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CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEETING

Chicago, Illinois

Friday, May 30, 2008

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P R O C E E D I N G S

(8:30 a.m.)

DR. HUSSAIN: My name is Maha Hussain. I will be chairing the meeting this morning. This morning's meeting is to discuss a new drug application for Promacta. The other name is -- I practiced that -- eltrombopag -- by GlaxoSmithKline.

I was going to ask them who came up with that name. The first thing that we're going to do this morning is read a statement for topics such as those being discussed at today's meeting. There are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record if recognized by the chair. We look forward to a productive meeting.

In this period of the Federal Advisory Committee Act and 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. Also, the Committee is reminded to please refrain from discussing the meeting topic during break or lunch.

I'd like to have the Committee members introduce themselves. And I'll begin on my left.

DR. CURT: Gregory Curt, medical oncologist, industry representative to ODAC.

DR. LESAR: Timothy Lesar, director of pharmacy, Albany Medical Center, Drug Safety.

DR. D'AGOSTINO: Ralph D'Agostino

from Boston University, statistician and consultant to the panel.

DR. SZYMANSKI: Irma Szymanski, professor of pathology, UMass Medical Center working at Boston University Medical Center.

DR. SANDLER: Jerry Sandler, Georgetown University Hospital, professor of medicine and pathology, and director of transfusion medicine.

DR. ALVING: Barbara Alving, hematologist and director of the National Center for Research Resources at the NIH.

DR. VOSE: Julie Vose. I'm chief of hematology and oncology at the University of Nebraska Medical Center.

MS. MASON: Virginia Mason. I'm with the Inflammatory Breast Cancer Research Foundation, and I'm the consumer rep.

DR. LINK: Michael Link. I'm a professor of pediatrics and a pediatric hematologist oncologist at Stanford and a member.

DR. MORTIMER: Joanne Mortimer, medical oncologist, City of Hope.

DR. VESELY: Nicole Vesely, designated federal official, ODAC.

DR. HUSSAIN: Maha Hussain, medical oncologist, professor of medicine and urology at the University of Michigan.

DR. LYMAN: Gary Lyman, hematologist oncologist, professor of medicine and director of health outcomes research at Duke University.

DR. BUKOWSKI: Ronald Bukowski, medical oncologist at the Cleveland Clinic in Cleveland, Ohio.

DR. ECKHARDT: Gail Eckhardt, medical oncologist, University of Colorado.

DR. HARRINGTON: Dave Harrington, statistician, Dana Farber Cancer Institute.

DR. PERRY: Michael Perry, hematologist and medical oncologist, University of Missouri, Ellis Fischel Cancer Center in Columbia, Missouri.

DR. DMYTRIJUK: Andrew Dmytrijuk, hematology M.O. for the FDA.

DR. BERKMAN: Suzanne Berkman, Office of Surveillance and Epidemiology, risk management analyst.

DR. RIEVES: Dwaine Rieves. I'm director of the Division of Medical Imaging and Hematology at the FDA.

DR. PAZDUR: Richard Pazdur, office director, FDA.

DR. HUSSAIN: Okay, thank you. Ms. Vesely now will read the Conflict of Interest statement.

DR. VESELY: The Food and Drug Administration (FDA) is convening today's meeting of the Oncologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act (FACA) of 1972. With the exception of the industry representative, all members and temporary voting members are Special Government Employees (SGEs) of Regular Federal Employees from other Agencies

and are subject to Federal conflict of interest laws and regulations.

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

FDA has determined that members and temporary voting members of this Committee are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special and regular Government 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 F the FD&C Act, Congress has

authorized FDA to grant waivers to special and regular Government employees with potential financial conflicts when necessary to afford the Committee essential expertise.

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

Today's agenda involves discussions of New Drug Application (NDA) 022-291, Promacta (eltrombopaq olamine), originally developed by Ligand Pharmaceuticals, Inc., in collaboration agreement with GlaxoSmithKline,

for the proposed indication for short-term treatment of previously- treated patients with chronic idiopathic thrombocytopenia purpura (ITP) to increase platelet counts and reduce or prevent bleeding.

Based on the agenda for today's meeting and all financial interests reported by the Committee members and temporary voting members, conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208(b)(3) and Section 712 of the FD&C Act to Drs. Maha Hussain and Gary Lyman. Dr. Hussain and her spouse own stocks in the sponsor firm worth between $50,001 and $100,000 and seven competing firms worth between $5,001 and $25,000. They also own stock in one other competing firm worth less than $5,001. Dr. Lyman's waiver is for his service on a competitor's Speaker's Bureau for which he receives less than $10,000 per year.

The waivers allow these individuals

to participate fully in today's deliberations. FDA's reasons for issuing the waivers are described in the waiver documents, which are posted on FDA's website at www.fda.gov/ohrms/dockets/default.htm. Copies of the waivers may also be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 6-30 of the Parklawn Building. A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript. Dr. Gregory Curt is serving as the industry representative, acting on behalf of all regulated industry. Dr. Curt is an employee of 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 issue.

Thank you.

DR. HUSSAIN: Thank you, Ms. Vesely. I'd like to invite Dr. Pazdur.

DR. PAZDUR: Thanks. On behalf of the FDA, I would like to take a brief moment to recognize several of our committee members whose terms will be expiring at the end of June. Drs. Hussain, Mortimer, Perry, and Bukowski have served on the ODAC Committee since July 2004, and their commitment and service to this Committee has been greatly appreciated.

Their involvement in the review process, however difficult, allowed the oncology divisions to provide safe and effective products for cancer treatments to

the American public in a timely manner.

I'd first like to recognize our chair, Dr. Hussain. Dr. Maha Hussain is a specialist in genital urinary cancer and has chaired the Oncology Drugs Advisory Committee for the last two years. She is professor of medicine in urology in the Departments of Internal Medicine and Urology, Division of Hematology/Oncology at the University of Michigan. In addition to chairing the Oncology Drug Advisory Committee, she also chairs the Advanced Prostate Cancer subcommittee of the Southwest Oncology Group. In appreciation of her service, the FDA would like to provide her with this plaque. Maha.

(Applause) Dr. Joanne Mortimer is vice chair

Of medical oncology at the City of Hope Comprehensive Cancer Center. Dr. Mortimer has been a member of the Oncologic Drugs Advisory Committee for four years, and during this term has served the Committee as

acting chair for recent meetings. Throughout her time on the Committee, she has provided the Agency with specific advice on specific topics and issues, and broader issues of drug development and clinical trial design. In appreciation of her service, the FDA would like to provide her this plaque. Joanne.

(Applause) Dr. Michael Perry serves as

Professor of hematology/oncology and the Nellie B. Smith chair of oncology emeritus at the University of Missouri Ellis Fischel Cancer Center. He is also director of the clinical trials office at the University Cancer Center. His knowledge of clinical trials, as well as his expertise in hematology/oncology has added immensely to the deliberations of this Committee. In appreciation of this service, the FDA would like to provide him with this plaque.

(Applause) Dr. Ronald Bukowski currently

Serves as emeritus staff consultant for the Cleveland Clinic Cancer Center. He has previously served as the director for experimental therapeutics program, as well as the director of the biologic response modifier program at the Cleveland Clinic. His credentials and experience have led to stimulating discussions of this Committee. In appreciation of his service, the FDA would like to recognize Dr. Bukowski's service with this plaque.

Drs. Hussain, Mortimer, Perry, and Bukowski, thank you again for your service on the ODAC. We highly appreciate your work that you do for us and value your opinions greatly. Thanks again.

DR. HUSSAIN: So I'd like to invite Dr. Roychowdhury to begin the sponsor's presentation. I was going to say Dr. Pazdur, gift certificates will be arriving later, right?

DR. ROYCHOWDHURY: Good morning,

Dr. Hussain, members of ODAC, and FDA.

My name is Debasish Roychowdhury. I am the vice president for clinical development in GlaxoSmithKline. My name is a little bit harder than eltrombopag, but I'm going to call it Promacta during my presentation.

I'd like to first of all thank the FDA and ODAC for giving us this opportunity to discuss our NDA for Promacta and ITP. Promacta is a small molecule. It's a new chemical entity. In our clinical studies, which are the largest ever conducted in ITP, we have demonstrated clinical benefit in patients with chronic ITP. We've also shown it to be safe and tolerable.

ITP is a disease where there remains an unmet medical need. There still remains -- there are a lot of patients with ITP that continue to have low platelet counts and continue to be at a severe risk for bleeding. There are many therapies that are

still available for ITP. Not all of them are approved. These therapies are often ineffective, have significant side effects, and can be inconvenient for patients.

Our agenda for this morning for GSK presentation, immediately following my introductory remarks, Dr. Jim Bussel, who is professor of pediatrics, medicine, and OB/GYN at Cornell University, will give an introduction to ITP and put into context the development of Promacta in ITP. Following that, Dr. Michael Arning, my colleagues from GSK will give you the overview of efficacy and safety results from our clinical trials, and then I will have some concluding remarks.

To help us with our presentation, answer your questions, provide clarifications, we have a group of experts who are sitting with us here. And some of these have actually participated in the Promacta clinical trials. We also have a group of internal experts who are sitting

also with us here.

As I said, ITP -- there remains an unmet medical need in ITP. Current treatments, which are listed on the slide, include corticosteroids, high dose IVIg, Anti-D, danazol, cyclosporine, chemotherapy agents of various sorts, rituximab, as well as splenectomy. These agents have not been tested in randomized placebo-controlled trials. The benefit risk is often unclear for these agents, and most of them are not approved.

They are, however, used to maintain the platelet counts in a safe zone. The safe zone being platelet counts greater than 30,000 per microliter.

In some instances, of course, the safe zone may be higher. For instance, before a major procedure, the safe zone may be 80,000 or above.

And these drugs are used in various ways. They can be used for short periods of

time to elevate the platelet counts, or they can be used for longer periods of time to keep the platelet counts in the safe zone.

Let's talk a little bit about how eltrombopag works. Eltrombopag is a small molecule, as I mentioned, and this cartoon is showing a megakaryocyte and the cell membrane of a megakaryocyte. And the thrombopoietin receptor. Eltrombopag binds to the transmembrane domain of this thrombopoietin receptor and stimulates downstream pathways that increase platelet production. This is different, of course, from the Ligand thrombopoietin which binds to the extra cellular domain or larger peptides or peptibodies. One other characteristic of this drug that we have seen is that it has some antiproliferatic effects in malignant cells in vitro.

Promacta's clinical development plan is in three areas. In ITP, of course. It's also in chronic liver disease, as well

as in chemotherapy induced thrombocytopenia. In ITP -- and Dr. Arning will go over these studies in detail -- we have conducted studies in short-term use of ITP in Promacta and ITP, and repeated short-term use of Promacta ITP as well as in long-term dosing. The studies of Part A and Part B have been completed, as well as REPEAT have been completed.

EXTEND is a study that we started to allow patients who have been on Promacta -- studies to be put onto another study where we could follow them in a clinical trial. And this study will continue to enroll patients till we stop the study at some point. So this is an ongoing study, but this is an ongoing study because we continue to allow patients to come in.

RAISE is a study that is a double-blind placebo-controlled randomized study where patients receive Promacta for a longer period, six months, with placebo. And

as I mentioned, we have clinical trials ongoing in hepatitis C, as well as -- I'm sorry, in hepatitis and chronic liver disease, as well as in chemotherapy induced thrombocytopenia.

Just a few words about our regulatory interactions. First of all, I'd like to thank the FDA for the regulatory interactions that we've had.

We've had excellent discussions with them throughout our interactions on the development of this drug. The INT was open in September 2004. We had an agreement on the type of Phase II study that needed to be done. Those finding study as well as the end points.

We received the initial results of our Phase II study in January of 2006. We started discussions with the agency as to the package that would support a filing for ITP -- short-term ITP. And in December '06, we had an agreement on the NDA data package for

submission and review of short-term ITP. A pre-NDA meeting was held in August 2007, and the NDA was submitted in December 2007. This NDA package consisted of efficacy and safety results from Part A and Part B, efficacy and safety results from REPEAT, efficacy and safety results from EXTEND, and blinded safety results from RAISE.

After the NDA submission, we've had a few meetings with the FDA and have updated the safety -- the 120 day safety update was submitted in April 2008, and the risk management plan -- updated risk management plan also in April 2008. Orphan drug designation was granted to us a few weeks ago. Based on the studies that we have performed, we feel that the favorable risk benefit profile should lead to an indication for Promacta in ITP and the proposed indication in the NDA. Promacta is indicated for the short-term treatment of previously-treated patients with chronic ITP

to increase platelet counts and reduce or prevent bleeding.

With this I hand over to Dr. Bussel.

DR. BUSSEL: Thank you, Debasish. Thank you for the opportunity to present on something I've worked on and done clinical trials in since 1981.

My disclosures. I've worked with a lot of the different pharmaceutical companies active in this area, including Amgen, GlaxoSmithKline, now ASI, and Ligand, on their products.

I believe that I've reported more patients in ITP and clinical trials than any other center, so I'm going to take the liberty of just sharing some of my experience with you. These are petechiae which are probably familiar to most of the audience.

Now we're starting to get to more serious bleeding. This is wet purpura. You can think of it as half of a grape hanging

off the inside of the cheek. That's been associated with intracranial hemorrhage and speaks to the idea that Grade 2 and higher bleeding is significant, not only to patients for the inconvenience, but also for the fear, and also to physicians as a sign that treatment is urgently warranted.

Intracranial hemorrhage. There is menanalyses (meta-analysis) that have looked at patients with chronic ITP with severe thrombocytopenia and have suggested that somewhere between 1 and 4 percent per year will die of hemorrhage if not successfully treated. While this is a relatively uncommon complication, I've had days in clinic where I've seen as many as four patients who have survived intracranial hemorrhages with ITP.

I just want to review very briefly certain manifestations. We think that ITP is a disease of platelet destruction, but in recent years the role of some optimum platelet production has become more apparent,

has significant clinical manifestations on health-related quality of life, that it's difficult to treat, and that we would ideally like better therapies, which is one of the points of this meeting today.

If you look at this cartoon, the idea it is the fundamental pathophysiology of ITP is that antibodies bind to platelets by their FAB portions. FC portions interact with FC receptors in macrophages and the spleen and elsewhere, and platelets get destroyed. That hasn't changed. Most therapies intend and inhibit this process by either blocking the interaction of the FC portions of the antibodies or by trying to reduce the level of platelet antibodies.

Recently, as I indicated, there's been issues that have become clear that platelet production is actually decreased or at least suboptimal. We now believe that this is due to the same antibodies that bind to the megakaryocyte membrane and either

damage the megakaryocytes or prevent them from releasing platelets. And finally, unlike a plastic marrow situation in which thrombopoietin levels are very elevated and ITP, even with severe thrombocytopenia, thrombopoietin levels are barely distinguishable from normal.

Chronic ITP has important adverse effects on patients dealing with the bleeding symptoms as we showed you on the previous slides, and the anxiety and fear of the thrombocytopenia. In addition, there were organic effects in a large survey done of patients with ITP. The side effects of prednisone were the single thing they minded the most about the disease. And in addition, there's poorly understood effects of the ITP itself on health-related quality of life. There are patients who know their platelets are low and they just can't get out of bed in the morning and feel that their plug is pulled.

In this particular slide you can see that using the SF36 to track health-related quality of life across several domains. The dark line on both graphs is ITP here in the same degree of severity as arthritis and hypertension, and almost as severe as diabetes.

So, the challenges of ITP treatment are that the current treatments work in some, but not all patients, and that you would like a treatment that works in a large majority of patients because at the present time prediction of efficacy is very difficult, if not impossible. And the current treatments are certainly useful, And I've worked with many of them, but they can have serious toxicities. IVIG can lead to very bad headaches, aseptic meningitis. The FDA has reported that anti-D can cause serious intravascular hemolysis. Side effects of steroids are well known. Rituximab has led in rare cases to CNS viral infects. And

there's the risk of not only sepsis after splenectomy, but also possibly stroke, dementia, and pulmonary hypertension, and other not well studied issues.

Short-term treatments are a typical way to treat many patients. Stop or prevent acute hemorrhage in a patient who may be having an uncontrollable nosebleed; allow surgery or another procedure; allow a work activity, like construction or police officer when there's extra risk of bleeding; minimize risk of bleeding if somebody doesn't have access to care over a short period; allow a course of medications that interfere with platelet function or lead to an increased risk of bleeding for short periods. For example, for six weeks of anti-coagulation after a DVT connected to a delivery in a pregnant woman. And there are others as well.

Treatments effective in the short-term can be very useful for the

long-term. These are some examples on this slide. And there are probably others as well.

So, we've talked about thrombocytopenia and ITP having an important component of suboptimal platelet production. The negative clinical impact on the health-related quality of life, especially in refractory patients, that they can be difficult to treat and at risk of serious bleeding. And therefore, that there is an unmet need for more effective and better tolerated therapies.

Thank you very much. I'll turn it over to Dr. Arning.

DR. ARNING: Thank you, Professor Bussel. Good morning. My name is Michael Arning. I am the medical director on the Promacta team, and I have the pleasure of giving a short summary of the main findings of our application.

In this NDA, we submitted data from

five studies. Two look into the short-term use, one into intermittent, and two in long-term treatment.

The two short-term studies, called 773A and 773B, enrolled more than 100 patients in placebo-controlled double blind trials. They have been completed and finished.

Sixty-six patients in the study called REPEAT looked at intermittent use, and we have, as you heard from Dr. Roychowdhury an extension study where at the latest update we have safety data for more than 200 patients and efficacy data from 107 patients available. The race study, the six month study, is blinded.

The main efficacy endpoint in patients with chronic ITP is elevation of platelet counts usually to levels about 50,000. However, for the first time we provide also bleeding data in our submission to look at the clinical benefit of reduction

in bleeding. We used the WHO bleeding scale, which has five grades. I would like to point out that Grade 1 and especially Grade 2 are clearly clinically meaningful. If you think about this includes macroscopic blood in stool and urine, multiple blood blisters, and moderate hemoptysis.

As observational information, we also asked our investigators to collect data on hemostatic challenges. What we mean by this is the conduct of diagnostic or surgical procedures, or the outcome after an unexpected trauma, like an accident. The reason for that is we wanted to provide some evidence, supporting evidence, that platelets that are produced in response to Promacta actually work and prevent harm from patients.

Here are the short-term treatment studies. Both together are the largest randomized double-

Blind placebo-controlled studies in chronic ITP. The study 773A was a dose

finding study where three different dosages of Promacta were compared to placebo, and the optimal dose from the Phase II was then to be taken forward into the Phase III setting where 50 mg. Promacta was compared to placebo with a 2:1 randomization.

The design of the short-term treatment studies was quite simple. It was a six week treatment duration with a daily application of a pill. And the patient was then followed up for an additional six weeks.

The baseline platelet count in all patients was less than 30,000, and the primary endpoint was a proportion of subjects with a platelet count rise to more than 50,000 by the end of the study at 6 weeks or Day 43.

Subjects who responded briskly to the study direct with a rise in the platelet counts to more than 200,000 were also counted as responders. However, if they stopped for any other reasons before the six weeks, they

were not counted as a responder.

I would like to stress that there was an upfront stratification for the use of concomitant ITP medication as baseline, splenectomy status, and baseline platelet count less or more than 15,000 per microliter.

Here are the baseline characteristics. I don't want to go into all the details, but if you follow me from the bottom up of this slide, it is evident that patients were heavily pre-treated. Half of them had seen more than three prior therapies and one in four had seen more than five therapies. And still, the platelet counts were less than 30,000 and they at a high risk of bleeding. In fact, 50 percent of patients had a baseline platelet count of less than 15,000. Roughly half of them were splenectomized and a significant proportion of subjects were on other drugs randomized. There was a slight majority of females in the

study population and the median age was between 40 and 50 years.

Here are the main results. It is evident that there is a clear dose response relationship and that the Promacta arms were far more successful than placebo, while only 11 percent of patients reached platelet counts of at least 50,000 by Day 43. There was a much higher proportion with 50 and 75 milligrams, and the patients who were on 50 mg and 75 mg were statistically more likely to achieve desired platelet count compared to placebo.

There was also an effect on bleeding. As you can see, as the dose increases, the bleeding decreases, but in this study it did not reach statistical significance.

Here are the main findings from the Phase III study. Again, a confirmation of what was seen in Phase II. Patients who were on the Promacta arm, 60 percent of them

reached the desire end point with platelet counts more than 50,000 while only 16 percent on the placebo arm had a rise in platelet counts at Day 43.

In this study there was also a reduction in bleeding with any grade as observed at Day 43. Sixty percent of patients with placebo arm had bleeding at the study end compared to only 39 percent with Promacta.

As you know from the briefing book, the FDA questions the relevance of the bleeding findings. This gives me an opportunity to tell you in more detail what statistical analysis we did and why. We looked first into the effect of bleeding at the end of the study. For that a logistic regression analysis was done. We were also interested to see what happens with bleeding over time. From the first time the drug evaluation took place on Day 8 up to Day 43, the end of the study. For that we used a

general estimation equation method, and we also looked at the severity of bleeding at the end of the study. With that we used the logistic regression method.

So these were pre-specified analysis. Based on the remarks in the FDA briefing book, we conducted additional sensitivity analysis. Two of them are listed here. And, in fact, all showed the same results, namely a statistically significant difference in favor of Promacta with regard to reduction of bleeding. And as you can see from the odds ratio, the effect is actually quite large, between 50 and 70 percent.

And I think this makes sense if you look into the platelet count dynamics. The pooled data -- said pooled data set means that we looked into the 50 mg group of the Phase II study population and the 50 mg group in the Phase III study population. And I think from this graph several conclusions can be made. First, placebo does not do much for

patients with chronic ITP. The platelet count remains flat throughout. On the contrary, in the Promacta arm, a rise in platelets can be seen as early as Day 8. The platelets rise to Day 15, stay elevated for the whole rest of the study period. In fact, for one week longer before they fall back to baseline levels at two weeks.

It's also evident if you see the medians that there is no systematic decrease in platelet counts after therapy compared to baseline.

If you look at the pooled data set, what happens over time, you'll see that 60 percent of our patients had any evidence of bleeding, and the Promacta arm, there was no increase in the percentage of subjects who report any bleeding while on the Promacta arm. Starting on Day 8, a reduction in the number of patients can be seen, roughly to 30 percent of patients. And this is then maintained for the rest of the study period,

actually, until one week after study because with the fall of platelets, an increase in bleeding symptoms can be seen.

Across all predefined strata, Promacta was more effective than placebo. Regardless of splenectomy status, concomitant ITP medication, or baseline platelet count. I would like to point your attention especially to the splenectomy graphs where there was no difference in response whether platelets were splenectomized or not. You know that splenectomized patients are a particularly difficult population to treat, and the fact that the drug works in this refractive population in a significant way, I think, is quite encouraging.

As I said, we tried to also collect data on hemostatic challenges. And these are the data from A and B. And you see that two short cystectomies were performed on the Promacta arm without any rescue medication or bleeding reported.

On the contrary, on the placebo arm there were three procedures. Two patients needed IVIg. One patient was given a platelet transfusion and one was given a therapy for removal of a small tumor on the throat.

I now switch to the repeated dose study, which as I said, is an ongoing open-label, intermittent study where we wanted to know about the consistency of response after repeated applications.

The primary end point was a proportion of subjects with response of at least 50,000 and two times the baseline platelet count in Cycle 2 or Cycle 3, provided that they responded in Cycle 1.

In this study the patients had platelet counts between 20,000 and 50,000. They were given the same kind of treatment compared -- as in 773A and B for up to six weeks, then had to take the drug off for up to four weeks, and then this cycle was

repeated two more times.

Here are the main results. The primary end point to show consistency was achieved. Sixty- six patients were enrolled, and out of the available population, 82 percent responded in Cycle 1. Confirmation again of the findings that we had in the short-term studies. And out of the 33 that were available in Cycle 2 or 3, actually 29, or 88 percent, responded. And from the 16 available patients in Cycle 2 and 3, 13 responded with a predefined endpoint for a response rate of 81 percent.

So, the results become more clear if you show them graphically. Again you see that there was a remarkable consistency how patients respond to the drug. Platelets start to rise as early as Day 8, continue to rise to Day 15, then platelets stay up until one week after the study before they fall back to baseline. And again, here from the medians you see there is no systematic

decrease in platelet counts in the follow up period compared to the baseline values.

We also saw an effect on bleeding, both for any bleeding of Grades 2 to 4. Cycle 1, 49 to 8 percent. Cycle 2, 59 to 8 percent. Cycle 3 there is an anomaly of 50 percent at the end of the study that is due to the fact that it's a data cutoff for the NDA. Only four patients were available. Two of them had petechiae at the end. The final results read 35 percent and 19 percent.

You'll also see with regard to significant bleeding that at the end of Cycle 1 or 3, there was no patient who had Grade 2 to 4 bleeding. I also want to stress that between the cycles, no rescue medication was given and that very few of those events were reported. We'll come back to this later.

In REPEAT, we also had hemostatic challenges. Eight procedures were done in seven subjects. All patients were responders, and again, there was no abnormal

bleeding as expected, and no rescue medications were required. I think you will agree with me that at least the top two are procedures that can be associated with bleeding complications.

I now go to the extension study. Again, this is the final rule for all of our patients who participated in other studies. They are allowed to continue in the study, and we have no predefined stop of the study right now. Two hundred seven patients were enrolled at the latest safety update.

The primary endpoint was safety, and the study design followed simple procedure. Stage 1 was to get the platelets up to platelet values between 100,000 to 200,000. Then, the physicians and patients were asked to taper or discontinue concomitant medication, especially steroids. Grade 3 then meant that we looked for the lowest possible continuous dose of Promacta to keep the platelets above 50,000. And in

Stage 4 we then collected follow-up information during chronic use on safety and efficacy.

Despite the fact that the primary endpoint was safety, I think both the FDA and we were interested in clarifying a few important efficacy questions. First, of course, is durable platelet count elevation possible. Second, does short-term efficacy in any way predict long-term efficacy. In other words, do patients that responded in the previous studies -- do they respond again in EXTEND?

What happened to patients who were on placebo in the earlier studies? Would they respond? Is there a continuous effect on bleeding reduction? And what about reduction/discontinuation of concomitant ITP medications?

This slide show is three graphs that depicts median platelet counts roughly at 3, 6 and 9 months. And you see that

similar to the findings that we had with the short-term studies as early as one week the median platelet counts start to rise. And in this patient population, the median platelet count remained elevated for the whole treatment period.

From an individual patient perspective, it is important to note that 54 percent of subjects had a continuous elevation of more than 50,000 for at least 10 weeks. And, in fact, one in four patients had a continuous elevation of platelet counts of more than six months. So durable platelet count elevation is clearly possible.

What about the responders to the previous studies? You see already the familiar graph. Ninety-two percent of responders in the short-term trials responded again, which is also nice confirmation of the findings that we had in the REPEAT study.

With regards to patients who were previously on placebo, they responded as

expected between 60 and 70 percent. Sixty-three percent, in fact, achieved platelet counts more than 50,000, EXTEND for more than 75 percent of their assessments.

With regards to bleeding reduction, again confirmation of the findings of the short-term studies, 60 percent of patients had any kind of bleeding, and 20 percent had Grades 2 to 4 bleeding at baseline. And this is reduced by approximately 50 percent during the follow up -- during the treatment period -- from 60 to 30 percent for any grade, and from 20 to 10 percent roughly for Grades 2 to 4. With regards to reduction or discontinuation of concomitant medication, we can say that 40 subjects reported use of ITP medications, and 24 of them attempted to reduce or discontinue use of it while maintaining platelet counts above 50,000. In fact, 18 successfully did so, 14 completely stopped treatment of other drugs.

Three of them danazol plus

steroids. Eight steroids. Two other androgenic steroids, and four patients were able to reduce, but not completely stop concomitant steroid medication.

So, with regards to efficacy, I think -- and I would stress -- that the data show that the drug can increase and does increase platelet counts.

It also reduces bleeding. Patients were able to overcome hemostatic challenges. I think there's evidence that short-term efficacy predicts long-term efficacy. And that we saw clinical benefits with short-term treatment, with intermittent- and long- term treatment.

I think from a clinical point of view this is what you expect. If the platelet goes up, bleeding is expected to go down. And if you give a drug that raises platelet count, for instance with IVIg, you expect that procedures can be performed. And this is exactly what has been seen here in

our patient population.

I switch now to the safety findings. Here are the exposure data. Four hundred sixty patients were exposed to Promacta. Six months data available. Four hundred fifty five patients and 39 patients were exposed to more than a year. If we look at the most common adverse events there were no clinical significant differences, with the possible exception of nausea where six patients reported and no one on the placebo group. With regards to Grade 4 lab abnormalities, again, no clinical meaningful differences between Promacta and placebo. However, there were some patients with ALT/AST elevations, and we will discuss this in a minute.

With regards to SAEs, withdrawals, adverse events, and death, again, a similar low incidence of SAEs and withdrawals due to adverse events in the short-term studies. And you also see that percentages do not go

up markedly in the REPEAT and EXTEND study. The RAISE study is still blinded. There were a total of six deaths in the study. Three of them on study. One was an unfortunate woman who died as a passenger in a car accident. One patient had a sudden death after participating in EXTEND for more than a year. And there was one brain stem hemorrhage in a patient in RAISE blinded medication with a platelet count of 1,000.

If you look at the bleeding SAEs from the pivotal studies, we saw them in 3 percent on placebo and 1 percent on Promacta. And as you would expect with an inverse relationship between platelet count and bleeding risk, all occurred in non-responders. All had platelet counts less than 15,000. Of therapy, there was a 3 percent incidence of serious adverse event in the Promacta arm. Again, all below 15,000. There was a patient with rectal hemorrhage who came at Day 9 after stop of therapy. One

patient five weeks after stopping therapy had subarachnoid hemorrhage as part of typhoic fever septicemia. One patient had epistaxis on Day plus 32. Interestingly enough, this happened one day after application of IVIg. There was one woman who came to the hospital with menorrhagia Grade 3, but she also had problems with menorrhagia before enrollment into the study. And there was one lady who came to the hospital with petechiae Grade 2 on Day 22. And these were the main findings. Previously in the studies only two patients had ever responded to Promacta -- the woman with petechiae and the woman with menorrhagia.

Based on our clinical survey and the data we have from the clinical trials, we did multiple safety assessments and I would like to discuss with you in detail four of them. Hepatobiliary lab abnormalities were seen in the study program with Promacta. They usually were mild, reversible, and

without evidence of impaired liver function. However, in order to rigorously assess it, we performed an analysis according to the recent issued FDA draft guidance document for drug induced liver injury, which asks for special scrutiny of patients that fulfilled one of those criteria listed here. You'll see if we do this, both the placebo and Promacta arm patients fell into this category without any meaningful difference for the short- term. And you'll see that on the longer term studies, the number of patients percentage-wise does not increase in the longer term studies.

Of particular interest, of course, are patients who have both. Transaminases of more than three times the upper limit of normal and total bilirubin more than 1.5 times upper limit of normal, and we had three patients who formally fit this criteria. However, these cases are confounded. The first patient is a patient who died from

multi-organ failure, probably due to sepsis of pulmonary origin.

This was a patient who had a pneumonectomy after an operation for non-small cell lung cancer, had COPD, was on steroids, and had died in 773A. There was one patient who had cholangitis with a history of biliary disease. And she responded to antibiotic treatment. There was one patient who had indirect hyperbilirubinemia, and this hyperbilirubinemia started more than a month before a rise in transaminases to this threshold was seen.

So all the three cases were confounded. And we discussed, of course, in detail these cases with internal and external experts. And we came to the conclusion that they do not represent Hy's law cases.

Post-therapy decrease in platelet counts is another important topic for the safety assessment. First, we need to be

aware that reoccurrence of thrombocytopenia after treatment discontinuation is expected. If we give a drug that raises the platelets and you take this drug away, platelets go back to the baseline levels and the bleeding risk increases again. We also keep in mind there is a natural disease fluctuation. The platelet counts do not stay, let's say, at 18,000. They may fluctuate between 10,000 and 20,000, and this might affect how you calculate transadversening of thrombocytopenia. There's also some imprecision of platelet count measurements with automatic machines, especially if the platelet counts are very low, between 10,000 or even below 5,000.

So in order to systematically assess this, we used a methodology that Purcell published in the New England Journal of Medicine in 2006 where he asked for special evaluation of patients who fulfilled the following criteria. They have less than

10,000 per microliter and less than -- 10,000 per microliter less platelets compared to baseline. And this within four weeks after discontinuation of the study drug.

If you apply those rules, you see that patients again in the placebo arm and in the Promacta arm preferred these criteria for 6 percent versus 10 percent. You see that in the REPEAT and the EXTEND, the percentages did not rise. But you keep in mind that the REPEAT patients had to have at least 20,000 per microliter to be eligible in the REPEAT studies.

During this time period that they had this very low platelet counts, two patients had bleeding adverse events. Again, one woman with menorrhagia, and one patient with Grade 1 gingival bleeding.

Thromboembolic events, of course, to be evaluated in a drug like Promacta, we had 11 subjects who had an event. Interestingly enough there was no association

with the platelet count. Six of the 11 had platelets below 100,000 at the time of the event. And in fact, two had less than 30,000. There was one patient with 14,000 who had a neurological complication, and another one had 27.

I also would like to stress that these often were complicated cases and the thromboembolic complications occurred, for instance, while those patients were evaluated in the hospital for other reasons. For instance, we had four patients where the thromboembolic events occurred weeks after hospitalization. No prophylactic anti-coagulation was given. Interesting, there were there patients who developed a thromboembolic event five to eight days before thee event. And it's known that IVIg can increase the risk of thromboembolic complications. And in our documents we have listed the risk factors that were detectable in the other patients.

So, how does this compare to other serious in ITP patients? If we calculate our data we come to a frequency of 2.6 percent. An incidence rate, if it's normalized to 5.1 per 100 patient years. It's also worth mentioning that when we looked into the CRFs of our patients, 3.2 percent of them had previously before they enrolled in our studies, a thromboembolic event. None of them had a thromboembolic event during participation in the Promacta studies.

There's not much literature out there about the risk of thromboembolic events in chronic ITP. The paper by Olador that gives a 3 percent frequency from the Romiplostin data that were discussed a few weeks ago. We got a 4.4 percent number with 4.3 percent in the placebo group. And in an epidemiological study that we did where we looked into a large U.S. health claim database, we looked into patients with chronic ITP for a period of 12 to 15 months.

And we came to a frequency rate of 6.9 percent.

So I think right now that the thromboembolic frequency that we see is comparable to what has been reported in other series.

Lastly, bone marrow reticulin has been brought up recently. Again, if you want to find information about what is normal, what is pathological, there is limited information available right now. Mild to moderate reticulin has been observed in ITP patients -- up to a third of them actually. And in fact, also in up to one third of subjects with hematologically normal blood counts and no blood disease.

So, in the intermittent and long-term dosing trials that we had, we did not demand a routine baseline bone marrow biopsy based on the strong feedback that we got at the time from both the treating physicians and the patients, that they were

unwilling to have this as part of a clinical trial program at a time where little, if any, treatment consequences would follow from an additional bone marrow biopsy in a patient with a known chronic ITP.

So we looked for indirect measures to gauge the health of the bone marrow. What we did is we asked the physicians to frequently do differentials to look if anything abnormal would show up. And if the automatic differential would show, let's say, immature white blood cells or newly created red cells then the sides were asked to follow up on this and do a manual red differential by an experienced lab technician or physician to confirm those findings. And if those findings were confirmed, the protocol clearly stipulated that then a bone marrow biopsy must be done.

Now, what we can say so far is that not a single bone marrow biopsy was done for abnormal blood smear results. Nevertheless,

based on the discussions on romiplostim and bone marrow fibrosis, we amended the EXTEND protocol in the middle of last year and asked patients who were on the drug for more than a year to consent to a bone marrow biopsy.

And so far we have collected 19 out of them, and 7 of them mentioned slight to moderate reticulin fiber accumulation. Two of them collagen fiber increases.

We are now in the process to compare that to previously done bone marrow biopsies. And for two of them we know already that these findings were preexisting.

Right now I would like to stress that the bone marrow findings did not result in any adverse events, any clinical consequences, any decrease in bone marrow similarity or any consistent findings in different patients.

So, the safety conclusion that we can draw, I think I've showed you that Promacta was well tolerated. The most common

adverse events that were seen at the placebo controlled trials were headache, nasopharyngitis, and nausea. Hepatobiliary lab abnormalities were seen. Usually they were mild and reversible. Post-treatment reoccurrence of thrombocytopenia has been seen in a few patients, however, they were also seen on placebo. And they were not accompanied by clinically meaningful increase in bleeding symptoms in our patients.

And with that I hand back to Dr. Roychowdhury for some concluding remarks.

DR. ROYCHOWDHURY: Thank you, Michael. I want to conclude by providing you with the reasons why Promacta should be approved. Dr. Bussel has already mentioned there is an unmet medical need in chronic ITP. It's a serious illness. Bleeding can be life-threatening and serious. We've already seen those in our own patients and our own clinical trials. And Dr. Bussel has mentioned it in his own practice.

The present therapies are often ineffective, have significant side effects, and are inconvenient. And many of them are not approved for ITP.

Treatment, such as IVIg, steroids, and anti-D are routinely used to elevate platelet counts for short periods. Promacta is a new chemical entity with a novel mechanism action. It addresses suboptimal platelet production. We have demonstrated clinical benefit in short-term and intermittent treatments. This is through increasing platelet counts, decreasing bleeding, as well as overcoming hemostatic challenges. We have demonstrated that there is clinical benefit that we have observed in long-term treatment. It is reliable, and it is convenient.

The data package we have given to the FDA and NDA includes the two largest reported controlled studies in ITP. The safety profile, it's a well tolerated drug

with no safety issues that preclude approval. Potential safety issues have been addressed in a comprehensive risk management plan that we have provided to the agency. Therefore, the risk benefit profile is favorable and should allow approval for Promacta in patients with chronic ITP.

And the label indication that we have proposed is in the slide.

With that we conclude our presentation. Thank you for your attention.

DR. HUSSAIN: Thank you. I would like to invite Dr. Dmytrijuk from the FDA to present the FDA review. I'm sorry, the FDA review.

DR. DMYTRIJUK: Good morning. MY name is Andrew Dmytrijuk. I am the FDA's lead medical officer for the Eltrombopag NDA, and I will summarize the major points from our ongoing review of the application.

Eltrombopag is proposed for the use in the short-term treatment of previously

treated patients with chronic ITP to increase platelet counts and reduce or prevent bleeding. The proposed indication is notable for two major points as underlined in this text. The indication specifically cites the short-term use of the drug to accomplish two treatment benefits. One, for an increase in platelet counts, and the other for the use of the drug to reduce or prevent bleeding. By specifically citing use of the drug for these purposes, FDA anticipates that the sponsor will have actually shown these benefits in the clinical benefit program.

As mentioned earlier, eltrombopag is a tablet that is to be administered daily. The drug binds to the transmembrane portion of the TPO receptor and stimulates megakaryocyte proliferation, differentiation, and platelet production. The preclinical testing of eltrombopag is notable both for its findings, as well as its limitations. Of the animal species tested, eltrombopag

stimulated platelet production only in chimpanzees. However, toxicity testing was extensively studied in other animals, and at high end repetitive doses was shown to cause chronic progressive nephropathy, liver abnormalities, and cataracts.

In the context of TPO mimetic products, the last bullet highlights the important observation that animal testing of another TPO receptor agonist, one that was active in platelet production showed the development of marrow fibrosis. Whether eltrombopag is associated with a risk of marrow fibrosis is under evaluation in the ongoing long- term clinical studies.

The clinical database for the eltrombopag NDA consists of exposure data from a total of 1,088 subjects. The chronic ITP program accounts for the largest specific program exposure, and to date, 330 patients have been exposed. The clinical development program also consists of studies in two other

patient populations. To date, 56 patients have been exposed in the studies for the treatment of thrombocytopenia in patients with hepatitis C, and 134 have been exposed in the studies that explore the use of the drug in the treatment of chemotherapy-induced thrombocytopenia.

Clinical pharmacology studies in 568 subjects account for the remainder of the eltrombopag exposure data. In addition to these data, approximately 100 ITP patients are estimated to be exposed to eltrombopag in an ongoing double- blind study.

The ITP program consists of two major components as highlighted in the major bullets. A short-term program and a long-term program. The final repots for the major clinical studies are available only for the short-term proposal. The term short-term proposal refers to six weeks of eltrombopag exposure and consist of two completed placebo-controlled studies which I will refer

to as 773A and 773B. The short-term program also contains an ongoing single arm study called the REPEAT study.

In REPEAT, subjects receive three cycles of eltrombopag separated by a period off the drug.

The long-term development programs refers to studies of six months or more duration and are intended to support the potential chronic use of the drug. One of the ongoing studies is a placebo- controlled study and is proposed to control the main comparative evidence of eltrombopag safety and efficacy over a six month time period. Another ongoing study, referred to as EXTEND, uses a single arm extension-type design in which subjects receive eltrombopag indefinitely.

Our review has focused upon the completed study reports supplied to support the short-term use of eltrombopag. This slide highlights our major efficacy and

safety considerations. With respect to efficacy, we are examining the extent to which the data have shown eltrombopag will increase platelet counts and reduce or prevent bleeding. Our concerns regarding safety relate predominantly to three items as shown at the bottom of the slide. The available clinical data signals a risk for hemorrhage following drug discontinuation, a risk which is also one of the hypothetical risks for the class of TPO mimetic products.

Liver toxicity signals are also evidenced in the clinical database and will be discussed later. Perhaps most notably, we are concerned that approval of eltrombopag for solely a short-term usage may result in effect in a long-term usage with possibly more hepatotoxicity and potential bone marrow fibrosis -- risks that have not been characterized yet because of the ongoing nature of the long-term clinical program.

My subsequent presentation will

focus upon the safety and efficacy data from the two completed short-term studies 773A and 773B. I will also briefly summarize the major safety data from the ongoing REPEAT, EXTEND, and RAISE studies.

The rationale for the short-term use of eltrombopag was articulated in the protocols for the major studies, specifically the protocol text noted short-term treatment may increase platelet counts in patients with chronic ITP scheduled for surgical or dental procedures where a low platelet count can be a hindrance or even prohibitive of the procedure due to the risk of excessive bleeding. Given this rationale, it is notable that the clinical studies were not designed to assess clinical benefits in the periprocedural setting. Instead, studies assessed changes from each subject's baseline status using a five component bleeding scale.

The design features for 773A and 773B are summarized here. Both studies were

double-blind, placebo-controlled, multinational studies. Patients enrolled in the studies had baseline platelet counts less than 30,000 despite at least one prior therapy.

The eligibility criteria did not select for patients who were planned to undergo evasive procedures or had a specific need for the short-term use of eltrombopag. Instead, the criteria selected for patients who had a clear diagnosis of chronic ITP and who lacked certain co-morbidities such as cardiac disease or recent thromboses. As noted at the bottom of the slide, subjects in 773A were randomized to four groups: Placebo or eltrombopag at 30, 50, or 70 milligrams administered daily. In 773B, study subjects were randomized between two groups: Either placebo or eltrombopag at 50 mgs daily.

Minimal or no dose adjustments were allowed in these studies. In both studies, subjects stopped all dosing with eltrombopag

if their platelet counts exceeded 200,000. The 773B study differed in the dose plan from the other study in that the 50 mg dose could be increased to 75 mgs at Day 22 contingent upon the platelet count. The major baseline and follow up evaluations consisted of CBCs and clinical chemistry, and various other routine evaluations. Notably, all patients were scored for evidence of bleeding at baseline, and each follow up visit using a unique scoring system, the WHO bleeding score.

The primary endpoint related to a comparison of responders where response was defined as the achievement of a platelet count of at least 50,000 by Day 43, or study drug discontinuation due to platelet count of 200,000 or greater. Most secondary endpoints were variations upon the platelet count response. The change in the WHO bleeding score was also one of the notable study endpoints.

This, and subsequent slides, show the major results from studies 773A and 773B with a pooling of the placebo and 50 mg eltrombopag treatment groups. As shown here, the major baseline characteristics were similar between the treatment groups with a median age of approximately 46 years and a 60 percent proportion of females. The studies enrolled patients who had and who had not undergone splenectomy. And in both treatment groups, approximately 40 percent of subjects had previously undergone a splenectomy. In general, the patients had received multiple ITP medications in the past, with 70 percent of the subjects reported as having two or more prior therapies. As shown in the last row, major median baseline platelet counts in the group were 17,000 and 18,000.

A subject disposition is illustrated here. Overall, six weeks of therapy with a study drug was completed by 78 percent of the subjects within the placebo

group, and 65 percent within the eltrombopag group. Hence, the study group discontinuation rate was 22 and 35 percent, respectively. The main basis for the imbalance in the study drug discontinuation rate was the study design feature that required cessation of all dosing when a subject achieved the platelet count of greater than 200,000.

As shown in the third row, platelet counts greater than 200,000 were responsible for study drug discontinuation in only 3 percent of the placebo group, but 27 percent of the eltrombopag group. Other reasons for the study drug discontinuation were unremarkable.

The primary endpoint for the studies was a comparison of the proportion of subjects who achieved the platelet count of 50,000 or greater by Day 43, including subjects who discontinued the study drug due to a platelet count greater than 200,000.

Overall, in study 773A, the primary endpoint response was 11 percent in the placebo group, and 70 percent in the eltrombopag group. Similar results were obtained in study 773B, with a response rate of 16 percent in the placebo group and 58 percent in the eltrombopag group. The utility of exploratory subsets is limited, although the response within the subset of patients who had undergone splenectomy is clinically notable. As shown on this slide, the response rate for splenectomy subjects was 15 percent in the placebo group and 59 percent in the eltrombopag group. These results appear similar to those obtained in the subset of subjects who had not undergone splenectomy where the rates were 14 percent and 64 percent, respectively.

This slide illustrates the distribution of the maximum platelet count during the studies. As shown in the second column, three placebo group subjects

experienced platelet counts in excess of 200,000, while 29 percent of the eltrombopag group had maximum platelet counts in excess of 200,000. Maximum platelet counts greater than 400,000 were reported for 9 eltrombopag subjects, and of the 3 subjects within this group who had a maximum platelet count greater than 600,000, 2 were less than 700,000, and 1 was 1.3 million. Following discontinuation of the study drug, platelet counts generally returned to baseline within two weeks.

The other notable efficacy assessment in the clinical studies was a comparison of the change in the WHO bleeding scores. As noted here, we cite three special concerns with this approach to estimating a drug effect upon bleeding outcomes with the scoring system. As noted in the first bullet, this bleeding assessment focused upon changes from baseline in the bleeding score. That is, subjects were assigned a bleeding

score at baseline and at follow-up time points, and the eltrombopag effect on bleeding was estimated from the changes in these scores, not from systematic collection of bleeding data that pertained to a surgical or other invasive procedure. Additionally, investigators were instructed to record unique bleeding events at each time point. Instead, a score was assessed.

The clinical meaningfulness of changes in this scoring system is unclear, especially for incremental changes as may occur for a shift from a score of two to one. This problem is illustrated by a quote from the publication that dealt with the bleeding scales in last year's British Journal of Hematology. The authors noted that a method for objective quantification of bleeding symptoms in ITP has not been established. The challenges of the WHO bleeding scale are also notable with respect to the study methodology. For example, few criteria and

definitions were provided in the study protocol such that it appeared investigators were to rely upon relatively subjective assessments when assigning the scores, and the scores could have been assigned with the knowledge of the platelet count results. These data may have biased the score assessment.

The WHO bleeding scale is a relatively simple scale as shown here. This illustration highlights the most notable scores, scores zero through two because the changes among these scores accounted for almost all of the detective changes. Specifically, a score of zero correlates with no bleeding; a score of one with the presence of petechiae; a score of two with mild blood loss; three with gross blood loss; and a score of four was to be assigned of the investigator thought the subject had debilitating blood loss.

This slide shows the distribution

of the subjects who experienced a change from their baseline score to a score of zero or no bleeding at the end of the study drug therapy. The denominators represent the number of patients with a baseline bleeding score listed in the column heading. The numerators represent the number of patients that had no bleeding at the end of therapy. We regard this type of descriptive summary as the most useful to display the data due to the unclear meaningfulness of incremental changes in the scale and several analytical concerns, especially with respect to the use of the scores in event definitions.

This table shows the baseline bleeding score in the column headings, and the rows show the rate of subjects who had no bleeding at the end of the study drug administration. As noted in the first column, most subjects with a score of zero or no bleeding at baseline also had a score of zero at the end of drug therapy -- a rate of

90 percent for the eltrombopag group, and 77 percent for the placebo group.

The second column highlights the group of subjects who had the most notable change in bleeding score. Of the subjects with a baseline bleeding score of one, which corresponds to the presence of petechiae, a score of zero was reported at the end of drug therapy for 59 percent of the subjects in the eltrombopag group, and 35 percent of subjects in the placebo group.

As the third column shows, this trend was reversed for subjects who had a baseline score of two or mild blood loss, where 24 percent of the eltrombopag group had an end of therapy score of zero, while 33 percent of patients in the placebo group had no bleeding reported at the end of therapy. However, we note that the sample sizes within these cohorts, especially for the higher score cohorts, are small and limit the conclusions from the data displayed.

Data pertaining to outcomes surrounding the occurrence of hemostatic challenges were obtained retrospectively for study 773A and prospectively in study 773B. And the pooled results are summarized here. Overall, only 7 of the 173 randomized subjects actually experienced a hemostatic challenge -- four patients within the eltrombopag group and three within the placebo group. As shown in the first column, most of the hemostatic challenge events were forms of surgery, such as gallbladder, eye, or hip surgery.

The second column shows the platelet counts prior to the event were generally considerably higher for subjects in the eltrombopag group than or subjects in the placebo group. And as shown in the subsequent column, medications to lessen the risk for bleeding were administered only to placebo group subjects.

The last column shows that only one

subject, a placebo group subject, received a platelet -- excuse me -- received a red blood cell transfusion in the perievent period.

The adverse event profile from the two clinical studies is summarized on this slide. Overall, the proportion of subjects experiencing an adverse event was numerically higher in the eltrombopag group than the placebo group, a rate of 66 percent versus 52 percent. In general, the occurrence of specific adverse events was similar between the study groups. The overall rate of serious adverse events was also similar between the two study groups -- 12 percent in the placebo group and 11 percent in the eltrombopag group.

However, it is important to note that serious events that appeared to involve hemorrhage that required rescue ITP medication usage occurred numerically more often among the eltrombopag group, with six patients in this group compared to only one

subject in the placebo group. These events will be summarized subsequently. One placebo group patient experienced a ruptured varicose vein as a serious event, but no use of ITP rescue medication was reported in this patient. As noted at the bottom of the table, only one subject died, a subject in the eltrombopag group. This death narrative is summarized on the next slide.

The death occurred in a 66-year-old man who had undergone a right pneumenectomy five years prior to the enrollment in the study. The patient began eltrombopag and on routine Day 15 visit was reported to have elevated liver enzymes. However, the drug was continued and on Day 21 the patient was hospitalized for an exacerbation of COPD, coincident with marked liver and renal abnormalities. The patient subsequently died in Day 26 of apparent cardiac failure caused by pulmonary failure, and an autopsy revealed thromboemboli and biventricular cardiac

hypertrophy. The sequence of these events suggests eltrombopag may have contributed to the liver and renal abnormalities and the overall decline in the patient's condition.

This slide shows the patient's major laboratory tests. As shown in the first row, the patient's baseline ALT was normal at 21. On routine Day 15 visit, the ALT was more than 10-fold increased, and by the time eltrombopag was discontinued, the ALT was nearly 2,000. At the time of drug discontinuation, the other laboratory tests were abnormal, including the AST, bilirubin, and rental tests. However, the patient's platelet count had responded to the drug with a value of 108,000 reported.

Together the data from the two controlled studies signal two major safety concerns -- a risk for liver toxicity and a risk for hemorrhage following eltrombopag discontinuation mainly in a situation of worsened thrombocytopenia when compared to

baseline.

As listed here, several aspects of the data are notable with respect to consideration of a risk for liver toxicity. As the first bullet notes, eltrombopag undergoes liver metabolism with significant biliary excretion of the drug, as well as renal excretion of metabolized drug. As previously noted, high doses of eltrombopag induced liver toxicity in animals following repetitive administration of the drug.

Finally, the clinical data have shown that a patient with underlying core morbidities developed progressive liver test abnormalities while receiving the drug and ultimately died. Additionally, the controlled clinical database shows a pattern of small imbalances in liver test abnormalities as shown on the next slide.

The major liver test results for the controlled studies are shown here according to the maximum toxicity grade.

Overall, most liver test abnormalities are low toxicity grades, Grades I or II, and the small imbalances suggestive of a drug effect are shown here in yellow. This pattern, combined with the background considerations, suggests that eltrombopag may be associated with a risk for liver toxicity and a need for regular liver test monitoring.

The second major safety concern evidenced in the controlled studies is the potential for hemorrhage, especially serious hemorrhage following eltrombopag discontinuation. The major background considerations for the risks are listed here. As indicated in the first bullet, a hypothetical risk for worsened thrombocytopenia has accompanied the clinical development of TPO mimetic products, especially since this product is not intended to treat the platelet destruction component of the disease and the drug effects may result in some suppression of intrinsic TPO

levels.

Secondly, the clinical database shows a small imbalance in the rate of transient worsening of thrombocytopenia compared to baseline platelet levels -- a rate of 10 percent for the eltrombopag group compared to 6 percent for placebo. Notably, as shown in the last bullet, the clinical data show a numeric imbalance in the occurrence of serious hemorrhage, specifically hemorrhage following study drug discontinuation.

The next slide summarizes the hemorrhages in more detail. In the entire database of the placebo-controlled studies, serious hemorrhagic events that required the use of ITP rescue medications were observed among seven patients in the eltrombopag group, but only one patient in the placebo group. The nature of these events are shown here in the second column and include events mainly indicative of mucosal or CNS

hemorrhage. Of the seven events in the eltrombopag group, five occurred following discontinuation of the drug in a range of 9 to approximately 30 days following drug discontinuation. In all serious hemorrhagic events, platelet counts prior to the events had last been recorded as less than 50,000 and most were less than 20,000.

This and the next few slide summarize the major safety findings from the ongoing clinical studies. The design of the REPEAT study is highlighted here. REPEAT enrolled subjects who had baseline platelet counts between 20,000 and 50,000 and who had received at least one prior ITP therapy.

REPEAT is a single arm study that importantly examines the effects of intermittent REPEAT courses of eltrombopag. Specifically, subjects are to undergo three sequential cycles of six weeks eltrombopag therapy with separation of these cycles by a time period of up to 30 days off therapy.

The primary endpoint of the study examines the proportion of subjects who achieve a platelet response given response in the first cycle.

While the study has several strengths, the major limitations are highlighted at the bottom of the slide. Most notably, the off therapy period can be shortened. That is, if subjects develop a platelet count of less than 20,000, eltrombopag is reintroduced at that time. Hence, REPEAT is not likely to full characterize the risk for worsened thrombocytopenia and hemorrhage following permanent discontinuation of eltrombopag after a six week course.

Additionally, the study uses an uncontrolled design, and to date, the available study results are preliminary findings.

This slide shows the preliminary estimate of the primary endpoint result.

Specifically, 77 percent of subjects responded in the first cycle, and the accumulating data appeared to indicate that most of these subjects, 80 to 90 percent, continued to respond in the subsequent cycles.

The preliminary REPEAT data contained reports of hemostatic challenges as is listed in this table. To date, seven patients have undergone a variety of invasive procedures, and all had platelet counts reported as greater than 50,000 prior to the procedures. All patients appeared to tolerate the procedures with no need for ITP rescue medications or blood transfusions.

The major REPEAT safety findings are listed here. Of the three patients with serious adverse events reported to date, one patient had a serious hemorrhage that consisted of epistaxis and ear hemorrhage at Day 55 following eltrombopag discontinuation. The last reported platelet count prior to the

event was less than 10,000, and the patient received rescue ITP medications.

The second bullet notes that to date 25 of 66, or 38 percent of enrolled and treated subjects have not been able to complete the Day 30 interval off eltrombopag therapy due to either worsening of platelet counts or bleeding symptoms. This observation raises questions as to the appropriateness of eltrombopag discontinuation in patients with relatively severe chronic ITP. As noted at the bottom of the slide, REPEAT data also show an approximately 15 percent incidence of low grade liver test abnormalities, all Grade 1 or 2.

EXTEND is the ongoing extension study that explores eltrombopag effects over a prolonged period of time, and eligible subjects have to have completed a prior study. EXTEND not only provides eltrombopag exposure over a long period of time, but it

also incorporates dose adjustments and features, as well as design-type features intended to reduce or eliminate concomitant ITP medications. Additionally, the study protocol has been amended to include the collection of bone marrow report data following one year of eltrombopag exposure.

Similar to the REPEAT study, the EXTEND study is uncontrolled, and the available data are interim results. As of the last report, platelet data are available for 109 subjects, and overall safety data are available for 207 subjects.

This table summarizes the exposure data in EXTEND and provides the most comprehensive summary of continuous long-term eltrombopag exposure. Although uncontrolled and in a population largely pre-selected for their ability to tolerate eltrombopag. To date, 74 subjects have received at least 6 months of exposure, 25 at least one year, and 9 subjects have received eltrombopag for at

least 15 months. No subjects have received the drug for more than two years.

As summarized here, to date 13 EXTEND subjects have been reported to have experienced invasive procedures or other hemostatic challenges.

None of the subjects experienced bleeding complications, and only 2 of the 13 required pre- procedure rescue ITP medications. Both subjects had complex courses with concomitant medication and eltrombopag dose adjustments.

The major safety findings in data from the EXTEND study are summarized here. To date, four deaths have been reported with one death related to a gastrointestinal hemorrhage that occurred approximately 55 days after the last eltrombopag dose. This patient had very severe thrombocytopenia and has received multiple platelet transfusions and other therapies prior to the death. Twenty subjects have experienced serious

adverse events, including three with pulmonary emboli, three with serious hemorrhages, and two with liver test abnormalities.

Overall, the pattern of less severe liver test abnormalities appears similar to the REPEAT experience with a rate of approximately 15 percent, with most Grade 1 or 2 severity.

The EXTEND study is notable for the collection of bone marrow data. As noted in the first bullet here, other TPO mimetic molecules have been shown to show marrow fibrosis in animals which raises a question of whether this class of products may be associated with a marrow fibrosis risk in humans. No serious bone marrow abnormalities were reported in the short-term eltrombopag studies, and bone marrow findings were not systematically examined in these studies. The EXTEND protocol has been modified to require the performance of bone marrows

following one year of eltrombopag exposure, and some preliminary data are available.

As shown in the last bullet, these data have some limitations, particularly due to the variability and interpretation of marrow histology.

The process does not use a central adjudication of marrow histology. Instead, reports from site pathologists are submitted and memorized in the study database. Hence, the terms and definitions may vary somewhat despite the study documents that encourage consistency in histological terms.

To date, 19 subjects in EXTEND have had bone marrow reports supplied to the database. Seventeen of these marrows were performed after 10 or more months of exposure. As noted in the last bullet, 7 of the 19 had reticulin deposition documented in the report. The two sub-bullets at the bottom of the slide illustrate some of the challenges in the use of the terms and

implications from the available reports. Both of these subjects continued eltrombopag following the bone marrow reports.

One report notes that a subject had reticulin and trichrome stains that showed moderate fibrosis, moderate increase in Type 3 collagen reticulin, and mild increase in Type 1 collagen. Another report concludes that a patient had myelofibrosis Grade 2 to 3.

RAISE is the ongoing clinical study intended to provide the major comparative data assessing eltrombopag long-term safety and efficacy.

RAISE is a randomized, double-blind placebo- controlled study in which subjects receive study drugs over a six month period of time. The study remains blinded, and 197 subjects have been enrolled. To date, one subject has died due to a CNS hemorrhage, and 26 subjects have experienced various serious adverse events while on therapy, including

five subjects with serious hemorrhages, four with cataracts, and three with liver test abnormalities. Three subjects have experienced serious adverse events post-therapy, including one case of CNS hemorrhage.

This, and the next few slides, summarize the major findings from our examination of the supplied data. As shown at the top of the slide, eltrombopag increased platelet counts in 60 to 70 percent of subjects. In addition to this efficacy outcome, the controlled studies assessed patients with a special bleeding score at each visit. However, the clinical meaningfulness of this scoring system is unclear, especially with respect to incremental changes. Additionally, the scores could have been biased by knowledge of a patient's platelet counts. Nevertheless, the available data show that the changes in the bleeding scores related predominantly to

the lowest grades, mainly a score of 1 to 0. As shown in the last bullet, hemostatic challenges were uncommon in the controlled studies, incurring only in seven subjects. In these subjects, rescue medication was administered only to the placebo group patients.

The major safety concerns are listed here. Overall, the controlled study data show a numeric imbalance and the occurrence of serious hemorrhagic events that required ITP rescue medications. Seven patients within the eltrombopag group and one patient in the placebo group experienced these serious hemorrhages. And most of these hemorrhages followed eltrombopag discontinuation when subjects had very low platelet counts.

The second major safety concern relates to potential liver toxicity. The controlled studies showed a small imbalance in the low grade liver test abnormalities,

1 although one patient with progressive liver
2 abnormalities ultimately died.
3 The notable findings from the
4 available long-term data are summarized here.
5 All these data are interim, and only
6 preliminary reports are available.
7 Additionally, the controlled clinical study
8 data remain blinded. In general, the data
9 continued to show signals of predominantly
10 Grade 1 and 2 liver test abnormalities with
11 isolated occurrence of other events, such as
12 cataracts, hemorrhages, and thrombotic
13 events. A potential risk for marrow fibrosis
14 is suggested by the detection of reticulin in
15 7 of 19 bone marrow examinations.
16 This slide summarizes our major
17 discussion considerations. With respect to
18 efficacy, we wish to consider the data with
19 respect to the changes in platelet counts, as
20 well as the available data that might support
21 a claim related to reduction or prevention of
22 bleeding. Our safety topics relate mainly to

considerations of the risk for bleeding following eltrombopag discontinuation, as well as hepatotoxicity.

Perhaps most notably from a usage perspective we are concerned about the implications from the marketing of the drug with a short term indication, yet actual long-term usage of the drug that might be associated with poorly characterized risks, such as hepatotoxicity and potential marrow fibrotic risks.

I thank you for your attention and return the podium to our chairman.

DR. HUSSAIN: Thank you, Dr. Dmytrijuk. We will take now questions to both the FDA and the sponsor. And I'm going to request that you raise your hand, we would recognize you, and then we'll go in turn.

DR. SANDLER: I have a question that relates to the FDA's presentation slide 12. It can be answered by the FDA or the sponsor.