acute variceal bleeding, I believe vapreotide has favorable benefit to risk ratio in the treatment of acute variceal bleeding. Thank you.

[Slide.]

Now, I invite Dr. Petrella to make concluding remarks.

Conclusions

[Slide.]

DR. PETRELLA: Thank you, Dr. Chalasani, for that comprehensive review of the vapreotide benefit-risk assessment.

[Slide.]

Together with our experts, we have presented information today that provides clinical perspective in regard to the treatment of EVB that is relevant for Sanvar. In summary, we have shown that:

EVB is a serious and life-threatening medical emergency; that practice guidelines recommend treatment with vasoactive drugs, typically somatostatin analogs, prior to and following endoscopic therapy for up to five days; that there exists an important unmet medical need for this indication in the United States.

[Slide.]

In conclusion, we have demonstrated that the body of evidence from VAP-14 and VAP-301 establishes the efficacy of vapreotide for the treatment of EVB.

Furthermore, the safety data sets analyzed demonstrate vapreotide's favorable safety profile.

The risk-benefit assessment, as shown by Dr. Chalasani, is favorable for vapreotide in patients with EVB.

The vapreotide formulation provides for convenient storage, preparation, and administration to patients with EVB. Collectively, we believe that these benefits warrant approval of vapreotide by FDA for the proposed indication.

Thank you.

Committee Questions to the Sponsor

DR. CHANG: Thank you. Now, we are going to open it up for Committee members. Do you have questions for the sponsor?

I have one question. I was looking at some of the data that you showed, that in 301, that the mean transfusion number of units was 2.6 versus the VAP-14 where with VAP it was 2.0 and then placebo was 2.8.

I was wondering if that was the higher number of transfusions in the 301 was based on a little bit different criteria, at least I got that from the briefing document, that in the first three studies, they were allowed to give transfusions that were clinically indicated, but I think in the latter two, they had to keep the hematocrit at 27 percent.

Was that the reason why there was a little bit higher transfusion units used in the 301 study, or is there a different reason?

DR. PETRELLA: In fact, as we presented, the VAP-06 study, the uninterpretable study, was the only one in which the hematocrit was actually part of the primary endpoint. In the other trials, the hematocrit was provided for guidance for transfusion, and the difference in the result we believe, as you know, that endpoint was a secondary outcome, not necessarily powered to show large differences.

DR. CHANG: But was the hematocrit in the patients in the 301 different than the patients in the 14?

DR. PETRELLA: As we presented the baseline medical conditions, hematocrit and other characteristics were very comparable between the two patient populations.

DR. CHANG: And then during the first five days?

DR. PETRELLA: We don't have that data. We have data at time of admission, which shows the comparability of the populations.

DR. CHANG: Yes, I saw that.

Dr. Silberg.

DR. SILBERG: Yes. I would like to know more about the discussions you had with the FDA regarding 301 prior to performing the study. I have two questions.

One, was there a discussion on advances in endoscopic therapy prior to going into that study?

The second one, what historical controls were to be used to do a comparison after the study was completed?

DR. PETRELLA: With respect to your first question, I will ask Ms. Laura King from our Regulatory Affairs Department to comment.

With regard to the second point, the historical controls were, as we understand, was the VAP-14 study published in the New England Journal comparing the clinical efficacy signal from VAP-301 to the result for the primary outcome in the vapreotide arm of VAP-14.

Laura, would you perhaps comment on the first question?

MS. KING: Laura King, Director of Regulatory Affairs, Debiovision.

There were some discussions about different forms of sclerotherapy, but no discussion about how that might have changed over time, and I would just like to confirm

that yes, it was the vapreotide arm of VAP-14 that was considered historical control.

It was also suggested to look at the control of octreotide in the literature.

Thank you.

DR. CHANG: Dr. Fogel.

DR. FOGEL: Thank you. I have a question related to the control of bleeding at the time of endoscopy, and then with a follow-up question.

In the VAP-14, the control of bleeding at the time of endoscopy was 50 percent in the placebo group, 64 percent in the VAP group, and in Study 301, it was 74 percent. Many patients at the time of endoscopy have a number of different endoscopic findings. In addition to the varices, you often see portal gastropathy.

What criteria did you use to determine that the actual bleeding was variceal, and not another cause?

Then, I have a second question, which is in the 301 study, the control of hemorrhage at five days was 77 percent, suggesting that there is no incremental benefit of VAP if you continued the infusion, that the banding ligation appeared to be having a major effect on prevention of re-

bleeding.

I wonder if you could comment on that also. Thank you.

DR. PETRELLA: Dr. Chalasani, perhaps would you like to comment on the panelist's questions in regard to the endoscopic issues?

DR. CHALASANI: Thank you.

The source of bleeding at the time of endoscopy was interpreted by the endoscopist. When it is stated lack of active bleeding, to a large part it implies lack of actively bleeding varices because bleeding from other source were excluded from ITT population.

So, for example, oozing was not considered as active bleeding. It has to be more than at least how we interpreted when we did the endoscopies on these patients.

If you could repeat the second question.

DR. FOGEL: In the 301 study, the control of bleeding bleeding at the time of endoscopy was 74 percent, and the control of hemorrhage at five days was 77 percent. Could you comment on that?

DR. CHALASANI: I think that reflects the differences in definitions. In the control of bleeding at

endoscopy is a discrete definition, whereas, control of bleeding over five days is a composite that indicated--also included survival and blood pressure, transfusion requirement.

DR. FOGEL: Let me be more specific. It suggests that there is no incremental benefit by continuing the infusion for five days.

DR. PETRELLA: If I may, as far as continuing the infusion, I think it is important to remember the conditions, the experimental conditions, in which vapreotide was assessed, and if I could call the slide, please. If I could have the Kaplan-Meier curve back on, please. Thank you.

As the slide is coming up, we showed that the effect of vapreotide manifests early, and when we superimposed the data from VAP-301, we see very consistent results between 14 and 301.

The goal of the study was to investigate a 5-day infusion, so as far as the data we can speak to, we only have that defined by the experimental conditions of our trials.

Dr. Grace, would you like to comment further,

please?

DR. GRACE: Good morning. My name is Norman Grace. I am Director of Clinical Hepatology at the Brigham and Women's Hospital in Boston, Harvard Medical School.

I think it is important to really explain why banding has replaced sclerotherapy as the treatment of choice. If you look at a meta-analysis of the studies looking at the acute control of bleeding, banding and sclerotherapy have comparable efficacy.

The advantage of banding is that there is less re-bleeding particularly at the 24, 48, 72 hour periods. There is a lower transfusion requirement, and most importantly, there are much fewer complications. You do not have the systemic complications that you see with sclerotherapy.

So, banding has really replaced sclerotherapy as the treatment of choice, and I think if we can get that slide up, you can see that.

I think that the second point is that there are, not shown today, but there are a number of studies and a meta-analysis by Roberto De Franchis is showing that vasoactive drugs when given as single therapy are comparable to endoscopic therapy in the control of acute bleeding.

That is both for somatostatin and for octreotide.

[Slide.]

You can see in this slide there is an incremental benefit of adding combination therapy; that is, you go with band ligation--you go from 60 percent control in the placebo arm to 77 percent control with combination therapy. This is better than the control that you see with sclerotherapy based on the difference in the banding technique. But both studies showed that there is an incremental benefit to endoscopic therapy.

DR. CHANG: Dr. Neaton.

DR. NEATON: I would like to kind of follow up on a couple of the questions about 301. Can you--precisely how did you determine that you needed, say, 70 or whatever it was patients in 301? What was the specific comparison and kind of question that was formulated there?

A couple of related questions that maybe you can clarify. There seems to be a much greater number of exclusions from the intent-to-treat population in 301 versus the earlier study, roughly two to three times more.

Kind of related to the last comment, the bleeding primary endpoint differences are comparable, but it seems

like in the presence of ligation, there are a lot more safety issues.

I wonder if there is anything that you can help me with there in terms of is there a concern with the use of this drug in the presence of ligation in terms of the higher mortality and the other safety issues that we don't have a control for, as you indicated, that we should be concerned about.

DR. PETRELLA: First, I would like to address your point in regard to the control rate used to assess success in 301. As indicated in the SPA document, accepted with the FDA, the objective of the trial was to demonstrate a clinical efficacy signal that was stated would be valued for clinical relevance.

We interpreted that to mean a rate of control of bleeding in the vicinity of that observed in the pivotal VAP-14 study since the historical control for the trial was the vapreotide arm from 14.

DR. NEATON: When you are using the term "historical control" here, you are not really using placebo controls from the other studies. You are basically saying you wanted to establish that the primary endpoint efficacy,

the success rate, was comparable to the earlier study.

DR. PETRELLA: That is correct. The goal of the trial was to show, it was to confirm and show consistency with the result of the vapreotide VAP-14 study.

DR. NEATON: Can you comment on the exclusions?

DR. PETRELLA: Can you be more specific in regard to the exclusions that you are referring to?

DR. NEATON: You put up a couple charts. It looked like about 30 percent of the patients were excluded from the intent-to-treat analysis in 301. That was closer to 10 percent I believe in the earlier study.

DR. PETRELLA: Yes. Although the numbers might be somewhat different. In fact, it is important to look at the reasons why the patients were excluded. Primary cause of exclusion from both VAP-14 and VAP-301 was failure to adhere to the time windows that we discussed earlier in the protocol, so less than 24 hours, for instance, between the bleed and the time of initiation of therapy, or less than 6 hours between admission to the hospital and start of drug.

So those were reasons that were, as was indicated by colleagues earlier, in some instances patients have to be transferred from a hospital and sometimes that is not

feasible.

In addition, in the VAP-301 study, many of the patients that were excluded have already been put, as per practice guidelines, on octreotide, so they were ineligible for the study. This is why we have those exclusions. Maybe I could just refer to the slide here.

[Slide.]

So, out of the 103 patients that we showed earlier that were enrolled at the 15 centers, there were 31 patients which were excluded at the time of diagnostic endoscopy. But I think you are probably referring to patients before enrollment into the study?

DR. NEATON: I am referring to the 31.

DR. PETRELLA: Oh, the 31; sorry. Perhaps I misunderstood your question. So, those patients were the patients which, at the time of diagnostic endoscopy, the bleeding, the source of bleeding was found not to be related to portal hypertension.

As you know, the protocols were designed specifically to investigate bleeding due to portal hypertension, so esophageal varices, gastroesophageal varices. Those patients, for instance, had bleeding from

gastric ulcers, causes not related to portal hypertension.

DR. NEATON: This seems to be much higher than the earlier study. This all kind of goes toward my concern that you are comparing apples and oranges here with this study versus the earlier study.

DR. PETRELLA: Actually, the numbers may be slightly different, but I think what is important to remember here is that in all the trials, VAP-14, the pivotal study, and VAP-301, we are assessing people with esophageal variceal bleeding, bleeding due to portal hypertension, and the baseline characteristics, medical conditions are very comparable for both patients. So what we have shown is that vapreotide shows a consistent result in those patients that do have bleeding due to portal hypertension.

DR. NEATON: I am sorry, I want to finish my last point. I look at this and it appears that you are similar with regard to the primary endpoint, but you are worse with regard to mortality and a number of other adverse events with the ligation procedure.

Is there any reason to be concerned that this drug and the use of this drug in the presence of a different procedure here may have safety concerns that you did not see

in your placebo-controlled trials?

DR. PETRELLA: I will ask Dr. Besseghir to comment on that. Dr. Besseghir.

DR. BESSEGHIR: Yes. Maybe I show back again CS-19, please.

[Slide.]

I show again the slide I showed you in my presentation. You see that if we look at deaths in the-- compare the 301 to the placebo-controlled studies, during drug infusion, we have the same rate of deaths that were observed in placebo-controlled studies. I am talking about 7 percent between the two arms and 9 percent for 301.

The mortality that we observed was observed during the five weeks following the end of the drug infusion. First, the mortality is comparable to what has been published recently, so we are will within the range of the mortality which is observed in that indication and, second, could I have 109, please.

DR. NEATON: Why is the mortality higher given the earlier comment that with this ligation procedure, there are fewer complications and better kind of mortality outcomes? It almost would seem like it would go the other way around.

DR. BESSEGHIR: This, I want to give for you to have an idea, because we don't have a control arm in 301, so it's difficult to make an interpretation.

[Slide.]

So the mortality of the six patients that we observed can partly at least be explained by the fact that there were some patients who had a comorbidity, HIV-positive, who died. You know, these are complex patients. But we can't draw any conclusion, of course, because there is no control arm.

DR. PETRELLA: Dr. Grace, would you like to comment further on this, please?

DR. GRACE: For those people who may not know exactly how banding is done, let me just run through it very quickly. You pass an endoscope and you see the varices, and through the endoscope you put rubber bands on the varix like you used to do for hemorrhoids.

The bands constrict the varix and after a few days fall off. It's a local procedure, there are no systemic manifestations of banding as there is with sclerotherapy where you are injecting agents that then can get absorbed systemically.

There have been about 14 or 15 trials now looking at banding in prospective controlled trials, and the complication rate is very low. It's local. There are no systemic manifestations.

DR. CHANG: Dr. Furberg.

DR. FURBERG: I think we all recognize that EVB is a serious condition with very high mortality. I have to say that the trial results are very disappointing. There is no effect on mortality in the trial, in fact, in 301, there is a 10 percent higher rate.

There is no effect on hospitalizations, length of hospitalization, so I don't see any health benefits in the trials. So this is hardly a breakthrough from a public health point of view.

I realize that there is a reduction in controlling bleeding. But I am puzzled. If controlling bleeding is so important, why is it there is no effect on mortality? In fact, the reduction is too small; it's 16 percent. So it either has no overall health benefit, or any benefit conveyed by that 16 percent reduction in bleeding is offset by harmful effects of the drug because the net effect is zero.

So, I am not impressed by the findings and I wonder about the arguments that were put forward that there were ethical reasons not to use placebo. If you have no health benefits, why can't you use the placebo? That is puzzling to me. Thank you.

DR. PETRELLA: Dr. Furberg, I will ask Dr. Groszmann to comment. Before, I think I just would like for the record to mention that the goal of all mortality was not an objective of any of any of the EVB trials investigated.

In light of the severity and high mortality rate, in the pathology, the people who develop the endpoints for these trials recognize that mortality would be a very challenging endpoint to demonstrate.

As far as to your second point where you commented on increased mortality in the VAP-301 study, I believe that Dr. Besseghir indicated that, for reasons related to comorbidities, mortality in the interval between 6 and 42 days may be explained by that. But we can provide additional context.

DR. FURBERG: My point is that this is a serious condition. From public health point of view, you want to have an effect on the patient's health, either make them

live longer or have fewer hospitalizations or be discharged earlier. You show nothing.

You have only shown that--to me it's a surrogate effect you have shown. You have reduced bleeding, and the bleeding is not translated into any health benefit. I am very underimpressed.

DR. PETRELLA: Perhaps, before Dr. Groszmann addresses this further, I could share with the group today some data. As you can see from this analysis, looking at the relationship between control of bleeding at five days, so the primary endpoint of all the studies addressed in the trials, and the outcome, mortality or survival outcome at 42 days or 6 weeks, we see that patients who achieve control of bleeding at five days, those people, there is a very highly statistically significant correlation between that endpoint at five days and survival at 42 days.

This is data actually extracted from VAP-14, our pivotal study, and it has also been shown in published studies that there is improved survival at Day 42 when you achieve the primary endpoint control. So, as we heard, the endpoint is very clinically relevant and is associated with outcome.

DR. FURBERG: You do your basic, and I am pointing to my second explanation; if controlling bleeding is so important, why don't you see it, overall the reduction in mortality? It means that the drug must have some harmful effect, as well.

DR. PETRELLA: We do not believe that, and I will ask --

DR. FURBERG: Well, but why is the net effect zero?

DR. PETRELLA: Dr. Groszmann, would you like to comment further on Dr. Furberg's comment?

DR. GROSZMANN: I was going to ask to see the slide. The slide is very representative. But, in this area, there have been a large number of studies. Unfortunately, none of the studies show increase in survival of 42 days. These are very sick patients and unfortunately, the most we can do is try to control the bleeding while the patient is actively bleeding.

In my mind, I am sure, and my colleagues that are sitting here, controlling bleeding while the patient is in intensive-care unit is absolutely necessary, and is a benefit for health-care in general. You don't want a

patient to be bleeding to death.

So, at the same time, control of bleeding has been helpful because it is demonstrated in this study and other previous studies, there is a relationship between controlling bleeding and survival.

These are patients, as I indicated in my first slide, that have multi-systemic failure. So the causes of death that happen from Day 5 to 42 are mixed. You know, patients are infected. They go into liver failure. They have hepatorenal syndrome.

So, it is very, very difficult to increase survival in these patients. The most you can do is to try to control bleeding because, as it has been shown, if you control bleeding during those days, you increase the survival.

DR. FURBERG: It is not right that you can improve survival. I was reading in some document mortality was around 40 percent some years ago. It is now down to 20 percent. Yes, you can cut it in half with the advances you have made. So I don't buy this argument that you can't affect mortality.

DR. PETRELLA: Dr. Grace.

DR. GRACE: I think that is a very important point, that the mortality has decreased. When I first started giving talks in this area, the mortality was 35 to 40 percent. It is now, based on some studies that were recently published from Europe, 15 to 20 percent. It is a composite, a complicated situation we are dealing with.

The only individual intervention that has resulted in a short-term survival is the use of antibiotics, which are now recommended as a treatment for all variceal bleeders. However, what has happened in the interval between the 40 percent and the 20 percent mortality rates is several things.

It is the use of endoscopic therapy, the use of vasoactive drugs, and better understanding of resuscitation and transfusion requirements. So, I think it is not one single thing that has resulted in the increase or the benefit in improved mortality, but a whole host of things that we have done in the last 20 years.

I should point out that, in that group of things that we have been doing, is the consistent use of vasoactive drugs for acute variceal bleeding.

DR. CHANG: Dr. Kane.

DR. KANE: Thank you. My question is about Slide CS-6, looking at the most common adverse events. Pyrexia was number one, and then upper GI hemorrhage was number two with equal percentages in the treated patients versus placebo.

So, if you have equal numbers of upper GI hemorrhage in the treatment and in the placebo groups, either your treatment doesn't work, because that number should be lower, I would think, or else you have many patients in the studies who have multiple causes of GI bleed at the time of endoscopy.

So, can you just clarify or comment on that for me about what was found at endoscopy? Obviously, they had to have bleeding varices to be treated in the ITT population. What do we know about other sources for their bleeding, so that this isn't just another negative data point towards the therapy not working?

DR. PETRELLA: Dr. Besseghir, would you kindly address the panelist's question?

DR. BESSEGHIR: Yes, thank you for the question.

We are analyzing here the safety population, which includes any patient who received at least one dose of

vapreotide, and we include here the patients with hemorrhage known due to portal hypertension.

So, the efficacy data are those represented by Dr. Petrella here representing the adverse events in the larger population, which is different from the ITT population.

DR. CHANG: Dr. Epstein.

DR. EPSTEIN: Yes, I have several questions for the sponsor.

Number one, can you show the effect of octreotide on portal venous pressure?

DR. PETRELLA: We have not investigated that in our clinical trials.

DR. EPSTEIN: Okay. Can you show a graph or a chart across all of your patients on platelet counts by day?

DR. PETRELLA: Dr. Groszmann would like to make a comment on portal venous pressure, and then Dr. Besseghir will address the point on platelets.

DR. GROSZMANN: The effect of octreotide in patients has not been studied in portal pressure. The measurement of portal pressure in patients is using the hepatovenous pressure gradient. It is an indirect technique.

There are studies showing that somatostatin analog has a mild effect on portal pressure. However, there are several studies with vapreotide in experimental models of cirrhosis showing that the 8 microgram/kilogram dose produces a mild reduction in portal pressure.

But more important perhaps is what I tried to show, and I don't know if I was clear, is the effect on the collateral circulation, the reduction in collateral flow that is measured in that splenorenal shunt that you can ever rate the vessels that fit the varices.

DR. EPSTEIN: Do you have data to show that?

DR. GROSZMANN: I show actually how the technique is, but this is described in two papers. I thought that, in one of my--yes; go ahead.

DR. PETRELLA: Perhaps while we are finding that data for Dr. Epstein, Dr. Besseghir, would you like to comment on the platelet data?

DR. BESSEGHIR: Yes.

[Slide.]

Again, we have not measured platelets on a daily basis. In our protocols, we have measured platelets at baseline and at Day 5, because at the moment when we were

writing the protocol, there were no signs that thrombocytopenia might be eventually a signal.

So, as you see here, we have, on the clear bars, the baseline values of platelets, and the dark bars, the blue dark bars, are the platelets reviews at Day 5, at the end of the vapreotide infusion. You see that, if anything, there is a slight decrease, but it is observed both in the placebo arm and the vapreotide arm.

DR. EPSTEIN: I find that difficult that platelet counts in bleeding patients were not measured throughout the 5-day infusion, being a very standard hematologic parameter that I would think one would want to watch.

But, in the absence of that, then, can you review in detail the serious adverse events in VAP-06?

DR. BESSEGHIR: Yes; we have that. Maybe, Dr. Groszmann, while we look for the slide, maybe you can answer that.

DR. PETRELLA: I believe Dr. Groszmann has some information on the earlier question.

DR. GROSZMANN: Can I see the slide, please.

[Slide.]

This is the slide that I was referring to. These

drugs work by reducing the inflow into the portal system by producing splanchnic arterial vasoconstriction and also by reducing the blood flow in the collaterals.

This is measured by applying the flowmeter to this collateral, this splenorenal collateral. There are two studies, one with vapreotide and one with octreotide that we performed showing that the reduction in this collateral is around 25 percent.

I'ts okay? Did this answer your question?

DR. EPSTEIN: That is the data, yes. Okay.

DR. CHANG: Dr. Smith.

DR. SMITH: I have several questions. One is the difference in the mortality rate between 301 and VAP-14 was 25 percent versus I think it was 14 percent or 15 percent. Wouldn't that indicate that you are really talking about two different patient populations with the 301 population being a patient population that is much more ill and that the comparison between 301 and VAP-14 is not valid? That is one question.

The other question I have is the issue about the placebo arm or lack of placebo arm in 301, and that is that since 90 percent of physicians in the United States use

octreotide in this setting by your own presentation, why in the world didn't you do a study comparing octreotide to Sanvar, which would seem to me like a reasonable thing to do, although it might not be practical because of the number of patients. But it would be a reasonable thing to do and would be an appropriate scientific study in this setting?

The third question is really about DIC, and that is that, being a hematologist, I see a lot of patients with DIC with end-stage liver disease, but what definition do you use to diagnose DIC? Are you talking about chemical DIC, you know, measurement of laboratory tests, or are you talking about people that have clinical DIC with over diffuse bleeding, et cetera, et cetera?

DR. PETRELLA: I will address each of the questions.

For the last point on DIC, I will refer to my colleagues who presented the safety data.

In terms of your point regarding the comparability of the populations, it is essential to remember that, in both trials, the goal was to measure the control of bleeding at five days, and not mortality.

In that regard, we showed consistent outcomes

between VAP-301 and VAP-14. Looking at predictors, which could influence the response to vapreotide for control of bleeding such as severity of liver disease at baseline the Child-Pugh score is another baseline characteristic we presented for both populations to show that they are, in fact, quite comparable.

There are differences in comorbid conditions in VAP-301 which, as Dr. Besseghir stated. may account for differences in mortality in the off-treatment period. However, even with those numbers, they are quite comparable with the results of published studies showing that mortality in this area can be as high as 25 percent.

DR. SMITH: But what you just said basically tells you that you are looking at two different patient populations. In the long term, if you have a greater mortality in 301 study than in the 14 study, then, you are talking about two different patient populations regardless of what happens at Day 5, which makes the studies incomparable.

I think the other thing is, in terms of the comparison between the mortality in the 301 study with what has been published in the literature, the Mountaineer study,

do we know what vasoactive agents were used in the Mountaineer study as compared to vapreotide?

DR. PETRELLA: Dr. Chalasani presented that information. I think he would be happy to comment further on that.

DR. CHALASANI: Thank you, Dr. Smith. I can answer some of the questions that you raised.

The first one is how the investigators in 301 described DIC. This is largely a biochemical disease in terms of prolonged PTT and high D-dimers.

About the higher mortality in VAP-301 compared to VAP-14, I would like to point out that mortality difference is mostly from Day 6 to Day 42, and you also would see there are many patients were made DNR in VAP-301. Perhaps there is a change in practice, and that may be a difference, not in the cohort, but how some of the terminal patients are managed in France as opposed to U.S.

You could also argue, though, if the vapreotide works in a slightly dissimilar cohort, that might be an advantage to vapreotide.

The final question about the Barcelona cohort that reported 26 percent, they used natural somatostatin as a

vasoactive agent. Thank you.

DR. PETRELLA: I would like to come back to Dr. Smith's second question regarding a potential study looking at vapreotide versus octreotide. As we presented earlier, there are no approved vasoactive drugs in the United States for this indication, and therefore, from a registration point of view, we could not have used vapreotide in the pivotal study.

DR. SMITH: Can I ask another question, too? The other question I would have is in relation to your safety data, which I think you said you included, the VAP-02 data in the safety assessment?

DR. PETRELLA: Yes.

DR. SMITH: But yet the VAP-02 study was closed because of unreliability in terms of performance of the study itself; is that correct?

DR. PETRELLA: Yes.

DR. SMITH: How in the world do you know--if you don't have efficacy data that is reliable, what would make you think you would have safety data that would be reliable?

DR. PETRELLA: From the perspective of the analysis of safety, as you know, any patient who received a

dose of vapreotide is eligible for that data set. In terms of the reliability of the data, the investigators were--and I will ask Dr. Besseghir to comment further--the investigators were adhering to the protocol requirements for reporting adverse events and serious adverse events in accordance with both regulatory and their local IRB requirements.

The trial was really stopped because of, as we said, very slow patient enrollment and some major issues with protocol non-compliance, which we do not feel affected or compromised the quality of the safety data.

Have we addressed that or would you like Dr. Besseghir to comment further?

DR. SMITH: No, I think that is fine.

Can I ask just one last question?

Somewhere in the background here that you presented, you indicated that 12 percent of patients, when they were endoscoped while receiving vapreotide, you were able to visualize the vessel; is that correct?

DR. PETRELLA: Are you referring to the control of bleeding at the time of endoscopy?

DR. SMITH: Right.

DR. PETRELLA: Yes.

DR. SMITH: During your presentation, you indicated that that is one of the major advantages of using vapreotide is the ability to visualize the vessel for the purposes of banding.

I am not a gastroenterologist, so I am asking you in general, do you think 1 out of 10 patients is --

DR. PETRELLA: I will ask Dr. Chalasani to comment. I think the point we made is that if you look at the control of bleeding at the time of endoscopy, let's remember that what we are seeing at that point is the native pharmacological effect of vapreotide, because the banding hasn't actually been done. In a higher percentage number, a higher percentage of vapreotide patients, the visual field, to look at the varices that we are banding and perform the procedure was unobstructed, facilitating the procedure.

I am not a clinician and therefore I will ask Dr. Chalasani to comment further.

DR. CHALASANI: Dr. Smith, that is a good point. What you might be pointing towards is the identification of precise varix that is bleeding. For example, the patients with variceal bleeding present, you look for other reasons--

for example, ulcers--and if you don't have any of those, then, you have large varices. That is sufficient to attribute the cause of bleeding to varices.

Rarely you see an active bleeding vessel, one of the varices, or you see a nipple sign or a red wale sign. I think the 12 percent you are pointing to is precisely identifying which variceal column is the source of bleeding.

DR. PETRELLA: Dr. Escobio, would you like to add something?

DR. CHANG: We have to keep this brief, because we only have five more minutes and two other committee members want to ask questions.

DR. ESCOBIO: Yes, very brief. With respect to mortality published in the literature, there is also a clinical trial in Factor VII conducted in 2008, or published in 2008, an international trial on mortality rate on the whole is 24 percent, and all the patients receive vasoactive drug, 30 percent somatostatin or vapreotide, in 253 patients.

DR. PETRELLA: Thank you, Dr. Escobio.

DR. CHANG: To finish up on Dr. Smith's question, in the VAP-02, I think the protocol violations, weren't

they, that they were given too much drug?

DR. PETRELLA: One of the major transgressions in VAP-02 was, in fact, overdosage in three patients which, as you can appreciate, placed the patients' safety at risk.

DR. CHANG: So, it would actually be a little bit more of a bias towards having safety concerns in that group, in that study?

DR. PETRELLA: In fact, as we showed, and Dr. Besseghir presented, even in the face of that overdosage experience, the adverse events were very mild, transient, and explainable on the basis of the broad pharmacological activity of somatostatin analogs.

DR. CHANG: Dr. Shih.

DR. SHIH: I would like to ask, following up Dr. Neaton's ITT question. Do you have data analysis on all randomized without exclusion, any patients, those results?

DR. PETRELLA: For all studies, or for which studies in particular?

DR. SHIH: For 01 and 14.

DR. PETRELLA: I will ask Dr. Platt, biostatistician, to address your question.

DR. SHIH: Without any exclusion, how did they

come out, the bleeding, and the mortality, those efficacy endpoints?

DR. PLATT: My name is Robert Platt. I am a biostatistician at McGill University. I am a consultant to the company. You asked about mortality, and what was the other thing, control of bleeding?

DR. SHIH: Right.

DR. PLATT: The patients in the non-ITT group, the ones who were found not to have esophageal variceal bleeding, were not followed for the 5-day control of bleeding endpoint. They were followed for mortality, which was presented in the safety--the safety population includes those patients, and the mortality rates in that group were part of that.

DR. SHIH: So, you don't follow patients that you exclude for the 5-day bleeding control at all?

DR. PLATT: That's correct, they weren't followed for the 5-day control of bleeding.

DR. SHIH: That's a shame. My follow-up question would be I saw you presented a Cox regression on the association between mortality and the stop of bleeding, those two endpoints. I think you showed that chart too brief

so I need further explanation of that.

Can you just go through this for the panel?

DR. PETRELLA: Dr. Platt, could you please review this for the panelists?

DR. SHIH: And what are the factors that you included in those models, and what do you try to show here?

DR. PLATT: With regard to your second question, I need to check with my colleagues regarding what was included in the model. However, what this is showing is simply the correlation between the primary outcome and its components and mortality at Day 42, which suggests, and we can look at these.

I think it is simplest to look at the odds ratios in the top row, and the Cox model hazard ratios are similar, that control of bleeding at five days is strongly correlated with a mortality at 42 days and the components of that, 6 hours and 48 hours are similarly strongly correlated.

DR. SHIH: What are the populations they included in here?

DR. PLATT: I am sorry, this is the ITT population of the VAP-14 study.

DR. SHIH: Only 14?

DR. PLATT: Only 14; that is correct.

DR. SHIH: Why couldn't you do it for all the studies combined?

DR. PLATT: We have done it as well for VAP-301 and the results are similar. We can try to access the combined studies as well. We don't have that immediately available.

DR. NEATON: Is this both treatment groups?

DR. PLATT: This is combined both treatment groups; correct.

DR. SHIH: That would be a good idea to show that.

DR. CHANG: Is that something you could provide in the afternoon, or is that something that you can't get readily?

DR. PLATT: I think we can provide it this afternoon. We have data available that we can look at.

DR. CHANG: Thank you.

Do you have a quick comment?

DR. CHALASANI: The non-ITT patients that were excluded, I would like to point out they were excluded because they do not have bleeding from portal hypertension. So, that is the reason why they were not followed for five

days. Because they got the drug, they were followed for safety, if that answers your question why you were concerned.

DR. SHIH: While you are providing the explanation of the model, what other factors included in there in the afternoon. Thank you.

DR. CHANG: Last question. Dr. Blum.

DR. BLUM: We have dissected this really horrible illness, and we have dissected all of these studies so far to see what this particular drug can do in association with banding.

I think we really have to take into consideration the standard of care in the United States against the drug we have no data on, we have no mortality, no morbidity or anything else when we have to consider what is going on here.

DR. CHANG: Thank you.

We will have opportunity in the afternoon to continue any other questions because, as of this morning, we didn't have any open public statements. But if there is anyone in the audience that would like to make a public statement for the open public hearing session in the

afternoon, please see the staff at the meeting table entrance at this time.

We are going to take a 15-minute break. We will reconvene again in the ballroom in 15 minutes from now. Panel members, please remember that there should be no discussion on this issue at hand at the break, amongst yourself or anyone in the audience. Thank you.

[Break.]

DR. CHANG: We will now hear the presentations from the FDA.

Presentations from FDA

Level of Evidence Requirements

[Slide.]

DR. KAMMERMAN: I am Lisa Kammerman and I will be reviewing requirements for the level of evidence of efficacy that we consider when we review an application. My goal is to provide a context for the information you have seen presented by the applicant and that you will hear in the subsequent presentations.

[Slide.]

How much evidence do we need when we are evaluating efficacy? In your background package and in the

presentations so far, you have read and heard about two submissions for this NDA. Together, they contain five studies. Our task as reviewers is to determine if the collective evidence is sufficient to support the efficacy of vapreotide.

The first submission contained three randomized clinical studies, only one of which was statistically significant. However, as I will discuss shortly, it was not statistically persuasive and cannot in itself support approval.

The current submission contains one randomized study which was not statistically significant and a single, open-label, historical-controlled study.

[Slide.]

This guidance document, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, is in your background package and it discusses the quality and quantity of information that we need to demonstrate effectiveness of a drug product.

I am going to review some of the issues pertinent to the vapreotide submission.

[Slide.]

The Food, Drug, and Cosmetics Act was passed in 1938. It required drug manufacturers to show their products were safe. However, because of concern over misleading and unsupported claims made about drug products, Congress amended the Act in 1962 to require manufacturers to establish a drug's effectiveness by substantial evidence.

[Slide.]

We hear that term a lot. So, what is substantial evidence? The Food and Drug Act defined substantial evidence as, "consisting of adequate and well-controlled investigations." Note the plural form of "investigation" is used, suggesting that at least two adequate and well-controlled investigations are needed. This is our usual requirement.

Moreover, the Act states that experts could conclude the drug will have the effect it purports or is represented to have. In determining whether there is substantial evidence, I want to emphasize that we look at the entire package of information submitted, not just one or two specific clinical studies.

[Slide.]

We saw that the focus is on at least two adequate

and well-controlled studies, but each of them has to be convincing on its own. We recognize this isn't always possible, and we attempt to interpret the requirement as broadly as possible.

For example, the second study doesn't need to be an exact duplicate of the first. We can rely on information from studies of other doses, other regimens, dosage forms, or other populations and, if a second study, for whatever reason, is not possible, then, the submitted study must meet a higher standard than if we had two studies to review.

As I look at why we need more than one study, and when a single study might suffice, please keep in mind that VAP-14, which is part of the first submission, was the only study of the three that were submitted that was statistically significant. However, it wasn't persuasive enough to fulfill the level of evidence needed from a single study, which is part of why we required additional information.

[Slide.]

Why do we ask for more than one study? We require more than one study because any one trial can give a positive finding due to chance alone and, moreover, a single

trial may be affected by biases that we cannot anticipate or even detect.

So, when we have independent substantiation of results, we can feel more confident that we are making the correct conclusion that a drug is effective.

[Slide.]

So, in general, there are two conditions under which a single trial might be sufficient. The first is when the trial has demonstrated a clinically meaningful effect on a serious endpoint, like mortality, irreversible morbidity or prevention of a disease with a potentially serious outcome.

In addition to the first condition that we have a serious outcome, the second condition is that conducting an adequate and well-controlled trial would be practically or ethically impossible. Note that these are the conditions that the applicant has cited when they decided to conduct Study 301, which as you know is a single-arm, open-label, historical-controlled study.

[Slide.]

What do we look for when we are considering whether a single adequate and well-controlled study is

sufficient to support the effectiveness of a drug product?

First, the study must be adequate and well-controlled, and I will go into some features of what that means in some subsequent slides, and if the study is adequate and well-controlled, then, the study should be large and have many centers.

We want to see consistency in results across the study centers. We don't want a single site to account for a large number of participants. So, we can agree that VAP-14 was indeed large and had numerous study centers. However, when we looked at the data, we discovered that one of the study sites appeared to differ from the others.

It was a larger study site, had 28 of 196 subjects, and was the only site that gave a statistically significant effect. Furthermore, at this site, the treatment arms weren't balanced with respect to variceal size. For example, 54 percent of the VAP-treated subjects had small varices versus 17 percent for the placebo-treated subjects and, at other study sites, 30 percent had small varices regardless of treatment effect.

So, because smaller varices are easier to treat than are of the large varices, this statistically

significant effect at this one center may have been influenced by the imbalance in variceal size among the treatment groups.

The p-value from the statistical tests of efficacy was 0.02 and, although this is statistically significant at our nominal level of 0.05, it isn't less than the two-sided p-value of 0.00125, which we use as a guideline in assessing a statistically persuasive finding from a single study.

With one study at 0.05, the chances of concluding a false positive is 1 out of 40. So we multiply that together, it becomes like 1 out of 1,600. So, taken together with the other two studies, which gave nonsignificant results, we didn't feel that VAP-14 was persuasive enough on its own in demonstrating the effectiveness of vapreotide.

[Slide.]

I am going to turn to the definition of an adequate and well-controlled study. This is relevant now to Study VAP-301.

The Code of Federal Regulations provides a definition for us; an adequate and well-controlled study is characterized by "a design that permits a valid comparison

with a control to provide a quantitative assessment of drug effect."

This, as I said, is relevant to Study 301, not only for efficacy, but also for safety. As we heard, there were questions of causality for safety events that may have been easier to answer had there been a concurrent control. Also, the questions about exclusions from the ITT population may have also been easier to answer had we had a concurrent control.

The review issues we consider in assessing whether a study is adequate and well controlled, is the type of control used in the study, the method used to assign subjects to treatment groups, and efforts taken to minimize bias.

[Slide.]

The CFR describes various types of controls that can be used to study the effect of a treatment, and one of those choices is historical controls, which is what we used for Study 301. The CFR states that historical controls can be the natural history of the disease or condition, or from the results of active treatment, in comparable patients or populations.

Comparable patients or populations is highlighted in this slide because this is an important consideration when evaluating the results from VAP-301. Our primary concern is that the subjects enrolled in VAP-301 are not comparable to the subjects enrolled in VAP-14.

Most subjects in 14 were treated with sclerotherapy, while most in 301 were treated with band ligation. Also, there were important baseline characteristics of the two-study samples that differed, which Dr. Marks will address in her presentation.

[Slide.]

The CFR further adds that historical controls are reserved for cases where the endpoints are predictable of mortality, or that the effect of the drug is self-evident, and the second bullet gives some examples.

[Slide.]

Another important characteristic of an adequate and well-controlled study is the method used to assign patients to treatment groups. We want assurances that the method minimizes bias and assures comparability of groups.

The design of VAP-301 was open-label and single treatment. Because of changes over time in endoscopic

treatment and differences in baseline patient characteristics between 301 and Study 14, we can't be assured that the vapreotide treatment arm in VAP-301 is comparable to either treatment arm from VAP-14.

[Slide.]

A third characteristic of an adequate and well-controlled study is the measures used to minimize bias on the parts of subjects, observers, and analysts of the data.

As Dr. Marks will present, because of the open-label design of VAP-301, there potentially was bias on the parts of the observers that could have affected the primary endpoint of the study.

Randomization and double-blinding are the typical procedures that we use to minimize bias and that allow for a cleaner assessment of a treatment effect. It should be clear right now that we don't consider VAP-301 to be an adequate and well-controlled study.

So, at this point, I am sure you are asking, well, what type of study design other than an open-label, single-treatment, historical-controlled or even a placebo-controlled study could have been used.

One possibility is an active control study, and

since historic**ally, even though you have heard that there aren't any approved treatments for this condition, and we couldn't have used an active control that wasn't approved, that really isn't the case. There have been situations where the active control can be an unapproved product.

In those cases, we usually require superiority because the active arm is unapproved, however, even if it didn't show superiority to the active control, I think we still would have been in a better place because we would have had the element of randomization and blinding built into the study, which we don't have with this open-label, single-treatment arm.

Another possibility of a study design would be a dose-response type of study where we would have at least two doses of vapreotide with the goal of showing a dose-response effect. Even in that case, if there wasn't a dose-response effect shown, we still would have the element of randomization built in.

[Slide.]

So, here is the totality of evidence that we are considering that is before us. In the first submission, there was only 1 of 3 studies that was statistically

significant, but it wasn't persuasive.

Taken together, the three studies did not provide substantial evidence of a treatment effect.

In the current submission, we have two studies. One is the open-label, historical control. However, the patient populations between the current study and the historical control are not comparable, plus the medical management has changed over the 10 years since VAP-14 was conducted. Not only is the bias now towards using band ligation, it is very likely that the ability and the way people are using band ligation has improved over the last 10 years.

The second study, VAP-06, didn't have any statistically significant findings. You have also heard some mentions of meta-analysis, however, even if a meta-analysis is probably done, it still cannot substitute for an adequate and well-controlled study.

Now, I will turn this over to Dr. Marks who will discuss the efficacy portion of this submission.

Clinical Efficacy

DR. MARKS: Good morning.

[Slide.]

I am Zana Marks, medical officer in the Division of Gastroenterology Products. I will be presenting the efficacy review for NDA 21-761.

[Slide.]

I will briefly discuss the background followed by the clinical trials, the efficacy results from the original submission, which received an approvable action, the efficacy results from the current submission, which is a response to the approvable action, and then I will summarize.

[Slide.]

The sponsor proposes that Sanvar will be used as adjunctive therapy to endoscopic intervention for the control of acute esophageal bleeding as a result of portal hypertension.

[Slide.]

Alcohol use and viral hepatitis, as we have heard, are the leading causes of gastroesophageal varices in the U.S. They are present in approximately 50 percent of cirrhotic patients.

Their presence and size are related to the underlying cause and severity of cirrhosis, and bleeding

occurs in approximately a third of cirrhotic patients.

[Slide.]

Predictors of hemorrhage include variceal size, decompensated cirrhosis, and the presence of red wale marks endoscopically. While these three are the most prominent predictors of bleeding, variceal size is the most important.

[Slide.]

In the occurrence of acute esophageal bleeding, a combination of vasoconstrictive pharmacologic therapy and band ligation is the preferred management. EGD is usually performed within 12 hours after admission to diagnose and treat variceal bleeding. Pharmacologic therapy may be continued for three to five days. Octreotide, another long-acting somatostatin analog, is not approved for this indication, but is used off-label.

[Slide.]

I would like to show the Cochrane meta-analysis slide that Dr. He showed in his introductory comments. This table summarizes the Cochrane review of the 8 to 9 low-risk-for-bias studies, which were randomized, controlled trials and double-blinded. They show an impact on active bleeding, but not overall control of bleeding or mortality.

The meta-analysis presented earlier by the applicant included eight studies, four of which did not achieve the level of evidence of the Cochrane low-bias trials and did not include four or five randomized, controlled trials that were double-blinded.

[Slide.]

Practice guidelines developed by the American Association for the Study of Liver Disease and the American College of Gastroenterology recommend band ligation as the endoscopic treatment of choice for the prevention and management of gastroesophageal varices and acute variceal bleeding.

[Slide.]

The reference review article, Lo et al., demonstrated a 20 percent advantage with band ligation over sclerotherapy, and acute esophageal variceal bleeding. 71 cirrhotic patients with active variceal bleeding were randomized to receive band ligation or sclerotherapy.

The etiology of cirrhosis in both groups in this study was comparable to the patients studied under NDA 21-761, and includes primarily hepatitis B, hepatitis C, and alcoholism.

The primary success rate, control of bleeding for 72 hours, was achieved in 97 percent of patients in the band ligation group and 76 percent of patients receiving sclerotherapy.

Re-bleeding within one month was observed less frequently with the banded group, transfusion requirements were less in the banded group, as well. Mortality was improved for banded patients compared to those who received sclerotherapy.

[Slide.]

Now, I will discuss the clinical trials.

[Slide.]

This table depicts all of the studies submitted under NDA 21-761. In the original submission, three studies were submitted; VAP-14 from France, VAP-07 from Egypt, and VAP-02 from Hong Kong.

In the current submission, two studies were submitted, VAP-06 from Eastern Europe and VAP-301 here in the United States. All of the studies were randomized, double-blind, placebo-controlled trials except for VAP-301, which was an open-label, single-arm study. All of the studies were multi-center except for VAP-07, which was a

single-center study. Of note, VAP-07 was originally designed as a Phase 2 study.

The etiology of cirrhosis varied among the studies. In the French study VAP-14, the subjects primarily had alcoholic liver disease. In VAP-07, cirrhosis was caused by parasites, and in VAP-02, 06, and 301, subjects had alcoholic liver disease, viral hepatitis, or a combination of the two.

[Slide.]

These are the pertinent inclusion criteria for all studies: female/male cirrhotic patients, ages 18 to 75; cirrhosis documented by at least one of the classical signs; hematemesis and/or melena thought to be related to portal hypertension; time interval of less than or equal to 24 hours between the onset of initial hemorrhage and the initiation of the study drug infusion.

[Slide.]

These are the key exclusion criteria for all the studies: atients treated with vasoactive drug, such as octreotide or vasopressin, for the current hemorrhage; known variceal bleeding in the previous 6 weeks; known Child-Pugh score greater than or equal to 13; known complete portal

vein thrombosis; cancer or chronic renal failure.

[Slide.]

Now, Sanvar was started within 6 hours of admission. A 50-microgram IV bolus was given, followed by a 50-microgram per hour infusion that was run for five days.

Endoscopy was performed within 12 hours of admission with patients receiving either sclerotherapy or band ligation, representation of the key components of the primary endpoint.

[Slide.]

The primary endpoint is a composite based on the control of bleeding and survival to Day 5. Control of bleeding is further divided into primary control of bleeding in the first 48 hours and the prevention of early re-bleeding from Days 3 to 5.

Control of bleeding in the first 48 hours was based on heart rate, blood pressure, and transfusion requirements, and the prevention of re-bleeding is also based on heart rate and blood pressure, but there is an assessment for hematemesis or melena as well.

Because of the open-label design, components of the primary endpoint may be subject to bias. For example,

the transfusion requirement that is based on the investigator's judgment. It should be noted that all the studies except VAP-06 used this primary endpoint definition.

The key difference in VAP-06 was an additional criterion of a target hematocrit level in the first 48 hours.

[Slide.]

This slide illustrates more completely the specific primary efficacy criteria for success by time after endoscopy. For the first 48 hours, the heart rate had to be below 100, and the systolic blood pressure had to be above 80.

The transfusion requirements had to be 4 units or less in the first 6 hours, and 2 units or less between 6 and 48 hours. After 48 hours, the heart rate could not increase more than 20, and the systolic blood pressure could not decrease more than 20.

The hematocrit could not decrease more than 10 from baseline during the 6 to 48 hours, and could not decrease more than 5 from baseline during the 48-hour to 5-day interval.

The patient could not have had hematemesis after

6 hours and could not have hematemesis or melena after 48 hours.

[Slide.]

The key secondary endpoints were control of bleeding by time periods and Child Class, and also the total number of blood units required during the 5-day period of the study drug infusion.

[Slide.]

Let's move on to efficacy.

[Slide.]

Looking at the original submission.

[Slide.]

These study results show that only one of the three studies in the original submission demonstrated the superiority of Sanvar over placebo. The treatment effect was approximately 16 percent, the other two were not statistically significant.

[Slide.]

In the French study VAP-14, the primary efficacy result was achieved in 66 percent of patients receiving Sanvar compared with 50 percent of patients receiving placebo.

The difference between Sanvar and placebo was significant in the ITT population with a p-value of 0.021, however, one center had the most patients in the study, and the patients from that center had a lower proportion of Child Class C than patients in other centers.

Notably, there was an imbalance of small varices in the Sanvar group, as well. If that center was excluded, the effect size decreased to 12 percent, and the results are no longer statistically significant.

This study qualifies as an adequate and well-controlled study. However, it does not meet the higher standard required for a single study to provide substantial evidence of efficacy as described by Dr. Kammerman.

[Slide.]

In the Egyptian study VAP-07, success was achieved in 71 percent of patients treated with Sanvar compared to 59 percent receiving placebo. This, however, was not statistically significant. This study differed from other studies in the etiology of cirrhosis which was: hepatitis associated with parasites; gender, all male; and the study was conducted at a single center.

The study was originally designed as a Phase 2

study. It may not have been powered to demonstrate efficacy.

[Slide.]

In the Hong Kong study VAP-02, there was no difference in the response rate between the two arms. Treatment response was observed in 55 percent of patients treated with Sanvar, compared to 51 percent in the placebo group. This was not statistically significant.

The ITT population included 102 patients, 51 in the Sanvar group and 51 in the placebo group. The sponsor states that this study was terminated because of protocol violations and poor recruitment. However, the rate of protocol violations was similar to that of VAP-14, and the ITT population was close to that expected based on the goal sample size.

[Slide.]

Approvable action was taken for NDA 21-761 in December 2004. Only one of the three studies, VAP-14, showed clinical and statistical significance. The other two studies, VAP-07 and VAP-02, were not supportive. It should be noted that VAP-07 was a single-center, Phase 2 study, and VAP-02 was a negative study.

We recommended that additional efficacy data from a well-controlled clinical trial would be needed to establish substantial evidence of efficacy for the use of Sanvar in the treatment of acute esophageal variceal bleeding.

It should be noted that another randomized, controlled trial, VAP-06, was ongoing at the time of the review of the original submission, but efficacy results were not available.

[Slide.]

Preliminary results of VAP-06 were submitted, but did not show superiority of Sanvar over placebo. The agency recommended that the applicant conduct another randomized, controlled trial. The applicant made a case that a placebo-controlled trial could no longer be conducted.

A superiority study using octreotide as the comparator would have been ideal, however, the sponsor chose not to conduct such a study. A non-inferiority trial comparing Sanvar to octreotide could not be done because there is inadequate information available to establish a treatment effect for octreotide.

[Slide.]

The current submission.

[Slide.]

Current submission, which is VAP-301, U.S. study, and VAP-06, Eastern Europe study.

[Slide.]

Study 301.

[Slide.]

VAP-301 was an open-label, single-arm st udy with 70 patients from 15 sites in the U.S. The primary endpoint was a composite endpoint, for control of bleeding and survival to Day 5, which is identical to that of VAP-14. There is also a qualitative comparison to VAP-14.

[Slide.]

Potential concerns with VAP-301 include the following: the open label design lends itself to potential sources of bias; there is difficulty in identifying a suitable historical control; difficulty differentiating the effect of Sanvar from the effect due to the different endoscopic therapies used.

[Slide.]

A look at baseline disease characteristics shows that in VAP-14, patient symptoms were primarily caused by

alcohol, while in VAP-301, patients had a more complex etiology of disease, alcohol and alcohol combined with viral hepatitis.

Alcohol plus viral hepatitis is often associated with more severe liver disease. Also, ascites and hepatic encephalopathy appeared more frequently in VAP-301. Hepatic encephalopathy and ascites are important markers consistent with decompensated cirrhosis.

[Slide.]

Child Class appears balanced across two studies. However, variceal size is different. Larger varices were more prevalent in VAP-301 than 14. In fact, 90 percent of patients in VAP-301 had varices that were greater than 5 millimeters compared to 72 percent in the VAP-14 placebo group.

A lower proportion of patients in VAP-301 than VAP-14 had more than three previous episodes of variceal bleeding.

[Slide.]

The two endoscopic modalities, band ligation and sclerotherapy, were used in both studies. However, band ligation, which is now considered the standard of care and

the treatment of choice, was performed more frequently in patients in VAP-301.

Less than a third of patients in VAP-14 received band ligation while 86 percent of patients in 301 were banded. As stated, the literature shows that banding provides benefits for re-bleeding. In addition, procedure-related complications, such as esophageal stricture and esophageal ulcers, occur infrequently with band ligation.

[Slide.]

When we look at the primary endpoint for the studies VAP-301 and VAP-14, we see that a 77 percent response rate was observed in patients from VAP-301 compared to 66 percent of patients treated with Sanvar in VAP-14 and 50 percent of patients receiving placebo in 14.

The higher response rate in VAP-301 might be due to the endoscopic treatment administered. When VAP-14 was conducted, sclerotherapy was the preferred modality. When VAP-301 was conducted approximately 10 years later, band ligation was used more than sclerotherapy and it is now considered the endoscopic treatment of choice for variceal bleeding.

Today, the therapeutic endoscopic community has

found the use of band ligation superior to sclerotherapy for this indication. Therefore, any treatment-related improvements seen in VAP-301 could be due to changes in endoscopic therapy, and not to drug therapy.

[Slide.]

This table illustrates the components of the primary endpoint. The components are consistent with the overall primary endpoint. At each specified time interval, VAP-301 had a higher response rate than VAP-14 Sanvar, which, in turn, had a higher response rate than VAP-14 placebo.

The observed higher response rate in VAP-301 compared to that in VAP-14 placebo might be due to band ligation and not solely to Sanvar.

[Slide.]

The number of units transfused in VAP-301 appear to be higher than that in the VAP-14 Sanvar arm and similar to that in the VAP-14 placebo arm.

[Slide.]

This table depicts control of bleeding by time period and Child-Pugh Class. Overall, as time increased, the response rate decreased. The overall results appear to

be driven by patients with Class B and Class C, but mostly Class C, which describes patients with more severe hepatic dysfunction.

[Slide.]

Survival at Day 5 was similar between the two studies. At Day 42, however, survival was lower in VAP-301 than VAP-14.

[Slide.]

Another subgroup analysis assessed the achievement of the primary endpoint by the underlying cause of cirrhosis between the study groups. In VAP-14, the number of patients in the categories of alcoholism plus viral hepatitis, and viral hepatitis only, was very small. Thus, it is difficult to discern the effect of the underlying cause of cirrhosis on achieving the primary endpoint.

In VAP-301, it is also difficult to discern the effect of the underlying cause of cirrhosis primarily because of the very small number of patients in the viral hepatitis-only category.

Comparing the alcoholism-only group to the alcoholism plus viral hepatitis group suggests that the alcoholism plus viral hepatitis group had a higher response

rate. No conclusions can be drawn, however, because of the relatively small number of patients in each of the two study groups.

[Slide.]

A similar proportion of patients in VAP-301 and in VAP-14 that received band ligation and Sanvar met the primary endpoint, 78 percent and 77 percent.

In VAP-301, only three patients received sclerotherapy, so it was difficult to discern the effect of this treatment modality.

In VAP-14, a higher percentage of patients receiving band ligation met the primary endpoint compared to those receiving sclerotherapy in both arms. As you can see, 77 percent compared to 63 percent here in the Sanvar group, and in the placebo, 60 percent compared to 47 percent.

This is consistent with the aforementioned MOST study where band ligation provided a 20 percent advantage or benefit over sclerotherapy.

[Slide.]

In summary, the overall response rate was 77 percent for VAP-301 versus 50 percent in the VAP-14 placebo group. A considerably higher proportion of patients in VAP-

301 received band ligation than VAP-14, and 86 percent versus 31 percent.

Based on the results of VAP-14, band ligation appeared to be associated with a 13 to 14 percent higher response rate for the primary endpoint than sclerotherapy. This suggests that the observed response rate in VAP-301 may be due at least in part to the higher proportion of patients who were treated with band ligation.

Because VAP-14 was conducted about 10 years before VAP-301, it is also important to consider possible improvements in operator performance of band ligation since that time.

Furthermore, because of the open-label design, components of the primary endpoint may be subject to bias. For example, the transfusion requirement in the first 48 hours is based on the investigator's judgment.

Finally, it is difficult to compare the results across the two studies because of differences in baseline characteristics. Compared to VAP-14, VAP-301 had a higher proportion of patients with larger varices and a higher proportion with a mixed etiology of disease, alcoholism combined with viral hepatitis, but a similar proportion of

Child Class C.

[Slide.]

Now, I will present the results from VAP-06, which is a randomized, double-blind, placebo-controlled study with 267 patients from 8 sites in Eastern Europe.

[Slide.]

Unlike the other studies, VAP-06 had additional criteria of a target hematocrit for blood transfusions specified in the study protocol. The primary endpoint in VAP-06 differed from that of the previous studies. The sponsor included an additional criterion in the primary endpoint of a target hematocrit for blood transfusions in the first 48 hours.

A criterion of systolic blood pressure greater than or equal to 70--whereas, the other studies had the systolic blood pressure of greater than 80--was included in the first 48 hours, as well.

VAP-06 did not have specific criteria for re-bleeding.

[Slide.]

A protocol amendment was introduced in VAP-06, which resulted in a major change to the primary endpoint.

This was a decrease in the target hematocrit from 27 to 21.

This implementation occurred as the result of chronic blood shortages at centers, causing delays in transfusion, and it occurred after approximately a fourth of the patients were enrolled in the study.

[Slide.]

A statistical analysis plan amendment was submitted in September 2005, one year after the end of the study. Major changes in the statistical analysis plan included the re-analysis of the data using VAP-14 criteria and separate analysis of the pre-amendment population.

The agency considers this an exploratory analysis.

This approach to the analysis was also presented to the agency in June 2005. At that time, the agency communicated to the sponsor that a post-hoc analysis on a subset of the study population would not be adequate to support the efficacy of Sanvar for the proposed indication.

[Slide.]

This table provides the primary efficacy results for VAP-06. The superiority of Sanvar over placebo was not demonstrated.

[Slide.]

The results of all the studies in both the original submission and the current submission are shown here. In the original submission, only the French study VAP-14 demonstrated superiority of Sanvar over placebo with a treatment effect of 16 percent and a p-value of 0.02.

In VAP-07, there was a difference between the two groups of 12 percent. Statistical significance was not achieved. That study was a single-center study of only 58 patients. Thus, it is possible that statistical significance was not achieved because the study was not powered to show efficacy.

VAP-02 was a negative study.

Let's move to the current submission.

VAP-06 was a negative study. In VAP-301, the rate was 77 percent compared to the historical control rate of 50 percent in the VAP-14 placebo arm. However, we cannot easily conclude that the difference of 27 percent is due solely to Sanvar, because there were a number of differences between the studies.

A key difference was that close to 90 percent of VAP-301 patients had band ligation compared to less than a third of VAP-14 patients. The results of VAP-14 suggests

that the response rate for band ligation was about 13 to 14 percent higher than for sclerotherapy.

We have to also consider the effect of possible improvements in operator performance of band ligation over the 10 years between 14 and 301. The magnitude of this effect is not known.

The cross-study comparison is further complicated by other differences between the two studies, such as variceal size. 301 had a higher proportion of patients with large varices, and the number of bleeding episodes. 301 had a lower proportion of patients who had three or more bleeding episodes.

Finally, because of the open-label design, components of the primary endpoint may be subject to bias. For example, the transfusion requirement in the first 48 hours is based on the investigator's judgment; thus, the total strength of evidence that is there is still only one study that shows superiority of Sanvar over placebo, three studies that are negative, and one study that is difficult to interpret.

Our next speaker is Dr. Gao, who will present the safety review.

Clinical Safety

DR. GAO: Good morning.

[Slide.]

I am Wen-Yi Gao, the safety reviewer of NDA 21-761. I would like to present my review to the Advisory Committee in the next 20 minutes.

[Slide.]

I will briefly talk about the sources of the safety review and the database, the drug exposure, mortality, serious adverse events, common adverse events, withdrawals due to AE and, at end of my talk, I will summarize the safety findings.

[Slide.]

The safety review was based on five variceal-bleeding studies. The total safety population included 469 patients who received at least one dose of Sanvar. Fifty-three percent of patients were new, 47 percent were from a previous study, previous submission. The placebo-controlled study was 78 percent, ucontrolled data were 22 percent.

[Slide.]

This slide shows the drug exposure. As I mentioned, there were 469 patients who received at least one

dose of Sanvar, approximately 70 percent of patients completed the 5-day treatment.

[Slide.]

This slide shows the overview of adverse events. The overall death rate, 42-days death rate were comparable between Sanvar and placebo. Patients with serious adverse events were slightly lower than the placebo. Withdrawals due to AE also were comparable.

[Slide.]

If you compare the uncontrolled study 301 with the placebo-controlled data, we find Study 301 had a death rate about 10 percent higher than the controlled Sanvar groups.

Patients with serious adverse events were comparable with the controlled data. Withdrawal due to AEs were numerically lower than the controlled Sanvar in the placebo-controlled group.

[Slide.]

Let's move on to mortality.

[Slide.]

Let's talk about the method we used in the analysis of 5-day mortality. We first compare the proportions of deaths and identify those only occurred in

Sanvar arm. We then determine the temporal relationship with Sanvar administration--for example, clinical deterioration shortly after drug exposure--focus on the 33 deaths that occurred during five days of treatment.

Attempt to find a common mechanism to explain selected causes of death that only occurred in the Sanvar group.

[Slide.]

This slide shows the overall mortality rate. The overall mortality rate was comparable if we exclude the uncontrolled study 301. The rate listed at the bottom of the slide was 15.3 percent versus 16.7 percent. Study 301 had highest death rate, 25 percent, as compared to Sanvar other study, 15 percent, placebo 16.7 percent.

[Slide.]

What about 5-day mortality rate? They are also comparable if we remove the uncontrolled study 301, the rate was 6.6 percent versus 6.9 percent. Study 301 had the highest 5-day mortality rate, 8.7 percent, as compared to Sanvar in other study, 6.6 percent, and placebo 6.9 percent.

[Slide.]

Now, let's focus on certain cause of death that

only occurred in the Sanvar group during the 5-day treatment; bradycardia followed by asystole, septic shock, respiratory failure, SIRS (severe systemic inflammatory response syndrome), disseminated intravascular coagulation, thrombocytopenia, followed by hypovolemic shock, cerebral vascular accident. Six of the 10 deaths were from Study 301. The potential pathogenic mechanism is discussed in the safety briefing.

[Slide.]

The most common cause of death was hemorrhagic shock, either caused by initial bleeding or re-bleeding.

The rate of the Sanvar arm was numerically lower than the placebo.

[Slide.]

The most common serious adverse events were upper GI hemorrhage, hepatic encephalopathy, and melena. These values were numerically lower in Sanvar arm compared to placebo.

[Slide.]

This slide shows that the Sanvar arm had numerically higher rate in renal failure, respiratory failure, thrombocytopenia, and bradycardia.

[Slide.]

The most common adverse events were GI bleeding, pyrexia, and hepatic encephalopathy. These AE rates were comparable.

[Slide.]

Withdrawals due to AEs were 8.3 percent in the Sanvar arms and 8.6 percent in the placebo arms. Upper GI bleeding was the most frequent cause of withdrawal. The rates were comparable.

[Slide.]

Withdrawals due to AEs that only occurred in Sanvar arms include multi-organ failure, cardiogenic shock, septic shock, cerebral vascular accident.

[Slide.]

Let's summarize the safety findings. The overall mortality rates were comparable between the Sanvar and placebo arms. The 5-day mortality rates were also comparable.

[Slide.]

Study 301 had a considerably higher 42-day mortality rate compared to that of other studies, 25 percent versus 15 percent Sanvar arms in other studies, 25 percent

versus approximately 17 percent in placebo possibly due to more patients with large varices and more patients with combined disease. But we cannot be certain of the reason.

The 5-day mortality rate for Study 301 also appeared to be slightly higher.

[Slide.]

Deaths that only occurred in Sanvar during the 5-day treatment include bradycardia followed by asystole, septic shock, severe systemic inflammatory response syndrome, disseminated intravascular coagulation, cerebral vascular accident, thrombocytopenia followed by hypovolemic shock and respiratory failure.

Causes of death were numerically lower in Sanvar than placebo--that is, hemorrhagic shock.

[Slide.]

Serious adverse events that were numerically higher in Sanvar arms include renal failure, respiratory failure, thrombocytopenia, bradycardia. Serious adverse events that were numerically lower in Sanvar arms include melena, hepatic encephalopathy, upper GI hemorrhage.

[Slide.]

The most common adverse even, both arms, were GI

bleeding, pyrexia, hepatic encephalopathy. The most frequent cause of withdrawal was upper GI bleeding for both arms.

[Slide.]

Many people have worked hard on this project are not present here today. I would take the opportunity to acknowledge the contributions of everyone on this slide.

With that, I conclude the FDA presentation. Thank you.

Committee Questions to FDA

DR. CHANG: Thank you very much.

We will now ask if the Committee has questions for the FDA.

I would like to start. I just wanted a little bit more clarification on the discussions between the FDA and the sponsor because, if you look at the briefing packet and what is also alluded to in the presentation, at the end of this first New Drug Application with the first three studies, it was discussed to do a dose ranging study, which it doesn't sound like it was ever done.

Also, it was agreed to do an open-label trial, and I understand that that is partly due to the fact that

octreotide is not approved although I still think. if that is standard practice and you believe the scientific data, that it is efficacious in patients with esophageal variceal bleeding, to me that seems like it is a necessary study, although apparently it must have been agreed between the FDA and sponsor to do an open-label study, or is that not agreed and the sponsor went ahead and did it?

So, just those two points.

DR. HE: You are right. We did discuss at end of first submission, and both sponsor and FDA did agree Study 301 for open-label, single-arm study is acceptable. Although I say so, but the sponsor has a responsibility to conduct a comparable study.

That means the sponsor has to try comparable between the two studies. That means try not to introduce the new variabled such as procedure difference between sclerotherapy and band ligation.

To answer your second question about the different study design compared to octreotide, we did suggest the sponsor to compare treatment arm versus octreotide. But to do so, you will need to provide us--to do a superiority study. We disagree to do an inferiority study, did not

because we do not have adequate evidence for octreotide for the proposed indication. I believe that is why sponsor did not conduct such study.

DR. CHANG: I think it would be nice to hear what the other committees think about whether the efficacy in 301 was due to the fact that there was more band ligation in those patients.

However, if you look at the comparison of efficacy in 14 with band, it was pretty similar with the drug. It was 78 and 77 percent and, on placebo, in the 14 study with band, it was 60 percent. But it was about 50 percent if you had placebo with the sclerotherapy group.

I think that some of that higher efficacy is due to the fact that you have band ligation. But doesn't to me appear that it is solely due to band ligation, but it would be good to hear what other people think.

I think Dr. Shih has a question.

DR. SHIH: I just want to ask FDA to clarify the revelation about any special condition for a drug classified as orphan drug, regarding the approval requirement.

We all know that we like to have adequate controlled, well conducted studies for other drug

categories. So I am not familiar with orphan drug. Is there any special consideration given to this kind of a class? This is my first question.

The second question is, like you said, if we think that variceal size is a factor, why couldn't we do a stratified--and I haven't heard from either group, the sponsor or the FDA--looking at subgroup for the larger variceal size.

We did see the stratified for band ligation but variceal size is not one that you can look at it. Also, from the time that FDA made a suggestion of a requirement for having another controlled study after the first approvable letter, were you thinking at the time that VAP-06 study wasn't really finished? If that were finished, that was a controlled trial, and too bad it turned out to be negative. I don't know whether that is a factor or recall another study, or you were waiting for the 06.

Another comment on here is that FDA classified negative studies for 02 and 06 there, and I thought that was a little bit unfair. I think you can say that is a study without conclusion especially for 02--that is a pilot study--but I don't believe that we can call that a negative study.

DR. CHANG: Why do you think you can't call 02 a negative study? What did you say? I am sorry.

DR. SHIH: It didn't show significance. But numerically, it is still better, and is a pilot study, it wasn't required to have that significance there. I don't believe that is positive, per se. But I don't believe that it is negative either.

DR. CHANG: Dr. He?

DR. HE: Study 02 was conducted in Hong Kong. Study was between the treatment arm versus control or placebo arm was only 4 percent difference. We don't consider that 4 percent difference is clinically meaningful. Neither study indicates that it does not reach statistical difference.

DR. SHIH: But that is not a negative study either. It is inconclusive, you can say that. But to say it is negative, and to balance--you look at the list, saying there was just one positive study, two negative studies, and I just think that is too harsh.

As you said of 301, you cannot render conclusion and, for these two pilot studies, for their purpose, for their design, they are not negative. They are probably not

positive either, but I won't call that a negative either.

DR. HE: Okay. Study 02 was a Phase 3 study. It was designed to show the efficacy, the safety, and the withdrawal. The patients, 130 patients, that study was designed to show the difference. But the study result showed, no different. That is why we call Study 02 was a negative study.

DR. SHIH: I am sorry, I meant 07.

DR. HE: Oh; okay.

DR. SHIH: That 12 percent difference there is a pilot study. That is what I meant.

DR. HE: Okay. Study 07, yes, you are right. That is a little bit different. That is designed for a Phase 2 study, and a Phase 2 study was designed not to be used as a pivotal study. That is why we list as a negative study. But, you know per definition, they did not reach statistical significance. But you can call it whatever, but we know what that means.

DR. CHANG: I think 07 suffers from a small sample size. The problem with 02 also, though, is that they had a higher number of patients with Child Class C and, if you look at some of the data that was shown, and if you stratify

by A and B together versus C, you are going to have less of a therapeutic gain with the drug because of Child C.

Dr. Smith.

DR. SMITH: One of the things that concerns me about this is how can the FDA expect a trial to be done, a single-arm trial to be done in which the patient populations are comparable, when the treatments that are used vary from one decade to the next, which is uncontrollable.

You know, after all, you are not going to be able to register anybody in a trial if their operative procedures that are used are considered to be inadequate.

It seems to me like, although 301 versus the VAP-14 studies aren't entirely comparable, you have to take into account the fact that in order to perform the study, you have to have a patient population placed on the study, and that would include those people that would be candidates for band ligation as opposed to sclerotherapy.

DR. HE: Yes; you are definitely right. At the time we did talk about open-label study design. Both sponsor and FDA did not consider, you know, this procedure difference between Study 14 and current. That is one thing we did not thinking very solidly. Yes; you are right.

DR. CHANG: Dr. Neaton.

DR. NEATON: There are two pieces of information that I think are missing here, and maybe they can be provided. The FDA referred to a meta-analysis, which is included in the reports, and I concur with, I think, their assessment that that is really probably not the right one to have done.

But I would like to have seen kind of an overview of all the trials that were placebo-controlled except for VA-14. What is the evidence kind, of collectively, from the other underpowered trending studies for any support for VA-14?

The other piece that was missing was referred to by Dr. Shih. The 301 is just terribly flawed as an historical-controlled study for the reasons you just indicated. But why would you ever do an historically-controlled study when you couldn't even go back to the same sites? In this case, you went to U.S. sites instead of French sites.

So, you have got a problem from the get-go. But I have not seen any analysis that attempts to at least control for some of the potential confounding variables that were

identified collectively in terms of what that overall comparison yields.

So, given the inherent flaws in it, I think that is kind of an important piece to kind of nail down, and then, if either the FDA or the sponsor can put that on the table for us, that would be helpful.

My third question actually is to the FDA, which I appreciate them going into the composite endpoint. This is a potential problem in my mind. I don't know whether you have any more information that you can share with us, but can you tell us, in 301 and 14, why people failed?

Is the reason for failure on the active arms, in the placebo arms, at the the different points--I mean this is a very complicated composite with different components, at different times, and I have not seen anywhere the reasons for failure.

There was an allusion to the fact that there is this potential bias for transfusion, so that is true in the open-label study. But were kind of transfusion requirements a greater reason for failure, for example? I have not seen any data on that. Was it blood pressure? Was it heart rate? What was it, what led to the failure at the different

time points in the different arms?

DR. HE: Maybe I should turn to sponsor to answer this question.

DR. PETRELLA: I will ask Dr. Platt. I know we have looked at some of the components of the composite that are responsible for failure throughout the 5-day period.

DR. NEATON: Maybe take the easy one, take them in order. Can you do the overview of all the trials besides 14? What does that give you in terms of an odds ratio and a confidence interval compared to what you saw in 14?

DR. PLATT: We haven't done that specific computation, but we can come back to you after lunch with that specific one in addition to the others.

DR. NEATON: The problem with what is in the packet, is it is not independent information. I don't want to see 14 put in there, because you want 14 by itself. It is kind of a hard sell, so what does the other data collectively show to support it.

DR. PLATT: Thank you. We can get that after lunch.

DR. CHANG: Dr. Baranski.

DR. BARANSKI: I would like to ask for a

clarification. In the presentation by the sponsor related to the April 06 FDA-SPA letter regarding the 301 study, the questions were does the Division agree a single-arm study will be acceptable? Yes. And two other questions.

In the materials sent to us for review, a statistical analysis was performed for review of the special protocol, and these questions were answered in a negative fashion. Does the Division agree that a single-arm study will be acceptable? The statistical response was "No." And there were three questions asked.

Is there a difference in the timeline or something else?

DR. KAMMERMAN: My colleagues are looking at me to answer that one. As you can see, there was a difference of opinion within FDA. Their statistician, Dr. Chen, argued in what you are reading why a single-arm, open-label study would not be sufficient to establish the efficacy of the drug product.

I think he goes on and talks about cross-trial comparisons, the lack of randomization, the lack of blinding, and a few other points. However, that was his opinion, and the Medical Division decided otherwise.

DR. BARANSKI: It's a direct opposite of what was presented.

DR. KAMMERMAN: Right.

DR. BARANSKI: By the letter.

DR. KAMMERMAN: I am in agreement with Dr. Chen's assessment.

DR. CHANG: Dr. Fogel.

DR. FOGEL: Yes. In the 301 results for the 42-day mortality, if I remember correctly, the sponsor said that there were five deaths due to HIV and I think 12 deaths that were probably related to Do Not Resuscitate orders.

In the VAP-14 study, what was the incidence of either HIV or Do Not Resuscitate, because I am trying to understand why the mortality was higher in the 301 study at 42 days.

DR. GOA: I think this question would best be answered by the sponsor first.

DR. PETRELLA: Thank you for the opportunity to comment. I will ask Dr. Besseghir. My understanding is that in the VAP-14 study, there was one case of HIV infection, and it is important to know in the practice and in the culture in France, DNRs are not common. But Dr.

Besseghir can speak further as he is from the region.

DR. BESSEGHIR: Yes, we observed two cases of HIV-positive patients in VAP-14, one in the placebo arm and one in the vapreotide arm. That was the first, to answer one of the questions.

The second one is that the DNR notion doesn't exist in France. I mean you don't simply decide, at least formally by the family, that you don't recussicate the patient. So it is difficult to compare that.

DR. FOGEL: My question to the FDA is does that really matter?

DR GAO: That is a good question. Actually, when we read these narratives of the virally infected, HIV-infected, patient with an alcohol history and cirrhosis, bit we find the death rate is actually not tightly associated with viral infection. But we cannot exclude the complications.

Complications doesn't mean directly linked to the viral infection. It could be caused by some other things--for example, activate immune system in the patient that could have some effect on the death of the patient.

DR. CHANG: I would like to know from the FDA,

summarizing all the studies, what do you think was really the main predominant cause of the higher 42-day mortality in the 301 versus the other studies because, if you look at the drug arm and the placebo arm, the mortality rate is higher in 301 versus the other studies for both drug and placebo.

So, is it the design? Is it the comorbidity, the inclusion of patients with comorbidity, because the Child Class was similar. The prevalence of C was similar in 301, at least versus 14.

DR. GAO: As I commented on my presentation, the reason for this, we do not know actually. It is possible due to a higher percentage of patients with combined disease because combined disease will bring combined, different, complications, more complications, and also due to larger varices, because the varices size, it does matter. The size does matter, but we do not know.

This is--as I said, we cannot be certain of this at this moment.

DR. CHANG: Thank you. Dr. Blum.

DR. BLUM: Dr. Gao just answered my question on the variability of the varices size and comorbidities and the mortalities.

DR. CHANG: Because 301 did have a higher prevalence of the larger varices, which would actually make their efficacy probably a little bit harder.

Dr. Silberg.

DR. SILBERG: From an industry perspective, I would just like a comment on the difference of opinion for the design of the study. When industry comes to FDA, you know, we take your word for what your suggestions are. It appears in this case that there may have been a disagreement, but overall, the study design was agreed on with the FDA to the sponsor.

So, now, coming back, there was a lot of criticism about the study design from the statistical standpoint. However, it was agreed on ahead of time. Now, yes, there were potential differences with band ligation. I think, though, that could probably be looked at even in a historical sense.

So, how is the sponsor supposed to respond now to this criticism when they are really taking the advice of the FDA as a whole, not just one aspect, to do the study? I mean, it is fine to have 20/20 hindsight, but we have to do studies prospectively.

DR. HE: Yes, you are right. We did agree with sponsor, Studie 301 to be single-arm, open-label study. There is no question. We come here today to ask the Advisory Committee members' opinion, how much we can rely on this data. And the data, yes; the study was done but maybe not done in a very conservative, comparative way and that is why they introduced so many new variables, such as the band ligation.

These kind of things, we did not think about 10 years ago, at the time we agree about this open-label study. But right now we need the Committee to think about how much we can rely on this kind of research. Does this study really provide the efficacy or not, you know? For that, we need your input.

DR. KAMMERMAN: I just want to add, so, say I agreed with this historical-controlled study, and the study goes on. It still has to meet certain rules for being an adequate and well-controlled study even using the historical controls.

As I indicated earlier, the populations need to be comparable, and there are some other issues involved. So, even if I had thought the historical controlled study was

okay, the choice of historical control is crucial to allow an adequate comparison for both efficacy and safety.

DR. CHANG: Dr. Epstein.

DR. EPSTEIN: Yes, I would like to go on a little bit further about the endpoint. If you take away all these various arguments about DNR and HIV, we all know that hepatitis C is the major contributor to liver death in HIV patients.

Do we have a good historical control comparator? I would have expected to see a substantially lower death, rate regardless of large or small varices in this group, because we know now we are much better at treating varices with banding, and actually, the death rate here is substantially higher in 14, in that 301 as compared to 14. And I am completely lost as to is there a historical control based on the literature.

We have heard the Barcelona studies are showing about a 20 percent. Here, we have got a higher than that. So, where is the efficacy of the drug? Has that analysis been done either by the FDA using traditional historical controls. since we don't have a control trial and we have to overlook that? But what are our historical controls and

comparators here, and do we have a side by side?

DR. CHANG: You are saying--because I guess what you have brought up is the size and the Child Class are important for efficacy, but I guess you are bringing up do we really know the efficacy in patients with cirrhosis with these comorbidities. Is that what you are stating, to compare?

DR. EPSTEIN: I think we have historical data now on what the mortality should be in a comparative group that has received banding. That data is well out there, so do we at least have a comparison between what is happening with this group and another group? I think it is very hard to explain away that this is a substantially higher mortality even as compared to the historical controls that we know. But I think it would be nice to see that side by side.

DR. CHANG: Dr. He, do you want to comment?

DR. HE: Yes, you are definitely right. We have this problem, too, in the past few months. We are struggling, trying to get this kind of data, trying to compare this 20 and 25 percent mortality compared to the Study 14, only--or 15 to 16 percent, We are struggling. We don't know how to explain this kind of finding.

Going back to the original agreement with the sponsor that we did agree to do an open-label study, open-label, single-arm study, and we asked the sponsor. That is why we agreed on the control is Study 14. We asked then try your best to use a comparable population and therapy for Study 14. Even Study 14 for placebo is the lowest, only 15 percent in the other placebo, half of 59 percent, you know, from 15 to 16 percent.

We agreed on that because we tried to--we anticipated this kind of problem later on, so we asked the sponsor trial base to use a comparable population, comparable therapy. But, right now--the problem is right now we don't know how to really understand and explain this finding.

DR. CHANG: Now that we do banding, would you have stated no, you should have a similar proportion of sclero and banding in the study that is comparable to 14?

DR. HE: At that time, we just agreed, you know, try to use Study 14 as a comparator to design this new study, Study 301. That means you have to try your best to use whatever you have, try to be comparable to Study 14, yes.

Think about if a study moved to another country, and they used sclerotherapy as a primary procedure, it may be more comparable than conducted in U.S. I don't know.

DR. CHANG: Dr. Raufman.

DR. RAUFMAN: I have some serious concerns about how FDA made these decisions. Five years ago, not 10 years ago, it was very clear that the field was shifting to band ligation rather than sclerotherapy. That was quite evident.

I don't understand why a green light was given to this study, which--I think every issue that we are facing today was entirely predictable five years ago.

DR. BEITZ: I think what we are hearing are things that we should have looked for and didn't, and potentially should look for to control in a new study. You will have opportunity to discuss some of that this afternoon with one of the questions. If we do move in that direction, it sounds like we could be a lot more smart about how we do it.

DR. NEATON: Could I just ask again, I asked this earlier, and Dr. Kammerman kind of brought it up again. What precisely was the design of this study in terms of how did you power it for kind of comparing.

Actually, I am kind of puzzled why the comparison

was with the active arm. But, given that is the case, how did you set this up and decide that 70 people were adequate? There seem to be a number of fundamental flaws in the way this was put together, the way the historical population was chosen, the interventions that were not considered, the comparability with the historical data. But just where did the 70 come from?

DR. PETRELLA: Before I ask Dr. Platt to comment on the sample size, I think it is important to point out, as the regulatory record will show under the SPA, it was agreed with the agency that VAP-301 was statistically constrained and that the results were not intended to be evaluated for a statistical inference but for their clinical importance in light of the field.

Having said that, there was a power calculation that Dr. Platt conducted, and he can discuss that further.

DR. PLATT: The sample-size calculation that was done was based on--because of what Dr. Petrella just said and what my colleagues at the FDA have mentioned--the sample size was based on just estimating a proportion.

In fact, there was some discussion with the FDA over how to define a historical control and whether a

specific number should be given and a specific statistical test should be proposed there, and it was the agency who told us in our discussions that they would prefer that we not do a specific testing sample size calculation. So we based the sample size entirely on the proportion of 70 patients.

DR. NEATON: I have to say I don't think that makes any sense, and I don't understand the difference between statistical and clinical guidance, the words that were used earlier, that this study is going to be looked at qualitatively for clinical significance as opposed to statistical significance. That is just out in left field as far as I am concerned.

DR. CHANG: Dr. Shih.

DR. SHIH: If you look at the difference of the populations between 301 and VAP 14, as I said earlier, you still can find a subgroup that is comparable to your best. Of course, you cannot compare U.S. with France, and so on, but other things, you really can come up with a close subpopulation to make a comparison. That is my suggestion.

The other comment that I would like to make to the FDA is about your exclusion of one study. Then, if you

exclude that center, then, it becomes inactive study, which I also object to. I think if you exclude that center, of course, you have to reduce number of patients and, therefore, you don't have the power anymore. But the effect size still exists. So I will not call that exclusion of a center become an inactive study.

I think it is giving the sponsor some credit. They did show lots of subgroup analysis to show the strength of the robustness of the conclusions. But I would like to see that they compare the subgroups with variceal size again so that there is a complete picture. Thank you.

DR. HE: I can answer you one question about size. If you only have one single study, the criteria is different. We tried to do analysis if that study qualifies as one single study, one single positive study. Then, when we do a subgroup analysis, we include size evaluation. To be qualified as a single positive study to get approved, you have to go through this kind of testing and have to be positive, no size effect.

But this study is not robust enough to pass such a test.

DR. SHIH: I just want to clarify. How do you

measure this robustness? You say the single study is not robust enough, which I do not quite understand, why it is not robust. I point out that, if you exclude a center, you don't show significance anymore.

That is understood, you reduce the sample size. But you don't do--like your slide showed the p-values for each center, which I don't do, because you have a multi-center study. You don't calculate p-values for each center.

DR. KAMMERMAN: I don't think we disagree that the study was not statistically significant and didn't show clinical evidence. I think the issue is, is this one single study sufficient on its own to establish the efficacy of the drug product.

One way we do that is to make sure we have lots of study sites in the particular study. So in this case there were many centers. If you look at the treatment effects by study site, you will see they are fairly consistent except for this one center, which was Center 18, which had the largest treatment effect and it was the only center that was statistically significant.

Part of that was that it was confounding with the variceal size, so we didn't know whether the treatment

effect of that particular center was really due to vapreotide or was it due to the imbalance in the variceal size distribution. So there was a greater proportion of the vapreotide-treated subjects who had small varices.

DR. SHIH: But that is a wrong analysis. If you just stratify by variceal size, you will get an answer, if that is what you thought.

DR. KAMMERMAN: Right. What I am saying, though, this is the situation, though, when we have one clinical study. If there was another study that had 0.02, it would be fine. All things being equal, it would be okay. Just that, when we have a single study, we want to be sure that there is consistency among all subgroups. And one of the definitions of subgroups is study site.

DR. SHIH: If you say this is the only study site that show the significance, I am actually quite happy. I don't expect in any multi-center study a single study site will show significance. And if it comes out significant, it may be caused by, as you said, at the variceal size. But then you can do a stratified analysis on the variceal size, you don't just exclude that.

You would reduce the sample size, which you fail

to show the significance. That is not proof of robustness or in robustness.

DR. KAMMERMAN: Right. And the second criteria was the p-value, When we have a single study, the probability or the chance of a false positive is 1 out of 40. When we have two studies, we went 1 out of 40 in both,. So taken together it is 1 over 40 times 1 over 40 for the second study. So that is 1 over 1,600, which corresponds to the twp-sided p-value of 0.00125.

So, in this case, the p-value was only 0.02.

DR. SHIH: We are talking about different issues. I agree with you that we need a second study; okay?

DR. KAMMERMAN: Yes.s

DR. SHIH: But we were talking about whether this study is robust, the result is robust, as a positive study or not. I think it is robust enough to say it is a positive study.

DR. KAMMERMAN: Oh, yes. I agree with you. I am not disagreeing with that.

DR. SHIH: That is what I was saying.

DR. KAMMERMAN: I was just addressing the issue whether it was robust enough to stand as the only

randomized, controlled study. I think that is where we were differing. I agree that it was a sound finding, but did it reach the higher standard that we ask for a single study.

DR. CHANG: We only have five minutes. Dr. Blum.

DR. BLUM: I just wanted to make one comment. When a patient comes into the emergency room bleeding, we don't ask him the size of the varices. They all have to be treated. So we have to take into consideration some people come in with small bleeds, and some people will come in with large bleeds. So, to exclude a study because some varices are lower doesn't mean I am going to send the patient out of the emergency room because he only has a small varix.

DR. KAMMERMAN: Oh, right. Maybe it is not clear. In the background package, you ought to have the statistical review of the original study. So, for example, at all the centers except that one particular center, the proportion of subjects on the vapreotide arm who had small varices was 27 percent, placebo 29 percent.

At that one center, 54 percent of the subjects on vapreotide had small sized varices versus 17 percent of placebo. So, it was the distribution of the varices that was imbalanced among treatment arms at that particular study

site.

DR. CHANG: I think we are out of time. So, Dr. Furberg, could you save your question for the afternoon, and you will go first.

DR. FURBERG: Yes.

DR. FOGLE: I have actually a very quick question.

DR. CHANG: Okay.

DR. FOGLE: This was asked before, but I didn't catch the answer. In the federal regulations, are orphan drugs treated differently? Are there different criteria for them than for drugs that are not orphan?

DR. BEITZ: No; the level of evidence for efficacy is the same whether they are orphan or not.

DR. CHANG: It is 12:15 and we are going to break for lunch. We will reconvene here at 1:00 p.m., so you will have 45 minutes. Again, I have to state that panel members, please remember that there should be no discussion of the issue at hand during lunch amongst yourself or any member of the audience. Thank you.

[Luncheon recess at 12:15 p.m.]

AFTERNOON PROCEEDINGS

1:07 p.m.

Committee Questions to FDA (Continued)

DR. CHANG: We actually don't have any speakers for the Open Public Hearing, so we are going to just continue the discussion before we get to the questions and the vote.

At this time, I think it would be good to have the sponsor address a couple of the questions and show data that they were going to collect for this afternoon.

DR. PETRELLA: Thank you, Madam Chair. Good afternoon, everybody. We have a response to the questions that we were asked this morning and are pleased to have the opportunity to share this information with you.

I also would like to apologize for neglecting to formally introduce some of our bull-pen respondents this morning. I also would like to mention that one of our colleagues, Dr. Robert Makuch, Professor of Biostatistics at Yale University, has been on the project for many years and regretfully could not be here today due to a personal emergency. He sends his regrets to the Committee and has asked our statistician, Dr. Robert Platt, to represent his

views.

These are the respondents: Dr. Norman Grace from Brigham and Women's Hospital; Robert Makuch, as we said, unfortunately, could not be here today; Dr. Platt, you have heard already; Dr. Bill Wheeler from MBS Pharma, cardiologist; Dr. Ana Maria Escobio, our medical advisor; and Laura King, who you have heard briefly, our Director of Regulatory Affairs.

Quickly, to the questions, outstanding questions from this morning. I believe there was a question in regard to the efficacy, with respect to efficacy size. I will ask Dr. Robert Platt, our statistician, to provide the information we have obtained to this.

DR. PLATT: Thank you.

[Slide.]

This slide is a slide that was presented in the efficacy presentation along with some additional information that we have added over the break. The question was over stratifying by small and large varices the results in the VAP-14 study and in the VAP-301 study.

You can see that the VAP-301 study was predominantly large varices, 63 out of 70 patients had large

varices, but that the effect or the rate of control of bleeding in VAP-301, in that subgroup, was, in fact, considerably higher than that in the similar subgroup in VAP-14, in the active control, active arm, as well as in the placebo arm.

I will note, as well, that, in fact, the control of bleeding in small varices, the effect of the drug in VAP-14--now, I am not going to make any claims regarding statistical interactions regarding the effect of the drug in small varices versus large varices. However, the argument that was made this morning that the effect might be larger in small varices doesn't appear to be true based on our data. Again, that is small numbers and I am not going to make claims about statistical interactions, but the numerical comparisons don't support the argument.

I will remind the panelists, as well, that there are a fair number of patients in the VAP-14 study who had band ligation, and that may serve as another appropriate historical control for the banding group in VAP-301.

DR. PETRELLA: There was also a question in regard to outcome by modality, and Dr. Norman Grace will be happy to address that. Dr. Grace.

DR. GRACE: What I would like to do is just to tell you how we came to the decision in the practice guidelines that we published two years ago. This was a guideline that was produced both by the American College of Gastroenterology and the American Association for the Study of Liver Disease, was reviewed by their Practice Guidelines Committee, reviewed by both boards and approved.

The reason that we ended up recommending combination therapy, if I can put that slide up, please, is based on this meta-analysis by Roberto de Franchis.

[Slide.]

And this is looking not just at vapreotide, but at all the studies including vasoactive drugs as combination therapy versus endoscopic therapy alone.

This includes not only vapreotide, it includes octreotide, somatostatin, terliressin. As you can see, for every point, the immediate bleeding control, the 5-day bleeding control for all studies, and then for the full papers, it is highly statistically significant in favor of combination therapy over endoscopic therapy alone.

I would be glad to answer any questions about how we came to these decisions or how guidelines are produced,

if you would like.

DR. NEATON: How does this overview differ from the one that was published in the Cochrane with 21 studies?

DR. GRACE: The Cochrane one included abstracts. It was not peer-reviewed literature.

DR. NEATON: There are studies that are included in the Cochrane overview that you do not think should be there?

DR. GRACE: I think it's a matter of interpretation of how you should do this.

DR. PLATT: I would like to make one small clarification, as well. The other difference between the Cochrane review and this review is the Cochrane review did not study the composite 5-day control of bleeding endpoints, so they may have had more studies available to them if they weren't using that as the primary endpoint.

DR. ESCOBIO: Ana Maria Escobio from Debiovision.

Another difference with the Cochrane review is the Cochrane review, this is a meta-analysis with combination with vasoactive drugs and endoscopic treatment. And the Cochrane review is somatostatin in any kind of analysis, somatostatin alone, versus placebo, somatostatin compared or

vasoactive compared to endoscopic treatment, so included any kind of clinical trial with somatostatin, which is absolutely different to the standard of care today and absolutely different from this.

DR. PETRELLA: Thank you, Dr. Escobio.

There was also an interest from several panelists this morning to better understand the composite primary endpoint used in our clinical trials and to understand in regard to which components patients failed for. We will ask Dr. Platt to present that analysis.

Dr. Platt, please.

[Slide.]

DR. PLATT: We didn't have time over the break to insert the VAP-301 results into this slide, but we do have the results for causes of failure by time period. What I would like to do is just point out the notable differences.

There are differences in biomarkers in the 6-hour period, and there is a difference in the use of rescue treatment because of uncontrolled bleeding during the first 6-hour period. That being said, then, most of the other differences are relatively negligible.

I have notes on VAP-301 that I can read if that is

of interest. I am sorry I am not able to put it on a slide.

In VAP-301, there were 16 failures. Of those 16, seven were deaths, three were discontinuations due to adverse events--I am sorry--two were due to adverse events. One was due to a nurse's error. One patient was considered a failure because critical data were missing. One patient was considered a failure because of tachycardia. Three patients were considered failures because of over-transfusion. They received more than the allotted transfusion numbers.

I don't know if one of my clinical colleagues would like to comment on the endpoints.

DR. NEATON: Can you leave that up? Can you just comment on the heart rate differences in the first 6 hours? That seems to be driving the big difference if you see them on the earlier graphs as failure; is that correct?

In your Kaplan-Meier curves that you showed, you saw a substantial difference in the first six hours, and it seems from this to be driven by the heart rate criteria.

DR. CHALASANI: That is a good observation. That is a good observation, but in acute management of variceal bleeders, it is not--significant tachycardia is an important

thing that we look out if there is continued bleeding.

In addition, also, there is a 1 versus 7 difference in rescue treatment as well. So it is not entirely on the heart rate alone.

DR. NEATON: But does this drug actually have a pretty immediate effect on pulse and blood pressure?

DR. PETRELLA: Dr. Besseghir?

DR. BESSEGHIR: To answer the question for the pharmacological effect of vapreotide, if anything, we feel that the thing is bradycardia.

DR. NEATON: What is BT?

DR. PLATT: Blood transfusion.

DR. NEATON: That is the one I guess that was raised by the FDA and the open label. Can you comment on that in 301 as to how many failures in 301 were--

DR. PLATT: There were three patients who were failures due to over-transfusion during the 301.

DR. NEATON: Okay. For six hours?

DR. ESCOBIO: Yes. one in the first six hours and two after six hours. But we determined that maybe--can Robert can give me right numbers. In VAP-14, there was statistically significant difference between vapreotide and

placebo regarding the rescue therapy.

And, when we are talking about rescue therapy we are talking another vasoactive patient was no controlled, TIPS, tamponade. And VAP 14 was statistically significance. We know that it is not the primary point or secondary point. It is a post hoc analysis.

DR. PETRELLA: Thank you.

DR. CHANG: Dr. Epstein has a question.

DR. EPSTEIN: Concerning that last slide, can you put that back up again? I am a little bit confused because we have a complicated multifactorial primary endpoint, and we have a drug that, as a clinical effect, causes bradycardia. And heart rate, increases in heart rate, was a substantial part of that endpoint.

So, if you have a drug that just slows the heart rate, by itself, would a beta blocker alone have given you this effect, and have you analyzed this data taking out the heart rate, knowing that your drug causes the heart rate to slow down which could give the endpoint a false positive result in this VAP-14 trial? Do you have that separate analysis?

DR. CHALASANI: Can you clarify, are you asking if

the primary endpoint was evaluated without heart rate?

DR. EPSTEIN: Given the fact that the drug has an effect of slowing the heart rate, could you have given any drug that slows the heart rate and gotten the same difference in effect, because the heart rate is part of that endpoint to begin with?

So, have you done an analysis without the heart rate given the fact that this drug causes a slowing of the heart rate?

DR. PETRELLA: Professor Groszmann, would you like to add something further to this?

DR. GROSZMANN: Thank you for the question. The endpoint is composite. It is not only heart rate. There have to be other parameters that change at the same time, arterial pressure, heart rate, the number of transfusions, the hematocrit. Dr. Petrella showed that is one of the specfic--

DR. PETRELLA: Could we have CE4, please, the structure of the composite primary endpoint.

DR. NEATON: I thought the primary endpoint, you had to meet all these criteria to be considered a success.. so if you failed any of them, you were a failure.

DR. GROSZMANN: No.

DR. NEATON: Then, I don't understand the endpoint.

DR. GROSZMANN: Heart rate alone is not a failure. It's a composite endpoint. You have to fail all of them.

DR. PETRELLA: That is not exactly correct, is it, Dr. Platt?

DR. PLATT: No. In fact, the way you interpret it, the way the panel has interpreted it is correct, that if you fail on one--yes.

DR. EPSTEIN: So, if heart rate is 3 times from 7 to 26, then, have you done an analysis taking heart rate out of the picture, knowing you have a drug that, by itself, changes the heart rate. That could change the entire outcome.

DR. PLATT: That analysis hasn't been done, but I will point to the secondary endpoints, many of which, most of which are --

DR. EPSTEIN: No, no, no, I am talking about the primary endpoint.

DR. PLATT: I understand that analysis.

DR. EPSTEIN: I really want to know about the

primary endpoint, not the secondary endpoints. That is not what I asked.

DR. PLATT: I apologize, I understand your question. That analysis hasn't been done, removing the heart rate.

DR. EPSTEIN: Do you think that should have been done given the fact that the drug affects the heart rate individually, do you think that should have been done?

DR. PLATT: It would be interesting to speculate post hoc on that. That being said, it is the consensus endpoint that my colleagues and their colleagues have agreed on.

DR. CHALASANI: The only thing, Dr. Epstein, I would like to point out is not octreotide or vapreotide causes bradycardia consistently in a predictable fashion. In the majority, more than 90 percent, actually, you don't see bradycardia, so what Dr. Besseghir said is if at all you see a bradycardia, I don't think it should be graded to every patient getting vapreotide gets bradycardia.

DR. EPSTEIN: But bradycardia was one of your significant adverse events that was higher in your drug versus placebo, so it is something that needed to be

controlled for.

DR. CHALASANI: Once again, good point, but there were very few events, though. You are talking about three out of a hundred.

DR. EPSTEIN: I am not talking about adverse events, I am talking about just the fact that it might reduce the heart rate, not necessarily adverse.

DR. CHALASANI: Okay. Good point, sir.

DR. CHANG: But now somebody, a group of experts have come up with this international consensus, so there must be some data to support that this, as a group, is a good primary endpoint including the heart rate.

I don't think we should be changing endpoint, but I don't know the data to support that this is an international consensus primary endpoint.

DR. CHALASANI: Thank you, Madam. This primary endpoint is what is used across different variceal bleeding studies. This has been endorsed by Reston, by Vanno, and other workshops, and the field is complex, and that is why this complex endpoint was proposed.

I am not so sure it is valid to take out one piece of the primary endpoint and re-analyze primary endpoint.

DR. EPSTEIN: That is not what I was suggesting. What I was saying is if I gave a beta blocker and it dropped the heart rate substantially by 25 percent, it would improve this endpoint enough to be statistically significant in and of itself.

So the question is since you have a drug that reduces the heart rate, did you do a second analysis without the heart rate to remove the confounding variable of a drug that slows the heart rate.

DR. CHALASANI: That is a very good point and, Dr. Platt pointed out, that analysis has not been performed.

DR. CHANG: Dr. Furberg.

DR. FURBERG: I agree with Dr. Epstein. The composite outcome that is used is not useful in a setting where you have a drug that lowers heart rate. That doesn't make sense to use that composite outcome as a measure.

DR. PETRELLA: If I may just add, I am obviously not an expert in the field but I believe, when Dr. Besseghir commented on bradycardia, he was alluding to preclinical pharmacological evidence that suggests a potential role or a possible role of this class of drug on heart rate.

I think the position that the sponsor has

presented today is that we do not believe there is causality between our drug and bradycardia.

DR. EPSTEIN: But you have bradycardia in a higher rate as your adverse events as it is.

DR. PETRELLA: Yes.

DR. EPSTEIN: So, there is clear evidence there for bradycardia.

DR. PETRELLA: We have information on those events, which I would like Dr. William Wheeler to clarify, because our position is that this is not a signal.

Dr. Wheeler, would you please?

DR. WHEELER: William Wheeler, external cardiology consultant. Typically, the effect of these kind of drugs in this class on heart rate is about five or six beats a minute, so it is not a big change. You might suspect you would have a problem with hypotension if you had bradycardia, but, as far as the AEs go, if we can go to SA-25.

[Slide.]

As you can see, there were four bradycardias in 301, three of which were nonfatal. One occurred during the bolus and was a self-limiting, short bradycardia that caused

no discontinuation of infusion. The same in subject 801. That occurred three days into infusion.

Patient 1605 was seven days post-infusion and. in three fatal events, all of these subjects had prior hemodynamic collapse and initiation of cardiac arrest prior to the induction of bradycardia.

Does that answer your question?

DR. EPSTEIN: I don't think what I have asked has been addressed at all. If you go back to the other slide, where it shows that there are three times the number of patients who had dropped out because their heart rate was high, that number alone is enough to skew your data and makes the whole end result very questionable.

DR. CHANG: Dr. Neaton.

DR. NEATON: I think my colleagues--I will let them comment on the relevance of the endpoint and your point about changing it. The key thing is when you have a composite endpoint, which is this complicated, which varies by three time periods, and has different components in each one, you really want to understand what is driving it.

It appears from that slide that the differences we saw are being driven totally by the heart rate. The

difference in the total number of successes was only 15, and so that the heart-rate difference there has to be a major explanatory factor in terms of the overall failure rate or success rate between the two treatment groups.

The adverse event data, I am just going to point out is irrelevant, and the fact that you have a drug that lowers the heart rate by five beats, actually, it is not surprising, then, because you are shifting the distribution and all you are saying is, if it goes above 101, it is a failure.

DR. CHANG: Given that the drug may have an effect on heart rate, what would be your recommendation? Can you re-analyze that in some way?

DR. NEATON: I would let others comment on it, but the key is this is a complicated composite, and I think you want to understand what is driving the composite for its clinical relevance. And I am hearing arguments by people on the committee here that it is not clinically relevant.

DR. CHANG: Dr. Shih, do you have any comments about--because this comes into play as far as later on about what recommendations we can make and what additional valuable information we can ask for the sponsor.

Given this topic of conversation, would you think about analyzing it in some particular way to try to get at this?

DR. SHIH: The sponsor had a slide on the subgroup, on the VAP Study 14, whether the patient had a prior beta blocker or not. But I think the suggestion was you can do the same thing with concomitant beta blocker or not, the two groups. You have a prior beta blocker.

DR. PETRELLA: That information was looked at. Would you like to see more information?

DR. SHIH: But do you have concomitant one? It may not resolve the whole thing, but I thought it may provide you some light.

DR. PETRELLA: Dr. Shih, we have the information on prior beta blockers.

DR. SHIH: I know you have prior. I am asking for concomitant.

DR. PETRELLA: I believe we don't have that information on concomitant beta-blocker usage.

DR. SHIH: As I said, you do have prior, but you don't have concomitant.

DR. CHALASANI: It is hard to give beta blockers

when a patient presents with variceal bleeding. We often discontinue, because they are hypotensive, so you may not see concomitant beta blocker.

DR. SHIH: So, you can't get that information.

DR. CHANG: Dr. Blum.

DR. BLUM: Let's remember that beta blockers have a half-life of 24 hours. They are going to be effective for 48. So, even though a person is not taking it concomitantly, they may have an effect from prior consumption.

DR. CHANG: I actually think this is a really important point about what is driving the endpoint, it really is. I am wondering if, even though we are not using non-14 and non-301, the other three studies, is there information about failing to meet the primary endpoint by drug versus placebo on the other three studies?

DR. PETRELLA: Does anyone know if this information has been looked at?

DR. CHANG: Just to clarify, the main reason why the placebo group did not meet the primary endpoint was heart rate, it really wasn't blood transfusions or blood pressure, and the other parts of the primary endpoint; is

that correct?

DR. PETRELLA: Dr. Platt, would you please comment on Madam Chair's observation?

DR. PLATT: In short, that's correct, yes. That being said, it is important to remember again the rescue therapy and again that the secondary endpoints all are in the same direction as the primary, and that the patients who fail due to heart rate at the 6-hour point may or may not, and we are seeing if we can gather this information, go on to have important sequelae after that.

We would like to know whether they are the ones who are dying, et cetera.

DR. CHANG: I don't know if you said this before, but what was the criteria by which you would use rescue treatment?

DR. PLATT: What was the criteria by which we would use rescue treatment?

DR. CHANG: When was it actually administered, by what criteria?

DR. PLATT: I will ask the clinicians to speak to that.

DR. CHALASANI: It comes down to the clinician,

and it is failure to control bleeding, that the patients are decompensating.

DR. CHANG: How do they know that exactly? Is it just based on still passing blood? Is it based on the vital signs? Because if it is based on heart rate, then, we have a little bit of a problem.

DR. CHALASANI: No, it is based on multiple things. They are continuing to need transfusions. They are having blood through the NG tube, passing blood, and also hypotension. It is just not one thing, but multiple observations.

DR. NEATON: Do you have information in the first six hours on just what the average heart rate differences are and blood pressure differences are?

DR. CHANG: Are you trying to make a specific point on that first six hours?

DR. NEATON: I mean that is where the difference is. I guess another question might be, if this is being driven by heart rate, are we talking about a heart rate difference, which is just three or four beats, or is it a heart rate difference which is much larger? I mean that may or may not be relevant to the conversation. I don't know.

DR. PETRELLA: We are collecting that information as we speak. Perhaps to respond to Dr. Shih's earlier question regarding the adjustments for the logistic regression model, we could ask Dr. Platt to provide the information while. As I said, we are scrambling to get the other information.

DR. SHIH: I think it will be useful to see the purpose of the question, is to associate your two endpoints, your mortality with your bleeding, the stop of bleeding.

[Slide.]

DR. PLATT: The question you had asked was a little bit about how this analysis was done, I believe. First of all, it's the entire VAP-14 ITT population, including both treated and control patients, and both of these analyses are unadjusted for anything. This is just the raw essentially correlation between the outcome and 42-day mortality.

DR. SHIH: You can interpret this for us.

DR. PLATT: Okay. My interpretation of this is just simply that the outcome, the control of bleeding signal, has a strong correlation with survival to 42 days, and what is perhaps interesting given the recent discussion

is the trend that seems to be getting stronger, control of bleeding at six hours, to 48 hours, to five days becomes more strongly correlated with mortality.

This shows up in the logistic-regression model and in the Cox model. We attempted to do more analysis of this at lunch. What we did end up doing only was control of bleeding at 5 days in the VAP-301 study correlated with the 42-day mortality, and the association is, in fact, a little stronger although the sample is small.

DR. CHANG: I just want to clarify. This data is from the 301 study?

DR. PLATT: I am sorry; this data is all from the VAP-14 ITT population.

DR. CHANG: Right. I thought you were going to also look at the 301 or was I mistaken?

DR. PLATT: We did. We didn't have time to put it onto a slide. The corresponding odds ratio to the 4.013 was approximately 6, but with a wide confidence interval because of the sample size.

DR. CHANG: Dr. Epstein.

DR. EPSTEIN: If the thesis which we heard from every speaker, and what you just said, is that the Boveno

criteria at five days predicts mortality at 42, what was your mortality across the board between the drug and placebo? What was the mortality rate across the board?

DR. PLATT: Are you talking at Day 42, Day 42 mortality?

DR. EPSTEIN: At Day 42. All studies combined.

DR. PLATT: For all studies combined. This follows up on another question that was asked before lunch regarding survival to day 42 in all randomized patients in the VAP-14 study. The question was related to the patients who did not have esophageal variceal bleeding, who were left out.

[Slide.]

So, this is not quite the answer to the question that you have asked, but it is in answer to a question that was asked before lunch. I will come back to your question as soon as we can find the slide.

Just to say that we see the survival curve, this is now all deaths between Day zero and Day 42. We can ignore everybody after Day 42. Those are censorings. But we see I would argue a trend towards a difference in survival. The p-value for this comparison is about 0.19,

suggesting higher survival to Day 42 in the vapreotide group compared to the placebo group.

Now, for all studies combined we have the similar analysis for the safety population. If I could have SA-107.

[Slide.]

It is a bit of a messy slide, but if we look at the third line from the bottom, the sub total, we have got the mortality comparing vapreotide and placebo again in this all randomized populations.

DR. EPSTEIN: I have a hard time seeing that.

DR. PLATT: I apologize, it's a busy slide.

DR. EPSTEIN: What are the numbers?

DR. PLATT: The numbers are from 1 to 5 days. I am looking at the sub total in the randomized studies for now, 6.6 percent in the vapreotide arm, 6.9 percent in the placebo arm to 5 days; for 6 to 42 days, 8.5 percent in the vapreotide arm, 9.5 percent in the placebo arm. Total; 15 percent in vapreotide, 16.4 in placebo across the 42 days.

DR. EPSTEIN: The FDA gave us different numbers. Can we explain the difference? The numbers we got from the FDA were 17.5 versus 16.7. What is the difference?

DR. GAO: If we include uncontrolled study 301

overall--I mean 42 days, 17.5 versus 16.7. If we exclude the uncontrolled study 301 overall, 42 days, 15.3 versus 16.7.

DR. PLATT: So, we have marginal differences in the decimal point there that I am not sure I can explain without seeing the FDA's results, but the main difference where the 17.3 then comes from is the inclusion of the VAP-301 study. I was looking specifically at the randomized studies to make the comparison with placebo.

DR. EPSTEIN: Dr. Chalasani said earlier that the most important thing was to control the bleeding at Day 5, so you would reduce the mortality at Day 42, and has that happened?

DR. CHALASANI: Good question once again. I think it just comes down to the sample size. I think the studies are not powered to detect mortality difference at Day 42. They were simply powered to show difference at 5-day control of bleeding. I think it is simply the power of the studies that have been conducted.

DR. EPSTEIN: Can you repeat that?

DR. CHALASANI: When the studies were designed, the sample size was calculated, and the studies were powered

for the primary endpoint, which is 5-day control, but not for 42-day mortality. That is why you are not seeing, if you include a large enough sample size, you might see a mortality difference.

That is why the field accepts the 5-day mortality as a valid surrogate measure.

If I may, I would like to clarify one thing that you had a concern about in the morning discussion. The VAP-301 mortality, 26 percent, you were concerned it's higher than other studies.

I would like to point out in my presentation, the Barcelona cohort mortality was exactly 26 percent and, moreover, as Dr. Escobio presented, the 2008, another study from Barcelona, once again showed a 42-day mortality of 29 percent. So, it is not outside what is being seen in the literature at the moment.

DR. EPSTEIN: So, no study showed any statistical or historical difference in mortality.

DR. CHALASANI: It is very hard to show mortality difference in survival studies. Even TIPS, that is so widely used has not shown consistently mortality benefit.

DR. CHANG: Does the sponsor have the information

about the heart rate difference in the first 6 hours?

DR. PLATT: That will take a couple of minutes.

DR. CHANG: Okay. The reason why I am bringing that up is maybe everybody could turn to FDA's presentation on the 301 study. It is number 18, page 18, but it is in the middle of the packet on the components of the primary endpoint for VAP-301 and VAP-14.

What Dr. Neaton brought up, which is true, is that you really see the benefit in the first six hours with VAP-301 being 94 percent versus in the VAP with the drug, it is 88 percent, and then placebo 60 percent. It drops off somewhat after that when you get to 48 hours a little bit, 83 percent, and then 77 percent.

What was discussed is whether, as a committee, should we think about when we think of efficacy, just throwing it out there, not just looking at the first five days, do we think it may be important to look at just very early on in the endoscopic treatment or the resuscitation of the patient and establishing efficacy maybe within the first 6 to 48 hours as opposed to just five days.

I just want to get some feedback. Do any of the committee members have any thought about whether, when we

answered the questions about efficacy, if we should look at the very initial data, first day versus the five days?

DR. KANE: Madam Chairman, as a clinician, I think that it might be hard to put that into context just because, as it has already been presented, all of the other studies that have looked at treatment of bleeding varices, does talk about this composite endpoint at five days and looking at mortality at five days.

So, I agree that this looks very compelling and it may make sense, but the primary endpoint was this five-day composite score.

DR. CHANG: Dr. Blum.

DR. BLUM: That may be set up as a standard, but from a clinician's point of view, you want to see the bleeding stop. And, you know, heart rates can go up and down from various different factors.

When you have a patient hospitalized and tubes are going in all different orifices, and heart rate is something that we take not into no consideration but put it down low on the list in a situation like that. But it is the cessation of bleeding which is what we are looking for, and that is the important point, whether we use a band on it or

a drug.

DR. EPSTEIN: That is not the endpoint.

DR. CHANG: Are you trying to make the point about the timing or are you making the point about focusing on the heart rate?

DR. BLUM: I don't think we have to focus on the heart rate in a hospitalized situation. It does vary a lot with various other factors that are not even being brought into control here.

DR. CHANG: That is a good point. Dr. Fogel.

DR. FOGEL: If you look at the sponsor's data with regard to survival, the Cox hazards and the odds ratio, it looks like the relationship has become stronger if you bleed--the chance of survival is reduced if you bleed between two days and five days after coming into the hospital, suggesting that 6-hour endpoint may not be as important long term as what happens after that first six hours, even after that first 48 hours.

I am not sure that we should be trying to parse out the different components of the endpoint rather than looking at what happens at the full five days.

DR. CHANG: Dr. Hasler.

DR. HASLER: Just a couple of comments on the heart rate. I believe the sponsor showed that the tachycardic response is specific just for the first six hours, and not the 48-hour time point; yet, they do show a benefit in the primary endpoints at 48 hours and five days. To me, that suggests the heart rate response is pretty much irrelevant. Whether it explains the difference in the first six hours, I don't know that it means all that much.

I mean, if you think about what is going on in the first six hours, these people are relatively hypovolemic and it just may be preventing an orthostatic response.

DR. EPSTEIN: Right, but where the problem is, that there is a substantial number of failures in the first six hours, which is due to heart rate changes. And, if you eliminate those, then, you may not show the statistical benefit. That is the statistics. That would change the whole thing down the line.

If, in fact, you gave a beta blocker, and it lowered the heart rate in the first six hours, then, that would change everything going down, because that is the way that the study was set up.

DR. CHANG: Let me just clarify, is that exactly

accurate what Dr. Hasler said, that the change, the difference in heart rates, is mainly the six hours, and not through the five days? I want to make sure that we have got that clear.

DR. BESSEGHIR: When we find the slide, the Kaplan-Meier curve, we show that there is a difference at six hours. But if the pulse rate was explaining the difference during the five days, yes. Then, we should expect the curve to return to controls after six hours, which is not the case here.

DR. NEATON: Why don't you go back to the slide where you showed the component

DR. PETRELLA: Could we have CD-4, please.

DR. NEATON: The reasons for failure.

DR. PETRELLA: Could we have that slide back, please.

DR. SHIH: I think the request for the heart rate during the six hours is very important to see, because I can imagine that a person classified a failure, if you have multiple reasons, [?] and you may easily go heart rate than other things perhaps, so that is another condition. In that case, you may face the choice, question. So is it important

to see the heart rate, the range, the median, and those things?

DR. PETRELLA: Do you wish to see the diagram of the components?

DR. NEATON: Put the components back up there, just to make sure we understand it.

DR. PETRELLA: The data or the schematics?

DR. NEATON: The data.

DR. PETRELLA: Can we have that slide again, please.

DR. CHANG: Putting down a NG tube would raise anybody's heart rate.

DR. NEATON: As I understood the slide, and if you count up the numbers just as an example, on the left-hand side, there is 10, 17, 18, 23, 26, 28 failures. Now, people can fail for more than one reason. There is a total in the analyses that you had 65 out of 98 successes, so I wasn't quite sure how--

DR. PLATT: That is an important question that I forget to mention when I was up here, that, in fact, because this was done relatively quickly, if a patient satisfies more than one criteria in that six hours, they are up here

twice.

DR. NEATON: That's fine, okay. The earlier question about ignoring the first six hours, you could essentially condition on that and look at the next two panels and count up the number of failures, recognizing that some people may contribute more than once.

But the Kaplan-Meier curve is being driven by the 26 versus 7, it has just got to be that way, and the fact that it stays the same suggests that the hazard for this event in the two arms is pretty much constant after six hours.

DR. PETRELLA: Do we have a comment on the panelist's remark?

Would you like the Kaplan-Meier curve, Dr. Platt?

DR. PLATT: Yes, I will put that up.

[Slide.]

Yes, your observation is correct that it does look like everything is being driven by the first six hours; however, a side bar result essentially from a study of 2-day versus 5-day treatment with somatostatin.

If I can have DO-6, please.

[Slide.]

This presents some additional results on 2-day versus 5-day infusion of somatostatin, and shows, first of all, the treatment failure at two days, which appears roughly equivalent between the 2-day and 5-day groups, and at five days where things have changed.

So, the inference that the drug is not doing anything after Day 2 is perhaps not supported by these data. Again, we don't have the data on vapreotide stopping at endoscopy or at Day 2.

DR. CHANG: I think we need to get something a little clearer. It looks like the heart rate failure to meet the primary by the heart rate in the first six hours and to a lesser extent 48 hours, and that five days it is not even in the primary endpoint.

A lot of that difference in the first six hours looks like it was heart rate driven, but I guess what we need to focus on, something that Dr. Hasler said, what is it that we are trying to determine.

If we look at our question, because we are going to eventually come to the question about the efficacy, there is actually not a time period. I just want to ask the FDA-- I had originally thought that the indication was for

efficacy within the first five days, because you are going to look at the data differently, because you don't really have a heart rate issue in there.

The way the question is worded: Does the New Drug Application provide substantial evidence of efficacy for the proposed indication of adjunctive therapy to endoscopic intervention for the control of acute esophageal bleeding as a result of portal hypertension?

DR. EPSTEIN: Are we on the questions now?

DR. CHANG: No, no, no. I just wanted to clarify because we are making a big point about the timing.

DR. NEATON: Can I just make one point here? I think, and correct me if I am wrong, the heart rate is in there at five days. Once you are a failure, you are always a failure. You are counting the number of failures or they are counting the number of successes at five days. It makes no difference when it occurs. It could occur in the first six hours, the next 12 hours, sometime before five days.

From the slide that we saw, most of the failures in the placebo arm are occurring in the first six hours, and most of those failures are due to heart rate.

DR. EPSTEIN: Can we put that Kaplan-Meier curve

back up again, because it went quick.

[Slide.]

Those two lines are the same except for the initial six hours. So that is where the heart rate difference is, and that is where the failures occur, and other than that, they are identical.

DR. CHANG: I think we have beat that down. Are there any other additional comments about the efficacy from a time standpoint? Okay.

So, we want to move to any other discussion points. I think Dr. Kane had a question.

DR. KANE: I was just curious for the VAP-07 study, why only males were enrolled and why you chose a different etiology of cirrhosis--i.e., schistosomiasis.

I know that is what you are going to see in Egypt, but why that when we had a discussion about patients who are alcohol or HCV or a combination cirrhotics?

DR. PETRELLA: Dr. Besseghir will provide some background.

DR. BESSEGHIR: Well, asically, we started to evaluate vapreotide in variceal bleeding by starting two Phase 3 studies, the 02 and VAP-14, 02 in Asia, and VAP-14

in France, and then, clearly, it appeared after a few months that 02 we are not reaching what we were expecting in terms of speed of recruitment and quality, so we decided to look outside where we could conduct a study, a placebo-controlled study.

It just happened that we learned that in Egypt, there is an epidemic of hepatitis C. Some of the villages in the Delta of the Nile, there was 2,000 of the population which is HCV-positive, and this one center that we had occasion to visit had something like 200 variceal bleeders per month.

So, we decided to check if you could conduct the Phase 3 study there. But we did a Phase 2 study just to see how it would work. And it just happened, in this Muslim country, women, you cannot enter into clinical studies plus also the fact that bilharzia was mixed with hepatitis C. So both this bias in gender, recruitment, and the background disease was such that we decided not to do a Phase 3 there.

DR. CHANG: Dr. Raufman.

DR. RAUFMAN: I just wanted a point of clarification. It is not exactly relevant to what we are discussing, but several times people have talked about this

Egyptian study as indicating cirrhosis. Schistosomiasis doesn't cause cirrhosis. It's a pre-sinusoidal lesion, and, yes, a lot of these patients develop iatrogenic hepatitis C genotype 4 from treatment for schistosomiasis, but that entire group is questionable as to what the etiology of the liver disease is.

DR. KANE: They still get portal hypertension, though, it is just not from cirrhotic liver disease.

DR. RAUFMAN: That's correct, but it is still not cirrhosis. And the defining disease here, this comes up in a number of slides. It came up in slides before where it said that all of these patients are cirrhotic. That is not necessarily the case.

DR. BESSEGHIR: Can I comment on that? We had bleeders, so these patients had external signs of cirrhosis, and they had superficial bleeding, and it's only post hoc analysis that the investigator could determine if it was pure schistosomia or mixed hep C and schistosomia. Most of the population had mixed etiology. They had both hepatitis C and schistosomiasis. We didn't know to what extent hep C or schistosomiasis were playing a role in the variceal bleeding.

DR. CHANG: Do you know--I am asking the sponsor--if there are differences in the prevalence of comorbidities in the 301 study in the placebo group versus the VAP group?

DR. PETRELLA: In the VAP-14 study, Madam Chair?

DR. CHANG: 301.

DR. BESSEGHIR: Wll, I think one of the main points was the HCV--HIV-positive patients. There were more HIV-positive patients in the 301.

DR. CHANG: Yes, sorry.

DR. PETRELLA: In the open-label study, yes.

DR. CHANG: Right. Are there any other points that people want to bring up for discussion before we go to the questions?

DR. PETRELLA: Madam Chair, I believe also one of the panelists was interested in seeing a meta-analysis of the totality of evidence with and without the pivotal VAP-14 study. I am going to quickly introduce the numbers and then ask my clinical colleagues to comment on this.

[Slide.]

DR. PLATT: This is the meta-analysis with VAP-14, and in this particular one, the VAP-06 data is split into the pre- and post-populations. I will remind the panel that

the VAP-06 with the significant protocol amendment had a change in practice after the amendment renders the efficacy data from that difficult to interpret.

That being said, I will move on to the next one, which is the one without VAP-14.

[Slide.]

This one has VAP-06 as a single study. I also have it with VAP-06 as the split studies if that is of interest, but this gives the results for VAP-07, VAP-02, and VAP-06 together, and the overall result is at the bottom. These are again excluding the pivotal. I will ask Dr. Chalasani to make a short comment on this.

DR. CHALASANI: One point I would like to make is once again this has been said before, conducting clinical trials in acute variceal bleeding is extremely difficult. In the last 15 years, I was also talking to Dr. Grace and Groszmann. There is not actually a single randomized control trial in the United States of variceal bleeding, extremely difficult to do. That is just a point I would like to make.

The last data or anything that came out from the United States are just largely cohorts describing variceal

bleeding. There is a risk that we may end up with a condition without an approved medication.

DR. PETRELLA: If there are no further comments--Dr. Besseghir, maybe one final remark, Madam Chair.

DR. BESSEGHIR: This is maybe an element of thought.

[Slide.]

This, we measured the difference between vapreotide and placebo-treated patients, and as a failure of the patients, those patients had to be switched to a therapeutic alternative. We see that either, if you look at the failures due to therapeutic alternative, we still have vapreotide doing better than placebo.

If we look at the therapeutic alternative required or death, the significance is still there.

This, there is no heart rate.

DR. CHANG: Dr. Epstein.

DR. EPSTEIN: That is not in our data set, so it is hard to know what it means with those patients, but I had a question. Patient 1201 had SIRS. Patient 0604 had severe thrombocytopenia. And Patient 409 had DIC. There were high rates of thrombocytopenia.

Can you--before VAP-14, can you go back and show your adverse events and also in the Eastern European study, can you show that, when did you start seeing thrombocytopenia?

DR. PETRELLA: Dr. Chalasani, would you like to comment on some of the events?

DR. EPSTEIN: Do you have the data?

DR. CHALASANI: I think the thrombocytopenia came after 301. That is when the three cases of thrombocytopenia came and then any potential for safety signal. The three open-label studies, that is when it came. I think that was your point, when you started seeing thrombocytopenia.

DR. EPSTEIN: You had 8 versus 1 in your earlier studies.

DR. PETRELLA: I believe reference is being made to VAP-06 where platelets were not collected at baseline.

DR. CHALASANI: There was no baseline collection. There was one site, there were six cases of low platelets. That was during infusion, but the difficulty was that there was no baseline platelet count measured in those six patients.

DR. EPSTEIN: Well, in your studies where they

were measured, how low did your platelets go in patients getting vapreotide, what was the lowest number you got?

DR. CHALASANI: While they collect that information, I can tell you one subject that you brought up, 0604, t went down to 60,000. And it started around 90,000. I can't remember right before, when the patient died and, as you know, they deteriorate. They do tend to go down.

DR. PETRELLA: We have that data. Perhaps we could bring it up again. Dr. Besseghir can speak to that.

Can you please bring up the slide?

[Slide.]

DR. BESSEGHIR: We don't have the data. I mean we can show the data, we can discuss that later if you wish, but we have here only means, and standard deviations of platelet counts. Those studies were baseline platelets, and platelets were measured.

DR. EPSTEIN: Right. I am looking for adverse events, the patients that had the severe thrombocytopenia. I think you had at least one that went down to 22,000 with infusion, isn't that correct?

DR. PETRELLA: Do we have information for Dr. Epstein?

[Slide.]

DR. BESSEGHIR: This is in the Patient 604. Maybe you can discuss it, Dr. Chalasani.

DR. CHALASANI: All that I want to point out is that this patient was quite sick and you could see gram-negative septicemia, Factor VII. Platelet did go down, but it seemed rather a concomitant event rather than a precipitating event. It was my assessment that the patient died from multi-organ failure.

You have other cases. Could you bring up the next one?

DR. PETRELLA: Dr. Chalasani, would this patient be representative of the other few instances where this was observed as well?

DR. CHALASANI: You know, if a cirrhotic is decompensated with gram-negative bacteremia and renal failure and multi-organ failure, it is not uncommon you see thrombocytopenia. I would like to think it is the norm rather than the exception, and not only thrombocytopenia, even DIC.

DR. EPSTEIN: But you have no data on what happened after the initial infusion to platelet count. Do

you have any data from any studies? Do platelet counts drop with the infusion of the drug?

DR. CHALASANI: Dr. Besseghir has shown the mean values--that is, during the infusions for five days--but it is the mean.

DR. EPSTEIN: Right, I understand that. I am talking about you give the bolus, what happens to platelet counts?

DR. CHALASANI: I see. Within the immediate 15-, 30-minute bolus, I don't know that information.

DR. BESSEGHIR: We have not looked into any of these data. We had all preclinical data both in dogs and rats in which we injected for 28 days for vapreotide. We have never seen anything calling for platelet monitoring. That was as a routine measurement in our protocol, that platelet had to be measured at entry at the Day 5.

DR. CHANG: Dr. Kammerman.

DR. KAMMERMAN: I have a question about the primary endpoint. Unfortunately, the materials I need to answer my question are back in my office. But I do have the study protocol, and it says that subjects who are lost to follow-up or withdrew from study are to be counted as

treatment failures.

I am wondering if you can tell us the number of subjects in the placebo and treated arms for both VAP-14 and VAP-301 that were counted as failures because of that.

DR. PLATT: I apologize. I was just trying to clarify with regard to VAP-301. In fact, we have got the results here for VAP-14 and I am just confirming that with regard to VAP-301, there were no failures during the first five days due to lost to follow-up.

DR. CHANG: Is this information answering your question about 14?

DR. KAMMERMAN: Yes, it did. Thank you.

DR. CHANG: Are there any other questions or comments?

DR. SHIH: I would like to make a request from our clinical colleague, if you are familiar with the Barcelona study, the cohort of 210 patients, that shows similar mortality to the 301. How would you assess the similarity between those two cohorts? Would they use the same kind of pharmacology treatment? T

This bothers us that the mortality is different from our 301 to the previous controlled studies but similar

to this cohort. But I am not familiar with the study, so it would be helpful.

DR. CHALASANI: You make very good points. When I first saw VAP-30 data, the 25 percent day 42 mortality was striking and then, of course, it was concerning. But as I look carefully at other cohorts, it seemed like that is in the ballpark of other unselected cohorts of patients.

The Barcelona is one example. It is 210 patients from multiple sites, and this is only presented as an abstract of the EASL meeting. So this has not been peer reviewed. There is a peer-reviewed publication that I will come back to.

This is all patients with variceal bleeding. The main purpose of the study, at least in the abstract, was to look at predictors of death at day 42. But, along the way, they describe different event rates, and patients received vasoactive therapy consisting of different modalities upon presenting to the emergency room, and then they received endoscopic treatment at varying intervals, but typically within 12 hours.

So, broadly, they are comparable to 301, broadly comparable to what we see in clinical practice. That is one

data set.

Second is a paper that was published last November in Hepatology. The author is Hami Bosch.

They had a large cohort of cirrhotics with variceal bleeding where they were randomized to standard treatment plus placebo versus standard treatment plus recombinant Factor VII. The primary endpoint was to see benefit for Factor VII. They did not see benefit there, but the point is even the placebo group in that arm, actually, the overall survival was comparable to 301.

So, looking at all these, I am comfortable to say 301 is within the clinical context of what we are observing.

Also, in 2003, I published a paper, a multi-center cohort study from the United States. The mortality rate was around 80 to 90 percent, not vastly different considering 301 only had about 77 patients.

DR. FURBERG: You can't compare mortality outcomes in a cohort study with the outcome in a clinical trial, because they have exclusion criteria in the clinical trials. You eliminate the sickest patients, so the event rate is almost every time lower in the trial, and here it is the other way around. You can't get away from that.

DR. CHALASANI: You make a good point. The 301 is an open-label, single-arm study. I am giving you some other data from the literature to make us understand better, that's all I am doing.

DR. FURBERG: But they still had exclusion criteria, so you eliminated the sickest patients. You saw the exclusion criteria.

DR. PLATT: Just as a point of clarification, the paper that Dr. Chalasani was referring to by Bosch, in fact, was a trial. You point is well taken regarding cohorts versus trials, but the Bosch paper regarding Factor VII was a trial, and, in fact, the standard treatment that Dr. Chalasani referred to included potential use of vasoactive drug. So, in that trial, both arms received octreotide or terlipressin or other vasoactive drugs, and Factor VII was the randomized agent there.

DR. CHANG: Dr. Epstein.

DR. EPSTEIN: It seems to me the best comparison is to compare historically the 14 with the 301, because here, if anything, we have much better therapy with banding regardless of slightly larger variceal size.

So, if you are going to look historically, you

have two studies where you have excluded certain patients based on your exclusion criteria. So, I would expect that the 301 study would have had a better mortality than the 14. And I was very surprised to see that the mortality rate was substantially higher when, in fact, I would have expected it to be lower based on the fact that most of those patients got banding, which we know is a much better technique than sclerotherapy.

So, I am at a loss to understand how you could make any other comparison.

DR. CHANG: I guess also the question, though, is it is not within the time frame of getting the medication. So, this was delayed, and these are patients--as we know, these are patients with complex liver disease.

So, I guess the question would be, or discussion, do we really think that the increased mortality is really drug related. When you see it in one study that is open label, correct me if I am wrong for those five days, and not 42 days later.

DR. SMITH: I don't think that is really the question. The question with that issue is whether you have two populations that are comparable, and it would appear

that you don't.

DR. CHANG: I was referring, at least in my mind, if we are looking, as far as safety of the drug, because that is what the question is going to be, that is what was in my mind.

DR. NEATON: I would offer that 301 is uninterpretable as far as safety. You are giving a drug on the background of a serious disease where there are lots of things going on. It is impossible to interpret it without a control group, and you have none. So I think we could speculate all day long about what the causes of death were, what the adverse events would do, but we don't know. And know that we are often wrong; that is, what we do know is that we often wrong and attribute kind of adverse events to specific drugs, and that is why we do randomized trials.

DR. CHANG: Are you stating that outside of 301, if you were going to evaluate the safety of the drug, you would exclude 301 and base it on the other studies?

DR. NEATON: 301, in my mind, doesn't contribute much to the safety question. Unfortunately, what it brings to mind is that the drug has not been used in the proper controlled setting in a way in which the disease is now

treated.

DR. EPSTEIN: I just wanted to get back to that safety question because, you know, there were some signals there, and I would be curious as to what the panel thought.

Thrombocytopenia was 1.7 percent versus 0.3 percent in all arms. So, if you multiply that out by a large number of patients getting the drug, do we really have enough data from the sponsor on what is happening to the platelet counts especially in those critical hours when you are trying to control the bleeding. We don't know if the platelet count is dropping low or how much it is dropping, and some of the other significant side effects, too.

DR. CHANG: I am wondering if it's just worth bringing up that data. Are you referring to a specific slide that maybe we could quickly look at?

DR. EPSTEIN: The combined data from all of the studies.

DR. PETRELLA: Could we have that slide for Dr. Epstein, please.

DR. EPSTEIN: It's the assays. It's not the mean.

DR. PETRELLA: The serious adverse events attributed to thrombocytopenia, please.

Dr. Besseghir, will you be speaking to this data? Perhaps we could bring the slide on the screen for the panel.

DR. BESSEGHIR: WELL The thrombocytopenia reported as adverse events were seen in the placebo-controlled studies in two cases, in the vapreotide, and in one case, and the placebo if you report that to the number of patients--I am sorry, six cases--that is 2 percent and possible 0.3, 0.4 percent.

In 301, we have two cases. There is no placebo control. In the pancreatic surgery study, we have two cases of thrombocytopenia that are reported in the vapreotide arm, and we have three cases in the placebo arm.

So it really looks like that the thrombocytopenia, as an adverse event, when it is observed, it is observed in the cirrhotic patients.

DR. CHANG: Dr. Raufman.

DR. RAUFMAN: Is the pancreatic surgery study the only other vapreotide study there is?

DR. BESSEGHIR: No; we have actually more than 1,200 patients who received vapreotide. Some of those studies were investigator-sponsored studies, which means

that the adverse events were not collected systematically unless they were severe. We have not seen one case of thrombocytopenia in any of those 1,200 patients.

DR. CHANG: Maybe we could make this the last comment, because we need to get to the discussion.

DR. GRACE: I would just like to comment on the thrombocytopenia. I chaired the Safety Monitoring Committee for the European study on recombinant Factor VII, and we were very concerned about hematologic changes particularly thrombotic events because of the recombinant Factor VII, so we monitored this very carefully.

Twenty-four percent of the patients received terlipressin, 28 percent somatostatin, and 48 percent vapreotide in the placebo group, and a similar distribution in treatment group, and there was no thrombocytopenia in either arm of the study.

Advisory Committee Discussion and Voting

DR. CHANG: If there is no further comments, we will be using a new electronic voting system for this meeting. Each of you have 3 voting buttons on your microphone: Yes, No, and Abstain. Once we begin to vote, please press the button that corresponds to your vote.

After everyone has completed the vote, the vote will be locked in. The vote will then be displayed on the screen. I will read the vote from the screen into the record. Next, we will go around the room and each individual who voted will state their name and vote into the record, as well, as the reason why they voted as they did.

Before we vote, does anyone have any questions just on that?

Okay. I will read the first question.

1. Does the New Drug Application provide substantial evidence of efficacy for the proposed indication of adjunctive therapy to endoscopic intervention for the control of acute esophageal bleeding as a result of portal hypertension?

Before we go to the vote, does anybody have a question about this particular question we are voting on?

[No response.]

DR. CHANG: If you could place your votes.

[Electronic voting]

DR. CHANG: For the record, the voting result is Yes 1, No 13, Abstain zero.

We are going to go around the room. If you could

state your name and the reason why you voted.

Dr. Silberg.

DR. SILBERG: I am a non-voting member.

DR. CHANG: Oh, you don't vote, I am sorry.

Dr. Baranski.

DR. BARANSKI: I believe that although the study,--I compliment the sponsors at providing a lot of information, I am not assured that the studies substantially showed overall that the drug is ready yet for approval.

DR. CHANG: Dr. Fogel.

DR. FOGEL: I don't think that the evidence that was presented is conclusive to show efficacy. There are some hints that there may be a drug effect, but if it's there, it is very small, and I think that the sponsor has been overtaken by changes in medical therapy, such that any effect that they may have had has disappeared with the improvement in our endoscopic therapies.

DR. NEATON: Jim Neaton, University of Minnesota. I voted No. I didn't think that the overview of the trials apart from VAP-14 were strong supportive information, the randomized trials; that is, the fact that the primary endpoint of VAP-14 was driven by heart rate, I thought was

also kind of a point against it.

The observational or the open-label trial has just got too many problems in terms of to make it interpretable. It is done in a different population, different etiology, different treatment, and I think it is just simply not interpretable, and there will have to be a lot more quantifiable kind of analysis to justify even doing a simple comparison.

DR. CHANG: Dr. Blum.

DR. BLUM: I am the outstanding one. I voted Yes, and the reason for it, these aren't good studies, they are not great. There is a little bit that looks like it may work, but at the present time, as a clinician, every single patient that is being treated for esophageal varices in the United States is the component of a study.

We have no data on everything else. We talk about octreotide, we talk about somatostatin as if we really knew what they were doing. We don't know what they are doing. At least we know a little bit about this. Is it great? No, but at least we know a little bit about it.

As a clinician, I would like to know everything, I would like to be able to tell my clinical pharmacists look

for thrombocytopenia, look for this, look for that, because that has been seen. Right now we are shooting in the dark.

DR. CHANG: Dr. Smith.

DR. SMITH: I vote No. I think the sponsors failed to demonstrate an efficacy advantage. I am particularly concerned about the difference in mortality between the 301 study and the VAP-14 study.

DR. CHANG: Curt.

DR. FURBERG: Curt Furberg. I also voted No. I agree with Dr. Smith, the sponsor has failed to show that the drug has substantial benefit or efficacy.

DR. CHANG: Ms. Sklar.

MS. SKLAR: I voted No. I felt that there were too many changes in the therapeutic methods over the past decade, and I didn't feel like the data was comparable enough for me to say that there was efficacy in this.

DR. CHANG: Dr. Raufman.

DR. RAUFMAN: Jean-Pierre Raufman, University of Maryland. I voted No, because the second study was not controlled.

DR. CHANG: Dr. Cullen.

DR. CULLEN: Joe Cullen, University of Iowa. I

voted No specifically because in the Slide CR-5, they say control of bleeding at 5 days is generally associated with improved survival at 6 weeks. From all the studies I did not see an improvement in survival.

In fact, one of the studies suggests an increase in mortality.

The other thing that made me vote No was really a lack of mechanistic studies in a patient population. They presented some rat studies showing a decrease in portal hypertension. But, going back to Dr. Blum, we don't really know what is going on here, and if you use the strict criteria--if you look at the criteria that the FDA has presented to us regarding substantial evidence, I don't think the studies done for this drug meet that.

DR. CHANG: This is Dr. Chang. I voted No. I feel that this has been a difficult situation because of the agreement made and that the sponsor did the study as best they could on the agreement that was made, and I do feel that there is some signal that the drug may be efficacious in these patients. However, I have to say that I was pulled in the direction that Dr. Neaton brought up about that a lot of it was due to the heart rate, and if a medication does

affect heart rate, that should be assessed at the beginning of the trial and determined what may be the best outcome measure for that particular trial.

DR. KANE: Susie Kane, Mayo Clinic. I voted No along with the reasons that were stated by my colleague, Dr. Cullen, that the word "substantial" within the question, I didn't feel that I had enough evidence from all of the data gathered. I certainly think that there is a signal from the VAP-14 study particularly, but right now I don't feel that there is substantial evidence for efficacy.

DR. SHIH: I voted No and, in viewing all the studies conducted I feel there is only one positive study--that is the VAP-14--and the rest are inconclusive. I sympathize with the company. So your lesson is don't take the FDA's agreements too seriously, just do what is right. This is an orphan drug category; it doesn't matter, you still needed to conduct the study according to the requirements.

DR. CHANG: Thank you, Dr. Shih.

Dr. Epstein.

DR. EPSTEIN: I would just like to mirror what Dr. Shih just said. Although I understand and I sympathize with

the fact that the studies were hard, the methodologies suffered on many different levels. We know this is difficult, and we know there was an agreement but, besides that, just making sure that you have the data that is going to really show and drive the efficacy. It is very important.

Secondly, the statistical analysis left a lot to be desired, and the collection of data, the platelets and other things, I think also should have been done, as well.

DR. CHANG: Dr. Hasler.

DR. HASLER: Yes, I agree with the other speakers. I voted No. I think there was only one study which showed any evidence at all that this was beneficial, which was the 14 study. The other studies were not only negative, but they included data which could not really be used including the Egyptian study, which looked at a disease entity we hardly ever see here in the U.S.

The Eastern European and the Hong Kong studies, both of which had protocol-related issues which made the data difficult, and then the 301 study which lacked a control arm, so basically presented that data which was hard to put into perspective with the 14 study.

DR. CHANG: I am going to just summarize all the statements made, so just collectively, some of the panel members believed that there was some small level of improvement mainly based on the VAP-14 study, but that it has been complicated because of the other studies that we can't really completely interpret or use to at least evaluate efficacy.

There has been some change in practice, just in clinical practice managing these patients with esophageal variceal bleeding, that there wasn't substantial evidence to prove or support its efficacy.

There was some difficulties or some flaws in the statistical analysis and collection of data that maybe could have been improved, and collectively stating to the sponsor to do more rigorous study protocols to actually determine if their drug is indicated in what they are seeking.

Does anyone want to revise that or make any additional comments?

[No response.]

DR. CHANG: We have one other vote, but before that we are going to have a couple discussion questions.

1a. If there is not substantial evidence for

efficacy, which basically we have stated, are there additional efficacy data or studies that should be obtained prior to approving Sanvar for the proposed indication? If there is, please describe the design of the studies, for example, placebo-controlled, dose-ranging.

Do you want to start with Dr. Hasler?

DR. HASLER: Sure, I will start out. I agree with the assessment of the FDA back in 2004 that it would be very difficult to do a placebo-controlled study in the current environment.

With respect to dose-ranging, I think before we design a dose-ranging study, I would like to know from animal studies is there a dose-dependent effect on any of the hemodynamic parameters within the abdomen.

I know from within my own work in motility, which is a different field, octreotide has an extremely flat dose-response curve, so I don't know that a dose-ranging study would be beneficial.

I think what would perhaps be useful if acceptable to the rest of the committee, would be a comparison to another drug that we commonly use, such as octreotide.

DR. CHANG: Does anyone else have any comments?

Dr. Blum.

DR. BLUM: Yes. On a pharmacologic basis, the only thing that would make sense is a head-to-head study. Again, another compound in the same field, whether it be somatostatin or octreotide, or any one of the others, do a head-to-head study using the same criteria, because I sit on an IRB and you will never get a placebo-controlled study through an IRB today. But you will be able to get a head-to-head study through an IRB today.

Look for the parameters that you want. Do you want heart rate as a parameter? If that is going to be a standard, set it up. Platelet counts? Set it up at the beginning and then stick to it. That is the only way you are going to really find out if there is a significant difference.

Again, I will reiterate, we are using octreotide, someone else is using somatostatin. We have no idea what they do. Somatostatin does raise pulmonary artery pressure. So, there are things that happen with others when it starts shunting.

DR. CHANG: Dr. Beitz.

DR. BEITZ: I just wanted to make a couple of

comments about a comparative study to an active such as octreotide, and a couple of things to keep in mind.

We really have two options. One would be to design a superiority study, and the other would be a non-inferiority study. So, in the first instance, if you are going to say that vapreotide beats octreotide or whatever you choose, how realistic do folks think that is?

If folks think that that really isn't a viable option, then, you are really left with a non-inferiority study design where you need to do a couple of things.

You need to decide from the literature and clinical experience what the effect size, what the treatment effect of octreotide is, and once you have calculated that to sufficient amount of confidence, then, you have to decide what amount of that effect are you willing to forego in your study drug.

So, there is a fair amount of research and assumptions that have to be made about the octreotide or the active. You have to really understand what it is doing before you can then design a study against it in a non-superiority type of setting.

Then, finally, on that design, those studies

typically are fairly large and in an orphan setting, that may not be feasible.

So, just some points to consider, and the statisticians may have much more to say about that.

DR. CHANG: I have a little list here of people in order, but does anyone want to make a comment on that particular active comparator? Dr. Fogel.

DR. FOGEL: One of the things that I would be concerned about if that study was done and did not show any difference, would somebody around this table say, well, you are comparing it to a drug that we don't know whether it works or not, so I am not sure that the company would be further ahead after making an investment like that.

DR. CHANG: Dr. Epstein.

DR. EPSTEIN: I think the first analysis that needs to be done is simply to go back and take the existing data and re-analyze it more carefully, and look at those Kaplan-Meier curves again.

I think if you take out the heart rate, you need to find out is that the thing that is driving this drug, because you have got enough data, you don't need to do more studies.

You have got lots of patients that have been treated. They are very difficult studies to do, and look at it and say hey, look, if it works without the heart rate change, then, there is something there. If it doesn't, you have got enough data to know is this going to work or not.

I think that is the simplest starting point rather than going back and doing these very, very lengthy, time-consuming, expensive, and probably impossible to do studies.

The second point is we have, I think, despite what Dr. Chalasani said, I think we have endpoint data mortality data, and we are not seeing a strong signal there. Even in this number of patients, I would have liked to have seen a significant signal coming through. Maybe it didn't reach total significance, but at least we would have seen the mortality, because that is the point of all of this, is the mortality.

DR. CHANG: Dr. Silberg.

DR. SILBERG: I just really agree with what was said about asking the sponsors to do another study that may lead them to a path of the same results we are getting today, and that again, as a committee, we have to be careful about leading the sponsor on, that this is then going to

come back as their solution.

It is the same thing of what the FDA had agreed on with them to do the open-label study, is that it is very difficult for the sponsor, because they take what we say very seriously, of course, and then do the study.

I think it will be very difficult to do a study, I agree to a superiority study, I think would not work at all, too many patients and I don't think that the mechanism of action is going to be the same. I don't think they are going to see much of a difference.

The best they would be able to do would be a non-inferiority type study. Again, would we, as a group, having them come back here, would we accept that, because it would be very similar to an open study. We would get very similar results, and then what would you compare it to.

I think just have to be careful about what we say would be the next step.

DR. CHANG: Dr. Furberg.

DR. FURBERG: I am old-fashioned. I think we treat patients in order to help them, so the outcome should be a benefit to the patient, and let's not think too much about blood pressure and heart rate, and so on. I think the

sponsor should go back and try to define proper health outcomes. Mortality is one. There are other ones we can look at - rehospitalizations, length of stay, functional capacity, and you can combine them in different ways.

The other one is that I wouldn't go away from five days. I mean you look, trying to help people live long term, and maybe even consider long-term follow-up.

DR. CHANG: Dr. Neaton.

DR. NEATON: I hesitate to say too much because this is an area that I don't know much about except from what I read for this meeting, but if you are going to do a non-inferiority trial, implicit in that kind of design is some information on the active comparator versus placebo, and I am not sure you have it.

You are going to want to have some strong evidence that the active comparator is better than nothing, in order to understand and interpret the results when you are done.

Given the results that I have seen today, and from these trials, and from the meta-analyses, there is not strong evidence here that these drugs impact things that are really clinically meaningful to patients.

So, I don't understand why IRBs are saying don't

do placebo-controlled trials.

DR. CHANG: I guess what is important to a patient and what they consider a benefit is up to the patient. Maybe that is something that hasn't been evaluated as carefully.

I mean, of course, mortality would be and probably hospital stay, but, you know, those are just two outcome measures, and we do probably have to do some work and understand from a patient's perspective what is important to them, what is as meaningful change or improvement for these particular patients.

MS. SKLAR: From a patient's perspective, when you are being rushed into the emergency room and you are vomiting blood--and you are not given a choice of what these side effects are because they are just going to put it into you. They are not going to stop and explain to you what the side effects are.

We have to make sure that it is a very, very safe drug, and we also have to make sure that it is going to impact mortality. I mean given the choice of whether or not I am going to live and if it's this drug, then, I will take the drug, but if it's not going to cause any great benefit

in that way, what's the point?

DR. CHANG: Well, there is a difference between mortality, which obviously is important, but also morbidity, and I would state even if it didn't alter mortality, there is still a question that it may improve some other outcome measure that would be important to you as a patient.

Dr. Blum.

DR. BLUM: We are doing that every day now. We are putting the drug into a patient and we have no idea. We think it's working, we hope it's working, but I think, you know, in pharmacologic studies, there is a thing called quality of life evaluation also, which is something would be very good to put into the patients here.

These patients at this stage probably are not working. Their quality of life may be just walking around the house or being able to go out and sit outside with the dog. So, that may be important to them.

DR. CHANG: Are there any other comments on this particular discussion?

[No response.]

DR. CHANG: I guess to summarize some of the information that will be useful is to, first, just look at

some animal data and determine if there is any dose-response effect with this medication and whether or not that is something that should be studied in humans.

We should also evaluate the different important endpoints to evaluate, not just this international consensus endpoint, but mortality, hospital stay, and other relevant endpoints for this particular target population that the company may want to evaluate if they go back and look at their data.

One thought was to do an active comparator study to octreotide, which is the first thing that comes into most gastroenterologist's mind, but what was brought up is that some of the data, there is variability, and it would be challenging to show a superiority result, and it would really show a non-inferiority type of study.

So, there would be challenges with that particularly since the medication octreotide is standard practice, it is not FDA approved.

The other thought that came up, which is very valid, is not to do another study, but re-analyze and go back to the data that is collected, that there is a large amount of data, that there may be important information that

you can determine from that, that is very relevant and useful, particularly looking at the heart rate effects, also perhaps looking at a subgroup of patients.

Maybe it's only the Child A and B that have more efficacy and you don't have the heart rate effects, and may just be more effective in a certain population of patients.

I think that's it.

Are there any other additional comments?

[No response.]

DR. CHANG: We are going to move to our next discussion question.

2. Are there safety concerns associated with the use of Sanvar in acute variceal bleeding?

Would anyone like to make a comment first? Dr. Epstein, you had a lot of comments about the safety, are there safety concerns associated with the use of Sanvar in acute variceal bleeding.

This is not a vote, this is discussion. This is just open for discussion.

Does anyone want to make a comment about safety concerns they may have? Yes, Dr. Furberg.

DR. FURBERG: I don't think we have enough

information either way to say whether the drug is safe or not safe. So, in a way, I would like to have a little bit more information particularly in terms of the trends that were pointed out by the FDA, thrombocytopenia, and others.

If we get a little bit more information, then, I can go either way.

DR. CHANG: Dr. Silberg.

DR. SILBERG: Given this patient population, I can see how it would be very difficult to determine which event. or the drug itself, because of the concomitant medications the patients are taking.

I think that in terms of what the sponsor said, and I understand how the FDA looks at the data, that, for example, thrombocytopenia is a very common event for patients who have cirrhosis and especially patients who are bleeding and getting transfused and getting resuscitated.

So, although there looked like there were trends, I think we have to be very careful about making conclusions when you have multiple things happening at the same time to say that it was particularly this drug, given what was happening. And since a lot of this happened during the 301 trial, which didn't have a comparator, you are getting a lot

of events that you can't balance to what is happening to placebo.

DR. CHANG: I think it would probably be important to see if there is a signal for something in particular because if you are going to re-analyze your data, you are going to study the medication in a different trial, you will probably want to have a more focused target population where you can maximize benefit and minimize safety problems.

Dr. Epstein.

DR. EPSTEIN: Just to Dr. Silberg's point, that is the point of having good control trials, so you can tease out those issues, and that is one of the reasons that we are struggling with some of these questions, is because we have somewhat limited data in those areas, not only limited data, but limited data collection in the areas that could be important.

When somebody is acutely bleeding, if they get a bolus of a drug, and they transiently drop their platelets a lot, that could make control of hemorrhage more difficult, and at least in one or two of the studies, hemorrhage was significant in octreotide group. That is why we want to have those studies in the first place, but we don't, so we

deal with what we have.

DR. CHANG: Dr. Neaton.

DR. NEATON: I was going to say the same thing. You need controlled studies. But I actually was reassured by the short term data on survival and discontinuations of treatment due to adverse events, which were very similar, and the placebo and active controlled arms. Those are two kind of outcomes that I would be concerned about if there were strong trends one way or the other, and they look pretty good.

DR. CHANG: Dr. Smith.

DR. SMITH: I keep coming back to this issue about the difference in mortality between the 301 study and the VAP-14 study. I don't think we can ignore that. There is no explanation for it at the moment except for perhaps the populations were different.

The other possibility here is that there are some yet untoward, undetected chronic effect of therapy with Sanvar that is detrimental to patients, and for that reason I think that we have to be aware of the fact that most drugs that we use have side effects, and the fact that this drug apparently is relatively well tolerated makes me suspect

that it also has very little activity.

The other thing is that this variation in mortality that has been detected here, that I would be fearful that there is something going on that just simply isn't being detected in the studies that have been published so far and that we have reviewed that are detrimental to the patients.

DR. CHANG: Dr. Blum, did you have a comment?

DR. BLUM: No.

DR. CHANG: Dr. Hasler.

DR. HASLER: I haven't heard anything that really raises major concerns about this. I think that what I have heard about the thrombocytopenia is perhaps it is clinically relevant.

I agree with Dr. Epstein I sure would have liked to have seen serial platelet counts drawn to get an idea as to how serious it is, but I would have suspected that truly clinically relevant thrombocytopenia would have teased itself out and made it self-evident in terms of an increased requirement for blood transfusions.

DR. CHANG: So, we would summarize that. There may be some trends or concerns of adverse events or series

of adverse events, but nothing definitive, and part of the reason why is that we don't have quite adequate controlled data to really determine that, and also that this is a very complex patient population who have a lot of events that are adverse that occur in them, and we are not necessarily sure if it's due to the drug or just due to their chronic condition.

There was some concern that there may be a chronic effect of the drug that may lead to more delayed adverse events.

If no one wants to also revise that or make any statements, we are going to move to our next discussion point.

2a. Are there additional safety data or studies that should be obtained prior to approving Sanvar for the proposed indication?

There is no suggestions or maybe additional safety data or analysis? Yes, Dr. Furberg.

DR. FURBERG: I don't know whether we should recommend another trial, but the least they could do is to set up the register of uses. The drugs approved in other countries; let's learn a little bit from the experience from

those patients, or if it is used in other studies, so we have a database to look at, and do that in a scientific way, prespecify the questions and identify the subgroups that you have a particular interest in, so you can learn something from it.

DR. CHANG: I think they showed some data at least in clinical trials with other conditions although it wasn't a registry of patients that have been placed on the medications. I guess also maybe looking at just this class or family of medications in the somatostatin analog family to determine if there are any signals or trends for safety, adverse events that maybe they could look a little bit more closely at their data, as well.

Does anyone want to make any other additional points?

[No response.]

DR. CHANG: I am going to move to our last question. This is a voting question. It is our last one.

3. Based on currently available data, do the potential benefits outweigh the potential risks of Sanvar for the control of acute variceal bleeding?

Does anyone have any questions on this question

before we vote?

[No response.]

DR. CHANG: Please place your votes.

[Electronic Voting]

DR. CHANG: For the record, the voting result is: Yes zero, No 14, Abstain zero.

We are going to go around the room again. We will start with Dr. Hasler. Please state your name and your vote and the reason you voted that way.

DR. HASLER: Bill Hasler. I voted No. The reason, I don't see a lot of obvious harm with this drug. But I also see very limited benefit based on the data presented and, based on that, I don't think that the benefit to risk ratio is high.

DR. EPSTEIN: Michael Epstein, Annapolis. I would just second what Dr. Hasler said. Having said that, I think going back and re-analyzing the data that they have would be useful in further discussions with the FDA.

DR. CHANG: Dr. Shih.

DR. SHIH: You know that, in mathematics, if you divide zero by zero is undefined. So, in this case, it is undefined, so I have to vote No. However I want a quick

comment on this drug maybe suffered as a victim that suffered from its one success earlier in the VAP-14.

So, to somehow change the practice a little bit, so it is hard to conduct this study because. as someone said, the IRB is hard to approve, and not a study that without active agent in there, it is very difficult. So, dose-ranging studies may be a possibility.

DR. CHANG: Dr. Kane.

DR. KANE: Susie Kane, Mayo Clinic. I voted No, again for the reasons that Drs. Hasler and Epstein have already pointed out, that there doesn't seem to be a strong signal for risk, but the potential benefit does not appear to be strong enough to warrant use right now.

DR. CHANG: Lin Chang. I voted No and I would completely agree with my colleagues on their reason.

DR. CULLEN: Joe Cullen, University of Iowa. I voted No. With the data presented, I am not sure if there is any benefit, and with the data now presented, I am not sure what the risks are.

DR. RAUFMAN: Jean-Pierre Raufman, University of Maryland. I voted No and I have nothing to add to the previous comments.

MS. SKLAR: Jill Sklar. I voted No. I didn't see a big benefit, but I did have a concern that wasn't spelled out in the data about the thrombocytopenia.

DR. FURBERG: Furberg. No substantial evidence of efficacy and unclear safety.

DR. SMITH: Roy Smith. I would just say ditto to what everybody else has said.

DR. BLUM: Dick Blum, Long Island. I agree there is no difference in the risk-benefit ratio against the standard that is out there now, which is non-standard.

DR. NEATON: Jim Neaton, University of Minnesota. I guess I agree with my colleague, Dr. Shih. There seems to be a zero in the numerator and the denominator here.

DR. FOGEL: Ron Fogel. I voted No for the reasons that have already been mentioned.

DR. BARANSKI: I am Dr. Baranski. I voted No also and I agree with the comments already made. I would like to add a further comment, however, or two. This study has provided a lot of useful information in the benefits to risks, and so forth, of the drug.

There is not conclusive evidence of the things that are benefitting the use of this treatment. I know it's

accepted treatment now using vasoactive drugs plus endoscopy, but there is a lot of information to be gleaned, and this study is one of the most detailed studies I think we have, really does not show all of the benefits that are potentially available with the use of this treatment.

The other comment I would have is I don't feel that approving a drug to continue an ongoing study is appropriate. I think if it's approved, it is approved on the efficacy and the risk, and so forth.

Thank you.

DR. CHANG: To summarize, I think the majority have stated that there isn't definitive benefit, as well as definitive risk, and so the benefits do not outweigh the risk, and there was still some concern about the safety.

So, we are ending two hours early. Oh, do you want to make a comment?

DR. BEITZ: I just wanted to make actually a question for some of the clinicians here today. Given the outcome of this meeting, what do folks think about the potential impact on our current clinical guidelines for the treatment of this disease?

DR. BLUM: I think at the present time everyone is

using it. I think they took the study from the New England Journal, translated it into the drugs that were available. We really don't have any studies done whatsoever on the safety or efficacy of those drugs in this situation. It is just being used on a clinical basis.

DR. CHANG: I would state that I don't--and please correct me if I am wrong--I don't think anyone here on this panel is a esophageal variceal-bleeding expert and have known the data, and there may have been a lot of work that was placed into the experts making the standard of practice.

Unless anybody knows the whole evolution of that, we may not really recognize why it has become standard practice.

DR. GRACE: As one of the authors of the guidelines, I can explain to you what we did, and it wasn't based on the one study.

What we did is, the way the guidelines work, there is a committee from the American College of Gastroenterology, made up of gastroenterologists, and a similar committee from the American Association of Liver Disease, made of hepatologists.

They asked so-called experts in the field to

assess the data and draft a guideline. This is what we did. We submitted it to these committees, and these committees do not have anybody who is actively investigating in the field.

They assessed the data. We went through eight or nine different drafts of the guidelines to reach acceptance by the committee of the College and the committee of the AASLD. Guidelines were sent independently to both boards.

Both boards reviewed the data, which is evidence based, for promulgating the guidelines, and both boards agreed that the evidence was there for these recommendations.

The evidence was based, not on one study, and the recommendation was not one drug. It was vasoactive drugs. So, we looked at the studies with terlipressin, somatostatin, octreotide, vapreotide. We looked at the combined data from all of them, and the data I showed you on the meta-analysis from de Franchis was highly convincing.

DR. CHANG: Dr. Fogel.

DR. FOGEL: I actually have a question for the FDA. If there is clinical evidence to suggest that a drug is effective, but the appropriate studies have not been done to meet the FDA criteria, and a drug company decides that

they don't want to make the investment in this particular indication because the market isn't there for them, is there any answer to this issue? I mean is there a way to address getting drugs for new indications that have been shown to be safe, or is the expectation people will just use it off-label?

DR. BEITZ: Well, the only thing that comes close to what you might be suggesting is something called Accelerated Approval Regulations, which allow approval of a drug based on a surrogate endpoint, but that endpoint would have to be thought of in a way that we would say that that would predict clinical benefit.

So, I don't know if that actually happens in this case, because we are talking about bleeding endpoints, and those are probably clinically relevant in and of themselves forgetting the mortality issue.

So, that is about the only other way to do this, and in those cases they do have to do follow-up studies to verify that clinical benefit has been shown, so they don't get out of the market with the surrogate endpoint demonstration.

DR. FOGEL: I guess my follow-up question is does

the FDA take clinical guidelines, do they assess them when they look at drugs? I mean do studies that look at clinical guidelines and recommend best practice evidence-based medicine impact any FDA decisions?

DR. HE: Like this one, the guideline, the basis, the study we haven't had a chance to evaluate. We do not have any raw data from any of those studies, and think about additional is the the meta-analysis, basically, they only--I shouldn't say only--the trend is they publish positive study. Most negative study, most negative studies they do not get achance to publish.

So, they evaluate the data just based on the paper data, and not,like FDA, have a chance to evaluate in detail. So, sometimes yes, we do think about the guidance followed by the professional association. But we have to think very carefully about, what kind of level of evidence to support such guidance.

DR. CHANG: I just want to say something. When I made the comment about not having experts on the panel, and then of the voting and non-voting, it is out of respect to our consultants, the people that were part of the conversation and voting.

Dr. Furberg.

DR. FURBERG: I think we shouldn't lose sight of the fact that we have over 1,000 guidelines in the U.S., mainly on the same condition, they are very contradictory, and many of them have very weak evidence base, so most guidelines are a mix of opinions and evidence, and I think it was a mistake for the FDA to rely on guidelines to make any decisions.

DR. CHANG: Dr. Shih.

DR. SHIH: I think that this question was asked, but nobody answered it. Is this drug approved in any other region, country for some indication?

DR. PETRELLA: The drug is not approved in any other jurisdiction at this time. There is a registration in Mexico, but it is simply a license. The drug is not being commercialized, therefore, there is no data available elsewhere outside the body of the studies that have been presented.

We are pursuing registrations in various countries, however, there is no place where the drug is now being used in the clinical setting.

DR. CHANG: Dr. Smith.

DR. SMITH: No questions.

DR. CHANG: Trying to get back to what Dr. Beitz was asking, I think this is a challenging condition because there is a standard of practice with a non-approved drug. I am just trying to determine if we could spend a little bit more time for our sponsor and others that are trying to develop or get approved medications to help patients with this condition.

If we have any other recommendations on how to approach this, for example, maybe turning to our expert colleagues or coming up with a consensus, when you have a condition where you are using a standard of practice that I guess has some criticisms of whether it is valid or not, although I think most people think it is efficacious of these vasoactive drugs of how would you approach when you are doing drug development in this particular situation, and then working with regulatory.

I think this is a challenge to sponsors who are trying to get a drug approved for a particular indication where there is a standard practice with a non-approved drug.

DR. SMITH: I think one of the issues here is whether you are doing a study for registration purposes or

not, you know, obviously, if you are not doing it for registration purposes, then, you would compare it to the standard of care.

In this case as a nonregistration study, I think a comparison with octreotide is a very reasonable thing to do. I don't see how you could do anything else since a placebo study would not be possible under these circumstances.

On the other hand, one of the dangers of doing that is that if your standard of care hasn't been previously compared to a placebo, is if you compare a new drug to the standard of care, then, there is a chance that you might be putting into a study a drug which actually may be inferior. There is no way of knowing that unless the original drug was compared with a placebo.

I think it's a difficult situation to be in, to take a drug that is presently unapproved and use it as a comparator for a new medication, because you run the risk that you are going to be spending lots of money and lots of time, get data that actually results in a reduction in level of care that is given the patients.

DR. CHANG: Dr. Blum.

DR. BLUM: Under the Over 90, which is the federal

law that permits the off-label use of drug, I happen to sit on the United States Pharmacopeia, which is one of the organizations that was acceptable to put into effect off-label use of drugs and, basically, it didn't require double-blind control studies. Basically, it was just a clinical consensus by a number of experts in the field, such as guidelines, that put it into effect, the off-label use.

We never really required--or let's put it this way; it was never really required to have double-blind controlled studies. If they were done, that was great, we would add it to the mix, but otherwise, it's just consensus.

DR. CHANG: Does anyone from the FDA want to ask any further clarification or questions of the panel?

[No response.]

DR. CHANG: I would like to thank all of the advisory panel members for coming, the sponsor, the FDA for their presentations. Thank you very much.

[Meeting concluded at 3:10 p.m.]