DEPARTMENT OF HEALTH AND HUMAN SERVICES
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ONCOLOGY DRUGS ADVISORY COMMITTEE

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Gaithersburg, MD

C O N T E N T S

C O N T E N T S (Continued)

FDA Presentations

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P R O C E E D I N G S

Call to Order and Introduction of Committee

DR. ECKHARDT: My name is Gail Eckhardt and I am the Chair of the meeting today. I would like to go ahead and call the meeting to order.

For topics such as those being discussed at today's meeting, there are often a wide 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. Also, the Committee is reminded to please refrain from discussing the meeting topics during breaks or lunch.

Thank you.

Before we go around the table to make introductions, just to remind everyone that we are here to discuss the BLA 125268 of romiplostim submitted by Amgen, so what we will do is start with introductions to my left.

DR. CURT: Greg Curt, medical oncologist and the U.S. Medical Science Lead for Emerging Products at AstraZeneca. I serve on this committee as the Industry Representative.

DR. KULKARNI: Roshni Kulkarni, pediatric hematologist/oncologist at Michigan State University. I am also the Director, Division of Blood Disorders, at the Centers for Disease Control in Atlanta.

DR. KATZEN: Harvey Katzen. I am a private practitioner in Hematology-Oncology in Maryland.

MR. PETOSA: Joe Petosa. I work in the nuclear industry. My daughter is an ITP patient, and I am the Patient Rep here.

DR. LINK: My name is Michael Link. I am a

pediatric hematologist/oncologist at Stanford.

DR. VESELY: Nicole Vesely, Designated Federal Official for ODAC.

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

DR. RICHARDSON: Ron Richardson, medical oncologist, Mayo Clinic, Rochester, Minnesota.

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

DR. PERRY: Michael Perry, medical oncologist, University of Missouri, Ellis Fischel Cancer Center. I am a hematologist, too.

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

MS. MASON: Ginnie Mason. I am the Consumer Rep. I am with the Inflammatory Breast Cancer Research Foundation.

DR. JAMALI: Faranak Jamali, FDA.

DR. RIEVES: Hi. Dwaine Rieves, Acting Division Director in Hematology and Medical Imaging at FDA.

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

DR. ECKHARDT: Right now we will have the Conflict

of Interest Statement.

Conflict of Interest Statement

DR. VESELY: The Food and Drug Administration is convening today's meeting of the Oncologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and consultants are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of 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 is being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants 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 who have potential financial conflicts when it is

determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular government employees with potential financial conflicts when necessary to afford the committee the essential expertise.

Related to the discussion of today's meeting, members and consultants of this committee who are special government employees 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, CRADAs, teaching, speaking, writing, patents and royalties and primary employment.

Today's agenda involves discussions of biologic license application (BLA) 125268, proposed trade name Nplate (romiplostim), sponsored by Amgen, Inc., for the treatment of thrombocytopenia in adults with chronic immune idiopathic

thrombocytopenia purpura (ITP) who are nonsplenectomized and have had an inadequate response or are intolerant to corticosteroids and/or immunoglobulins, or patients who are splenectomized and have an inadequate response to splenectomy.

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

We would like to note, however, 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 consultants 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. ECKHARDT: We are going to start out this morning with the FDA presentation starting out with Dr. David Frucht.

FDA Presentation

Introduction to Romiplostim

[Slide.]

DR. FRUCHT: I am David Frucht and I am a product quality reviewer from the Division of Monoclonal Antibodies in the Office of Biotechnology Products.

[Slide.]

I will be giving a brief description of a cellular target of romiplostim and its mechanism of action and, as background, I will give a brief summary of other therapeutic proteins that have targeted this pathway.

Thrombopoietin, or TPO, is constitutively produced in the liver and is subsequently released into the circulation. It is degraded following uptake suggesting that the overall number of platelets could regulate the circulating levels of TPO.

It binds the TPO receptor, also known as c-Mpl, which is the abbreviation for murine myeloproliferative

leukemia proto-oncogene. This receptor is present on hemopoietic stem cells, progenitor cells and platelets.

TPO interacts with TPO receptor dimers, whether these are pre-formed or induced by TPO is not known. TPO binding leads to phosphorylation and activation of the JAK/STAT pathway, the most important being JAK2 and STAT5, as well as activation of the map kinase pathway.

Activation of STAT and MAP kinase pathways leads to cellular proliferation and differentiation, respectively.

The major effect of TPO is to promote the viability and growth of megakaryocyte colony-forming cells, thereby increasing platelet production.

[Slide.]

Based on information that is publicly available, there are two therapeutic protein products that have been studied under IND.

The first is recombinant human TPO with the identical amino acid structure to full-length endogenous TPO.

The second product is pegylated human recombinant megakaryocyte growth and development factor, PEG-MGDF. This molecule is truncated TPO, containing the first 163 amino

acid residues of TPO coupled to polyethylene glycol.

Sustained thrombocytopenia, associated with immunogenic responses that cross-reacted with endogenous TPO, was observed in some healthy subjects receiving PEG-MGDF.

Development of both products was discontinued, despite evidence that this class of products promoted platelet production in humans. For this reason, there has been an ongoing effort to develop TPO receptor agonists that do not induce immunogenic responses that cross-react with endogenous TPO.

[Slide.]

Romiplostim is a product designed to achieve this goal. It is a homodimer of 59 kD single-chain subunits. Each subunit consists of a human IgG1 Fc domain covalently linked at its C-terminus to a peptide chain containing two thrombopoietin receptor binding domains. This type of molecule is termed a "Peptibody" by Amgen.

These receptor binding peptides were identified through phage display technology and it is important to note that the receptor binding domain has no homology within endogenous TPO.

[Slide.]

Romiplostim has an in vitro mechanism of action similar to TPO. It binds to receptor with even higher affinity than human TPO, leading to phosphorylation of the TPO receptor, JAK2 and STAT5. It displaces TPO on human platelets suggesting but not proving that it recognizes the same binding site as endogenous TPO.

Romiplostim leads to increased megakaryocyte colony formation in vitro.

[Slide.]

Romiplostim is manufactured in E. coli and is purified using standard bioprocessing technology.

DR. ECKHARDT: Our next speaker is Dr. Heather Mannuel who will give us an overview of ITP.

Guest Speaker

Overview of ITP

[Slide.]

DR. MANNUEL: Thank you very much for allowing me to participate. I am Heather Mannuel. I am a hematologist/oncologist at the University of Maryland. I have been in clinical practice and had the opportunity and the pleasure and the challenge to treat and interact with a

fair number of ITP patients.

I want to give you a basic overview of what this disease entity or syndrome is.

[Slide.]

ITP, also known as idiopathic (or sometimes immune) thrombocytopenic purpura, is basically defined as thrombocytopenia in the absence of other blood cell abnormalities; that is, if you look at a patient's peripheral smear or the lab work that you obtained from them, their red blood cells and their white blood cells are normal.

There are no other clinically apparent conditions or medications that we can find in these patients that account for their thrombocytopenia, so, in other words, it is idiopathic, we are really not quite sure what is going on with these patients.

[Slide.]

Looking briefly at the statistics, there have been several studies that look at this. One study noted that there is a incidence of at least 22 million per year, and the prevalence is probably much more than this because, as I will go into a few slides down here, often this disease is

chronic.

Segal and colleagues noted that there was probably a prevalence of 100 million patients per year, making an age-adjusted prevalence of about 9.5 patients per 100,000. Approximately 1.9:1 females per males were noted in this study although it is postulated that there may be more males than what we are picking up because they just may be more asymptomatic.

[Slide.]

Again, this graph basically will give you an idea of age and incidence of TTP, looking at the age, the peak incidence in children generally is around age 3 through 5 and, as you can see here, female to male ratio is approximately equal in these. As the statistics are pointing out, there tends to be more of a female predominant disease at least in terms of the patients that we are picking up as age progresses.

[Slide.]

In terms of the clinical manifestations of ITP, it can be very acute. These can be the patients that, as a hematologist, you get worried about because you hear about them at 2 o'clock in the emergency room, or it can be a

fairly insidious onset and it can be picked up somewhat incidentally by a primary care physician that is just getting routine lab work.

Characterized by what is known as mucocutaneous bleeding, which is more of mucous membranes on the surface as opposed to joints and the kind of deeper bleeding that one would see in hemophilia; for example, we can see petechiae, purpura, ecchymosis, bruising on these patients.

There can be epistaxis and gum bleeding noted in women. There can be menorrhagia. Although overt bleeding and very dramatic bleeding like CNS bleeds or GI bleeds are rare, they can occur more often in elderly or compromised patients.

[Slide.]

This is just a picture of kind of typical petechiae in these patients. It can just look like a very fine red rash.

[Slide.]

This didn't translate quite as well, but this is supposed to be a close-up view of it.

[Slide.]

In terms of the etiology of ITP, it is a little

bit more known in terms of children as opposed to adults and, as I treat adults, I am only going to touch briefly upon children. But it is often seen after infections in children. Up to 80 percent of children, you can correlate some kind of a pre-existing infection.

There are several theories about this, either that the antibodies produced in response to the virus or bacteria are going to create a cross-reactivity with the platelets. H. pylori, one of the bacteria that is implicated in a lot of peptic ulcer disease, is also implicated as potentially a cause at least in children and possible in adults, as well as bacterial lipopolysaccharides which may interact with the platelets.

[Slide.]

In adults we are not so sure. We think there may be auto-antibodies involved, but everything becomes murkier.

[Slide.]

So the diagnosis essentially becomes one of exclusion. It is going to be very important to rule out any other causes. Maybe it is as easy as a lab error, platelets may be clumped, which is why we have to look at the peripheral smear very closely. Certainly, there are a lot

of drugs and medications that can cause the interaction. Very importantly, infections like HIV and hepatitis C absolutely need to be ruled out.

[Slide.]

Thyroid conditions, both hypo- and hyper-thyroidism, as well as autoimmune diseases like lupus can be accountable for thrombocytopenia. Other hematology problems that as a hematologist would give me chest pain at 2:00 in the morning, is I want to make sure that there are no destructive processes like TTP, any other type of autoimmune hemolysis that might translate over to the platelets.

Again, bone marrow disease like leukemias and myelodysplastic syndromes truly need to be ruled out.

[Slide.]

That leads me to the next question which is somewhat of a fundamental question even for the consensus panel of ITP, which is to marrow or not to marrow these patients, do you have to put a bone marrow needle and do a biopsy in everybody who comes in with a suspected diagnosis.

Overall, the consensus is that if your patient is 60 years or older, if they are poorly responsive to the treatment that I will go into in a few minutes, or if the

picture is unclear, then, it is certainly better to err on the side of obtaining a bone marrow biopsy. In my own practice, I do tend to give bone marrow biopsies and aspirates to patients who are older, you know, who are in their 60s and above.

Certainly, I have done that in some younger patients that just don't quite add up to the picture and I think that certainly, if you are going to commit somebody to a splenectomy or to something which can be fairly dramatic and a sort of life-altering procedure for them, then, generally, most of us would clinically err on the side of doing a biopsy.

[Slide.]

Anti-platelet antibody testing is kind of a hot topic of contention among hematologists in the community and I can say, working between private practice and academic medicine, I have seen a lot of different approaches to this.

The ASH Practice Guidelines, which were established and published in Blood journal, I believe 1996, generally went against recommending for anti-platelet antibody testing basically because you don't get a lot of real pertinent information from it.

There are very poor positive or negative predictive values. The sensitivity is pretty poor. You can see anti-platelet antibody positivity in patients with ITP. You can also see it in patients with lupus, in patients with thrombocytopenia related to pregnancy and a wide variety.

Most importantly, it doesn't change the management. We are going to do the same essential approach.

[Slide.]

So management of ITP in adults--again due to my practice, I am going to stick mainly to talking about adults--really boils down to emergency versus chronic treatment. Again, the goal, most importantly, is going to be prevention of bleeding, not cure, because the vast majority of these patients are not going to get a platelet count of above 150,000 again.

There are a few adults that can go into spontaneous remission but, generally, we have to take our focus away from a number and really look more at the patient.

[Slide.]

So, the general principles of therapy is that

major bleeding is rare if platelet count is greater than 10,000, and I think any of us who have treated patients with leukemia or patients with postchemotherapy thrombocytopenia can attest that that is the number that tends to get us nervous.

Again, we want to get this level to a safe level even if we are not really specifically curing the ITP. Generally, the consensus is that if we can get the platelet count to 30,000, to possibly 50,000, again depending on your individual patient and what he or she does for a living and their other medical conditions, generally is considered to be a safer level for the patient to live at.

[Slide.]

Jumping ahead here, the moderately thrombocytopenic count of 30- to 50,000 generally is considered safe, again, as long as these patients are not bleeding. If they are asymptomatic, this is probably a good level to leave them at. In fact, in the consensus guidelines, any platelet count of 50,000 or over generally was considered to be a patient that you really don't have to intervene with.

I would say to be very cautious with the elderly.

They tend to be more prone to CNS bleeds and there actually is a small, but real, risk of mortality from CNS bleeds in these patients.

Speaking from personal experience, any younger patients that I have that have a sort of more vigorous lifestyle, I will tend to be more aggressive with, construction workers, people that are athletes, people that are going to be exposed more to issues where they may get injured, even if they are not elderly, if they don't look like they are frail, I am going to feel more obligated to jump in and try to get that number up.

[Slide.]

But again, as with anything in medicine, you really want to titrate this to your individual patient. Again, you need to weigh the bleeding risk versus the risk of therapy because they are not benign.

[Slide.]

The initial therapy for almost all patients with ITP would involve steroids and the mainstay is prednisone. Generally, our role is 1 mg/kg/day, normally orally, if the patient can tolerate it; if not, you can certainly give them steroids like methylprednisolone or Decadron and you can do

this in an IV form.

Normally, patients, if they are going to respond, will respond within two weeks. Generally, they respond faster than that. The idea is to taper them off after the platelet response because again this is not the world's most benign drug as we all know if we have ever been on them or treated patients with steroids. But the duration of use of when you should start tapering and for how long remains controversial. I will go back into that in a few minutes.

[Slide.]

In terms of second-line therapy, the mainstays tend to be IV immune globulin, also known as IVIG, which we tend to give as 1 gram/kg/day for a period of 2 days, or WinRho, which is an anti-D, and this has to be if the patient is RH-positive.

Again, the thought with this is that you are dealing with an autoimmune process with an antibody-mediated process and these are thought to, so to speak, clog up the macrophages that clog up the clearing mechanisms of the cells and the system that would normally clear these platelets out of your system.

This tends to also produce a good response and a

quick response in the majority of patients. I mentioned emergency treatment if somebody is actively bleeding in the emergency room, IVIG tends to be a mainstay of first line treatment. You can get the platelets up to a manageable level within days often compared to steroids, which may take a week or more.

[Slide.]

Treatment side effects. Everything comes to the cost unfortunately. Steroids, this is just touching the surface of what they can cause. But a big worry, of course, is bone density loss.

Again talking about elderly patients or patients with multiple comorbidities, GI effects are going to be important. You get a lot of nausea/vomiting. You can get GI bleeds, muscle weakness, which I think we can see in a lot of patients that are on chronic steroids, weight gain, hypertension, unfortunately, the list goes on.

In terms of IVIG or anti-D, there can be hypersensitivity reactions to this. Some of the reactions fall on more the line of annoying like headaches or nausea or vomiting. But you certainly can get renal failure in a small percentage of these patients, as well as an alloimmune

hemolysis particularly with the anti-D.

Again, it is something that your really need to weigh the risks and benefits and watch your patient carefully on this, which leads to splenectomy, which is, so to speak, the gold standard that we have for patients that are refractory to the other treatments.

[Slide.]

Again, it is not benign. You need to weigh your balance and risks of a patient bleeding versus a patient's lifestyle. The risks are not only to that it is a surgical procedure but, also, that the patient undergoes loss of immune function.

I think from a primary care perspective and from a follow-up perspective, you need to be very careful that these patients are appropriately vaccinated. Remember they are about to lose their ability to really take care of encapsulated organisms and this is, of course, particularly important in children, but also in adults.

You want to make sure that they get their Pneumovax, that they are treated for meningitis vaccine as well as for the hemophilus vaccine generally at least two weeks before they are splenectomized if possible.

[Slide.]

This is just a schematic of when to do a splenectomy. I actually took this directly from the data from the Consensus Panel. This was a panel of 11 experts that were given a hypothetical patient, a 30-year-old woman who presented to the emergency room bleeding with epistaxis, menorrhagia, with petechiae, and she had a platelet count of less than 10,000.

The question was she was given I believe steroids and IVIG and she failed to respond, and at what time do you give this hypothetical person a splenectomy, at what time do you say that your standard treatments are not working and we are going to take her right to the operating room.

They stratified this by saying, you know, she is less than 10,000, if her platelets have then kind of crawled up to the 10- to 30,000 range, or if her platelets are now up to 30- to 50,000.

Each point on the graph represents different opinions basically. As you can see, these are very well-respected, very intelligent, experts and none of the data really comes into anything cohesive.

Even in the case of a patient who remained below

10,000, one of the experts wanted to bring her into surgery within two to three weeks of failure. One was waiting 10 weeks and beyond.

I think again it illustrates that there is no real great consensus even among the leaders in the field because the data just unfortunately isn't there and also, again, I think you need to really tailor it to your particular patient.

[Slide.]

The response post-splenectomy is usually pretty good immediately if the patient is going to respond. I definitely have seen patients come out of surgery and by the next day their platelet counts are up over 100,000. They may climb up into the 4- or 500,000 range.

Normally, if you are going to get patients with normalized platelets, you will get it within the first few weeks, and younger patients tend to do better at longer. A recent review evaluated patients that were looked at for over a period of up to 153 months and they noticed approximately a 65 percent complete remission with patients.

Unfortunately, looking at approximately 12 variables that they were hoping would account as factors

preoperatively, there was no real cohesive decision or ability to interpret what was in your favor of responding well after a splenectomy. So you may respond well post-splenectomy, unfortunately, you may not.

[Slide.]

Again, what happens with those patients that are not in the 65 percent, another quick graph for you, this is just age less than 40 and age greater than 40, which is our age cutoff here. As you can see, the patients who are less than 40 years old tend to do better for a longer time as opposed to the patients that are older, but it still starts to drop off.

[Slide.]

So, even years after a splenectomy, these patients can still get into trouble with their platelet count dropping again, in which case they are considered chronic refractory ITP. It is defined as ITP that would be persistent for greater than 6 months, the platelet count is less than 50,000 and again, unfortunately, there is a failure to respond to splenectomy.

[Slide.]

At this point you are in the "when all else

fails," and there are a variety of medications that can be used to try, as well as surgery. Some patients do have accessory spleens or splenules and they may need to have an accessory splenectomy.

H. pylori eradication is being looked at. Again, we seem to have better data in children than in adults. Some patients will go back on steroids or IVIG. We do use rituximab to get responses, which is an anti-CD20 agent, which we use in other forms of cancers and lymphomas, as well but, unfortunately, these are the patients who still will have problems, and these are patients that obviously will be in need of a lot of close follow-up.

[Slide.]

So, wrapping it up, ITP is often a chronic disease in adults. Multiple therapies may be needed over time and unfortunately, often you will still have complications and still have thrombocytopenia just by some pretty intense and, in the case of splenectomy, invasive procedures.

The goal in these patients is going to be prevention of complications both from the treatment, I would say, as well as prevention of complications from the bleeding, from the thrombocytopenia.

Again, as with everything in medicine, therapy needs to be tailored to your individual patient.

Thank you.

DR. ECKHARDT: That you for that excellent overview.

Now we will begin with the Sponsor Presentation.

Sponsor Presentation

Background and Introduction

DR. MILETICH: Thank you, Madam Chairman, members of the Advisory Committee, ladies and gentlemen. Good morning. My name is Joe Miletich and on behalf of Amgen, I would like to thank the FDA for the opportunity to present the data on our new product romiplostim, a platelet stimulator studied for chronic use in the management of immune thrombocytopenia purpura.

[Slide.]

This is an outline of our presentation. After my brief introduction, Dr. David Kuter will provide a short overview of thrombopoietin biology and the clinical management of ITP.

Dr. Dietmar Berger will then review the romiplostim data we have collected in ITP covering both

efficacy and safety risk assessment.

Finally, Dr. Paul Eisenberg will provide details of our proposed risk management plan and some closing remarks.

Platelets are small, but they are remarkable. Circulating in the bloodstream, they react in milliseconds to breaches of vascular integrity, sealing wounds, and minimizing blood loss.

A platelet count of 50 times 10^9 per liter or roughly 20 percent of the normal level is sufficient to gain most of this protective benefit and this is what we are proposing as the goal for therapy with romiplostim in ITP.

It is worth pausing to reflect that this corresponds to less than half a teaspoon of platelets in a total blood volume of approximately 5 liters.

[Slide.]

A treatment to increase platelet production in patients with counts lower than this and unfortunately, at risk for serious or fatal bleeding has long been imagined. But it wasn't really feasible until the natural stimulator thrombopoietin became available for study.

Amgen scientists were one of the five groups who

finally accomplished this in 1994 and, as you have heard, Amgen quickly advanced a potential therapeutic that was based on the thrombopoietin protein sequence in the clinical trials.

Also, as described by Dr. Frucht, unfortunately, antibodies did develop in a small number of patients that neutralized both the therapeutic candidate and the patient's own thrombopoietin. The clinical trials had to be stopped, but encouraging evidence for efficacy in ITP patients had been observed by that time.

[Slide.]

Also, as you have heard, romiplostim is the product of an intensive effort to discover a molecule that acts much like thrombopoietin but minimizes the risk of developing anti-thrombopoietin neutralizing antibodies.

Again, as nicely summarized by Dr. Frucht, it works through a completely novel peptide that is not based at all on thrombopoietin's protein sequence but which binds and stimulates the thrombopoietin receptor.

This peptide is repeated and spaced to optimize its activity, and it is also linked to the Fc domain of a human IgG1 to extend romiplostim's lifetime in the

circulation.

[Slide.]

Throughout the development of romiplostim, Amgen has consulted with the FDA on an appropriate program for chronic use in the management of ITP. ITP is considered an orphan disease and FDA has granted both orphan designation and priority review for romiplostim.

The Phase 3 pivotal studies were performed under special protocol assessment to address an acceptable study design particularly choice of endpoints and duration of exposure.

Amgen is proposing a risk management program for romiplostim and is committed to working with FDA to minimize both identified and potential risks once marketed.

With the ongoing priority review of romiplostim, discussions with FDA are occurring at a fast pace. I would like to point out that Amgen has enhanced our proposed risk management program since the briefing book was sent to committee members.

This enhanced program incorporates a risk minimization action plan including a proposal for controlled distribution of romiplostim. Committee members will find

this revised proposal in a brief summary document in front of them and this has already been provided to the FDA.

We were, unfortunately, unable to distribute it to committee members ahead of this meeting but Dr. Paul Eisenberg will review the details in his presentation.

[Slide.]

Now, I would like to introduce Dr. David Kuter, Professor of Medicine at Harvard and Director of Clinical Hematology at Massachusetts General Hospital.

David.

Thrombopoietin (TPO) and Management of Immune Thrombocytopenic Purpura (ITP)

DR. KUTER: Thank you. You have already heard a bit about ITP from Dr. Mannuel. I would like to elaborate a bit upon her comments to discuss the management of ITP and also to illustrate the rationale of why we think thrombopoietic growth factor, such as romiplostim, might be indicated in this particular disease.

[Slide.]

As you heard, ITP is an autoimmune disorder. It is defined as isolated thrombocytopenia with exclusion of other causes of thrombocytopenia.

It is characterized, as you have heard, by an antibody that binds to platelet proteins and this leads to platelet destruction. But, as I will amplify in a few minutes, it also prevents and inhibits platelet production. The net results is thrombocytopenia with its clinical sequelae of bleeding and bruising.

Current treatments, as you have heard, are primarily directed at decreasing the rate of platelet destruction. These include immunosuppressive or immunomodulatory therapies up to and including splenectomy.

As you also heard, this is an uncommon disease. It occurs in adults at a frequency of 1.6 to 3.3 per 100,000 adults per year. The prevalence is approximately 3 times higher.

This is also a disease in which there is a high frequency in young children, which is usually acute, acute thrombocytopenia is usually a pediatric disease characterized by brief periods of thrombocytopenia often after a viral infection.

The disease we are talking about today is a chronic disease of adults with a thrombocytopenia. The ITP results in a chronic disease and, in most adults, it is not

an acute disease but a long-term disease which is present for months, decades for the entire life span, as some of the patients in the audience can attest to.

[Slide.]

The diagnosis of ITP is based upon some criteria which were elucidated in Dr. George's seminal work at the ASH guidelines, also, the British Hematology Society Guidelines. Dr. George is on our panel this morning.

The diagnosis is based upon history, physical examination and review of blood counts and a peripheral blood smear.

As you have heard, there is no confirmatory test. There are no antibody testing of drugs or therapies which are currently used to diagnose this condition. Bone marrow biopsies are not routinely performed, an aspirate or a biopsy is recommended in patients over 60 or in those patients who are considering splenectomy.

The diagnosis for most clinicians is validated by the response to corticosteroids or to other forms of therapies, such as IVIG or anti-D.

Treatment of patients with ITP is usually indicated only when the platelet counts are less than 20- or

30,000 or in the rare patient less than 50,000 who has concomitant major bleeding.

30As you heard from Dr. Mannuel, the goal of therapy is not to normalize the platelet count. Our goal is to make the platelet count rise to a range of about 50,000, which is hemostatically effective in most clinical conditions.

[Slide.]

Now, there is no routine course or algorithm for treating ITP. What is shown here is an algorithm which sort of summarizes the practice throughout North America and also in Europe, a diagnosis of ITP is made.

If the platelet count is stable above 30,000, these patients are usually observed. If a platelet count is less than 30,000 and, particularly when there are signs of significant bleeding risk, the initial therapy is corticosteroids of several different types.

As you have heard, most patients respond to these. But when the corticosteroid is withdrawn, particularly in adults, the thrombocytopenia recurs in most patients. This leads to a wide variety of other medications which are used to treat the thrombocytopenia including IVIG and anti-D,

which are approved as indication, and a wide range of other nonapproved drugs including rituximab and Danazol in an attempt to bring the platelet count back up.

Eventually, many patients remain refractory or do not respond to these medications, or have side effects to these medications which preclude their continual use, and many patients, as you have heard, undergo splenectomy.

Nonetheless, some patients, approximately 30 percent, still fail splenectomy. This leads to a wide range of other therapies including chemotherapy regimens, such as azathioprine and cyclophosphamide, which are used to treat these patients.

In addition, therapies called "rescue" therapies are applied to both groups of patients if a significant bleeding event occurs, a GI bleed or a heavy menses, things like that, and these include a brief use of corticosteroids, the administration of IVIG, anti-D, or indeed platelet transfusions.

[Slide.]

Now, the problem with most current ITP therapies, as the patients in the audience will attest to, is that they are fraught with complications. Corticosteroids are a main

line of therapy which gives responses in 80 percent of patients, but long-lived in a small percentage, has as a complication depression, diabetes, hypertension, osteoporosis, cataracts and infections.

Anti-D and IVIG, which are drugs which give responses about 60 percent of the time, which are brief lasting meaning they last for days to weeks, have as complications anaphylaxis to drug infusion, as well as infusion reactions and a theoretical, albeit low, risk of infectious transmission by viruses in these products.

Rituximab is commonly used to treat ITP. It is not FDA-approved for indication, its complications are known to many. They include infusion reactions, progressive multifocal leukoencephalopathy, hepatitis B reaction, also hepatitis C reaction.

Danazol is an attenuated androgen. It works in about 40 percent of patients. Its complications, particularly in women, are androgenic side effects, which are mostly unacceptable, as well as LFT abnormalities.

Other agents include azathioprine and cyclophosphamide. These are chemotherapy agents. The long-term complications are immunosuppression, pancytopenia and

the risk of secondary malignancies.

[Slide.]

What about splenectomy? Splenectomy has been the standard of care for ITP for many years. But in the last decade or so in this country and also in Europe, this is becoming increasingly less to use because of patient preference and because of recognition that some patients have a long-term problem with exposure and potentially life-threatening fatal infections with bacteria.

Laparotomy, when splenectomy is performed in this fashion, has a mortality of 1 percent and a morbidity of about 13 percent. When laparoscopic procedures are used, the mortality drops to 0.2 percent and a mortality of about 10 percent.

The real problem with splenectomy is although it gives an effective response initially in up to 80 percent of patients, in approximately a third of all patients they soon relapse and this is not a permanent form of therapy for many individuals.

[Slide.]

What about bleeding risk in ITP patients?

One of the major problems with ITP is one fails to

quantify in any academic study the daily nuisance with heavy menses, GI bleeding, bruising, nosebleeds, things like that which occur in this patient population.

In a review of 17 studies with about 1,800 ITP patients, what has been analyzed are the fatal events, which are the tip of the iceberg to the ITP patient.

Forty-nine cases were identified out of the 17 studies for a fatal bleeding risk at 1.6 to 3.9 percent per patient year and, as we will talk about a little later on, the bleeding risk rises with age. And indeed the frequency of ITP, which was not commented upon by Dr. Mannuel's talk, has two frequencies.

The high group of ITP patients and the young patients below 5 years old, a bottom of the curve, and it rises. Like most things as you become older, there is a higher frequency of ITP.

[Slide.]

What about patients who fail to respond to many therapies, do they have a significantly good or bad prognosis?

Well, again, in 105 patients who had been characterized by having what is loosely defined as

refractory ITP, having failed many prior therapies, if you follow such patients for 110 months, you can see two major problems with the treatment of ITP in this particular group of patients.

The first is that 10 percent died of bleeding. In addition, 6 percent died of treatment-related adverse events going back to a point we will commonly make today, which is sometimes the treatment is as bad as the disease.

[Slide.]

One further point before I turn to thrombopoietin is we now recognize another attribute of ITP and it is important to think about this, this morning. We now know that patients with ITP, in addition to having increased platelet destruction, have decreased platelet production.

For example, thrombopoietin, which is the major platelet production in all of us, is normal in ITP patients most of the time. Here is the normal individual with a normal platelet count, thrombopoietin levels are appropriately low. In aplastic anemia patients with platelet counts of 20,000, the thrombopoietin levels rise about 15-fold.

However, in ITP patients with a comparable level

of thrombocytopenia, the thrombopoietin levels hardly rise out of the normal range.

In addition, platelet kinetic studies done by infusing radiolabeled platelets into patients have shown that platelet production is reduced or normal in two-thirds of ITP patients.

This is probably because the ITP antibody, which is destroying the platelets in the periphery, also inhibits megakaryocyte growth and causes megakaryocyte apoptosis in these patients. This is a new finding in terms of ITP and it has led rise to the following model of ITP.

[Slide.]

This is me. I am thin and happy. I have got a normal platelet count, I am making my platelets here. My platelets are being destroyed in different RE systems in my body. If I could turn on ITP by adding antibody to my circulation, the spleen now destroys platelets at a rapid rate and my platelet count drops to a low level.

In the classic model from some 40 years ago, it was assumed that platelet production rose dramatically to try to compensate for this and give us a higher platelet count. The studies I have just shown you is that in most

patients with ITP, this is not true.

What currently happens in most patients is this, that we have a somewhat increased rate of platelet production but not high enough to compensate fully for the destruction of the platelets in the periphery.

Our current theory, which we now know to be correct, is that by giving a thrombopoietin to individuals, we increase platelet production, more platelets enter the circulation and we can ameliorate or totally correct the thrombocytopenia despite the continual persistence of platelet destruction in these patients.

[Slide.]

What is thrombopoietin? You have heard a bit about it already. Thrombopoietin is a natural form in all of us. Romiplostim is a form of thrombopoietin. Both of these molecules bind in active receptors on target tissues. It results in activation of receptor and signal transduction events that give rise to a wide variety of things.

In summary, what it does, it prevents progenitor cell and megakaryocyte apoptosis and this is probably how it enhances platelet production ITP. It stimulates megakaryocyte growth and maturation and the net result is it

increases platelet production.

[Slide.]

If you give romiplostim or any other thrombopoietin to a normal healthy volunteer at day 1--and these are studies that have been recently published--there is a 3- or 4-day lag before the platelet count rises and then there is a dose-dependent rise in platelet count that peaks at day 14 or 15. There is no effect upon the white cells or red cell count or leukocyte count in these individuals.

[Slide.]

Now, when thrombopoietic growth factors first hit the horizon in 1994, there was a lot of excitement about them. This is a list of theoretical concerns that were generated at that time to address what might happen with pharmacologic use of these agents and we have postulated thrombocytosis, thrombosis, stimulation of tumor growth, stimulation of leukemia cell growth, autoantibody formation, and increased bone marrow reticulin might occur.

In the first generation of thrombopoietic growth factors to which about 2,000 patients have been exposed, we have found that although thrombocytosis could occur, even in

cancer patients, it did not result in thrombosis.

Furthermore, in chemotherapy studies in cancer patients with solid tumors, there was no stimulation of tumor growth in breast cancer or lung cancer patients of these agents.

When given to leukemia patients for induction chemotherapy, there was no effect upon leukemia progression or response rates to AML induction chemotherapy.

You have already heard about autoantibody formation and I will digress for one or two minutes to tell you about bone marrow reticulin.

[Slide.]

This is a bone marrow biopsy and the squiggles here in black are what is called bone marrow reticulin. It is identified by a silver stain, which is over 100 years old. All of us have reticulin. It is a normal component of bone marrow. In 75 percent of the people in this room, if I stain your bone marrow, you will have reticulin, not quite up to this grade in all of us.

Higher Grades 3 and 4 may be abnormal, but they are abnormal in a wide variety of situations. They are increased in infectious, inflammatory and oncologic

disorders. They are also increased when people are exposed to GM-CSF, IL-3 and IL-11. In all situations, this is reversible and does not affect blood counts.

[Slide.]

In contrast is bone marrow collagen. Bone marrow collagen is shown here at these blue strands where the arrows are pointing. This is identified by another ancient stain called a trichrome stain. This may be accompanied by reticulin in the bone marrow, but it is associated entirely with clonal malignant disorders, such as metastatic cancer, hairy cell leukemia and myeloproliferative disorders.

The fibrosis here is reversible with treatment of underlying clonal disorder and it is the underlying clonal disorder which accounts for the thrombocytopenia and pancytopenia in these patients.

[Slide.]

What about thrombopoietin in humans, what do we know about that? There is only one study and that is with recombinant TPO some four or five years ago.

When given to AML induction therapy to patients up to 21 doses, 8 of 9 patients had increased reticulin, 2 of 6 controls had increased reticulin as shown in these strands

down in this bone marrow biopsy. But, upon cessation of drug, this was fully reversible in all patients within 30 days.

[Slide.]

In summary, ITP is a disease of accelerated platelet destruction, but also a disorder of suboptimal platelet production.

Thrombocytopenia in ITP may lead to severe clinical consequences including life-threatening bleeding but also to severe bleeding, which is not life-threatening but is a nuisance to the patient.

Current therapies for ITP are often unsuccessful and oftentimes plagued by complications and side effects. Thrombopoietin is a key regulator of platelet production in all of us, and. in ITP, circulating TPO levels are inadequate. And TPO administration, as we have shown, can increase platelet production and ameliorate the thrombocytopenia in ITP.

[Slide.]

With that, I will introduce Dr. Dietmar Berger, Director of Global Development for this product for Amgen.

DR. BERGER: Thank you, David.

[Slide.]

Dr. Kuter has described the unmet medical need in adult ITP and romiplostim represents a new treatment approach in this setting. I will now review the clinical data on efficacy and safety of romiplostim in the chronic treatment of adult ITP which support the approval of romiplostim in this orphan indication.

Overall, we have conducted 11 studies in 308 ITP patients and additional studies in healthy subjects in patients with thrombocytopenia and MDS and after chemotherapy.

A total of 271 ITP patients were exposed to romiplostim with a duration of exposure of about 6 months in 153 patients and about 1 year in 114 patients. Thirty-six patients were treated for more than 2 years.

Since the issuance of our briefing book for this meeting, Amgen has provided FDA with an update of all exposure and safety data for romiplostim in an effort to provide also the Advisory Committee members with the same data as submitted to FDA, Amgen is including the safety update in our presentation.

Consequently, some of the exposure data shown today will differ slightly from those in the briefing book, however, the overall conclusions from the updated data sets are fully consistent with the original data.

[Slide.]

The core of the romiplostim data in ITP consists of 2 randomized, controlled, Phase 3 trials and a long-term extension study. In the Phase 3 trials, patients were randomized 2:1 to receive romiplostim or placebo over a 24-week treatment period.

Study 105 included patients after splenectomy. The sister study, 212, included non-splenectomized subjects. Patients with a platelet count of 30 x 10^9/L or less were eligible.

Romiplostim was started at a dose of 1 mcg/kg applied subcutaneously each week. The dose was adjusted on a weekly basis and the treatment goal was to increase platelet counts above 50 x 10^9/L.

In both romiplostim and placebo arms, concurrent medications, which are baseline medications for ITP, and rescue medications were allowed as defined by the ITP standard of care.

After completion of the treatment period, platelet counts were followed for up to 12 weeks. Once platelet counts were falling again below 50 x 10^9/L, patients were eligible for the long-term extension study of open label romiplostim on slide on the right. This study is ongoing and patients have been treated for up to 156 weeks.

[Slide.]

The dosing regimen for the Phase 3 trials was developed on the basis of Phase 1 and Phase 2 studies. For example, the starting dose of 1 mcg/kg/week had been established as the minimum active dose in healthy volunteers and had also been studied in ITP patients.

The weekly dosing interval was supported by Phase 2 data and the dose adjustment were based on considerations of the treatment objectives to bring platelet counts above 50 x 10^9/L, as well as intrapatient and interpatient variability of platelet counts.

[Slide.]

The primary endpoint for the Phase 3 studies was rigorously designed in close collaboration with FDA during a special protocol assessment. Durable platelet response was defined as weekly platelet counts of at least 50 x 10^9/L

again during 6 out of the last 8 weeks of the treatment period. Patients who had received ITP rescue medication at any time during the study were classified as nonresponders.

Maintenance of a platelet count of at least 50 x 10^9/L, as Dr. Mannuel and Dr. Kuter have discussed, is clinically recognized as a target at which the risk of spontaneous bleeding is felt to be minimized and the primary endpoint of durable platelet response was chosen to allow for description of stable platelet responses at this level over an extended period of time.

[Slide.]

Secondary efficacy endpoints of the Phase 3 studies include analyses of additional platelet response criteria, ITP medication and patient-reported outcomes.

Overall platelet response and number of weekly platelet responses were designed to describe the degree and duration of the platelet response in more detail.

Concurrent and rescue ITP medications were assessed to describe the impact of romiplostim treatment on the standard of care.

[Slide.]

ITP is an orphan disease and the sample size of

the Phase 3 studies is limited. Small imbalances between the groups are observed, however, across the two trials the post-splenectomy and the non-splenectomized patient population describe a representative adult ITP population.

I would like to draw your attention to platelet counts at entry and prior ITP medications. As discussed, the platelet entry criterion for both studies was a platelet count below 30 x 10^9/L in accordance with ASH guidelines for treatment initiation.

However, the mean platelet count in the post-splenectomy study at entry was 14 to 15 x 10^9/L. Patients in this group had received a median number of 6 prior therapies indicating a heavily pretreated, highly refractory ITP population. In clinical practice, these patients have very limited treatment options.

In the sister study, in non-splenectomized patients, subjects had received a median number of 3 prior therapies and romiplostim and mean platelet count at entry was 17 to 19 x 10^9/L, again indicating an extensively pretreated and poor responder ITP population.

[Slide.]

This slide now demonstrates results for the

primary endpoint: subject incidence of durable platelet response. Results are given individually for study on the left, as well as across the two trials on the right; romiplostim data indicated by the yellow bars and placebo data by the gray bars.

Romiplostim-treated patients showed a statistically significant increase in durable platelet response in 38 percent in the post-splenectomy study, 61 percent in non-splenectomized patients and 49 percent across the two trials. A single placebo patient met the response definition.

Considering the rigorous design of the primary endpoint and the heavily pretreated patient population, especially in our post-splenectomy study, these efficacy data indicate that romiplostim represents an important therapeutic option for adult ITP patients.

[Slide.]

Subject incidence of overall platelet response was a key secondary endpoint and overall platelet response was defined as at least 4 weekly platelet counts above 50 x 10^9/L during the treatment period. Again, platelet counts were excluded within 8 weeks of rescue medication and,

across the 2 trials, 83 percent of romiplostim-treated patients and 7 percent of placebo patients showed an overall platelet response.

[Slide.]

Platelet count responses in romiplostim-treated patients were achieved on top of reductions in the standard of care. And you have heard about the side effects of all those medications, for example, corticosteroids or IVIG.

Rescue medication was allowed in both treatment arms according to the standard of care. Whenever investigators felt that a patient was at risk for imminent bleeding, 60 percent of placebo patients and 22 percent of romiplostim-treated patients received rescue medications across the two studies and a similar difference was observed in the two individual trials.

[Slide.]

Similarly, a majority of romiplostim-treated patients who came on study with concurrent or baseline medications were able to reduce or discontinue these medications. Across the two trials, 87 percent of romiplostim-treated patient and 38 percent of placebo subjects were able to reduce or discontinue their baseline

ITP medications, which again included corticosteroids, immunoglobulins and others.

[Slide.]

Analysis of the median weekly platelet count over time demonstrates the durability of the romiplostim effect. In this graph, the romiplostim group is indicated by the yellow line, the placebo group by the gray line. Error bars are giving the first and third quartile of platelet counts.

There are a few important points here. A median platelet count of 50 x 10^9/L was reached after 3 romiplostim injections. The median platelet counts were maintained between 50 and 100 x 10^9/L over the 24-week treatment period.

It is also important to note that the normal platelet count is defined by the range between 150 and 400 x 10^9/L as you have heard. Normal platelet counts were reached in a minority of subjects only and were not aiming to normalize the platelet count.

A platelet count above 50 x 10^9/L is clinically recognized as a target at which the risk of spontaneous bleeding is minimized. For placebo patients, the median platelet counts remained below 20 x 10^9/L throughout the

treatment period.

[Slide.]

After completion of the pivotal studies, platelets were followed for up to 12 weeks and, as soon as platelet counts fell below 50 x 10^9/L, patients were eligible for the open label romiplostim long-term extension study.

Platelet counts in patients treated with romiplostim fell below 50 x 10^9/L after a median of 2 weeks without drug. Both prior romiplostim patients, as well as prior placebo patients, responded rapidly to romiplostim, and median platelet counts rose above 50 x 10^9/L after 2 injections.

The median follow-up in the long-term extension study is now 65 weeks and subjects have been receiving romiplostim for up to 156 weeks. The median platelet counts were maintained above 50 x 10^9/L across the entire study.

[Slide.]

Summarizing the efficacy data, romiplostim is effective for treatment of ITP as evidenced by platelet count response, reduction of rescue medication used and reduction of discontinuation of concurrent ITP therapies.

These results we feel are of high clinical

relevance especially as they were obtained in a heavily pretreated adult ITP patient population. The treatment options for these patients are limited particularly after splenectomy.

Durability of platelet responses was demonstrated in the Phase 3 trial, as well as in the long-term extension study.

[Slide.]

In the following slides, I will summarize the adverse events observed in the clinical studies and describe the data for specific events of interest.

Adverse events were observed in the majority of patients in our Phase 3 trials. Serious adverse events, however, occurred in 20 percent of placebo and 17 percent of romiplostim patients. Deaths occurred in 3 placebo patients and were due to cerebral hemorrhage, atypical pneumonia following hospitalization for intracerebral hemorrhage and pulmonary embolism.

One romiplostim patient died of an intracranial hemorrhage after discontinuation of romiplostim. Three romiplostim patients and 1 placebo subject withdrew from study due to adverse events.

[Slide.]

This withdrawal rate due to adverse events is low in our romiplostim-treated patients. On this table now, we summarize adverse events with an at least 5 percent higher incidence in the romiplostim group.

It is important to note that the majority of these adverse events were mild to moderate, were transient, did not require any intervention and did not lead to discontinuation of study drug.

[Slide.]

As discussed earlier, the primary and secondary endpoints for the romiplostim study program were agreed in discussion with FDA during the special protocol assessment process. Bleeding events, although of high clinical relevance, were not a predefined endpoint for the romiplostim trials in ITP.

However, bleeding events for romiplostim-treated and placebo subjects were documented as adverse events in the clinical database, and significantly less severe bleeding events occurred in the romiplostim group.

Using a prospectively defined grading system, Grades 2 and higher bleeding events occurred in 34 percent

of placebo subjects and in 16 percent of romiplostim subjects during the course of the 24-week treatment period of our Phase 3 trials.

Grade 3 and above events occurred in 12 percent of placebo subjects and 7 percent of romiplostim patients.

An analysis of the severity of bleeding events versus platelet counts demonstrated that all Grade 2 and higher bleeding events occurred at platelet counts below 50 x 10^9/L. Platelet counts below 20 x 10^9/L were associated with Grade 3 and above bleeding events.

[Slide.]

On the following slides I will review romiplostim and placebo data regarding specific adverse events in the Phase 3 trial. These event categories were selected based on the biology of ITP and thrombopoietin data as detailed earlier by Dr. Kuter.

We look at the occurrence of thrombocytopenia after cessation of romiplostim treatment, at the potential increase in bone marrow reticulin, formation of neutralizing antibodies, thromboembolic events and the potential for progression of existing hematopoietic malignancies or MDS.

[Slide.]

Reoccurrence of thrombocytopenia after cessation of romiplostim treatment is an expected event and it has been reported as an adverse event in 4 out of 57 romiplostim-treated subjects participating in our Phase 1 and 2 trials.

The reduction of other ITP therapies that may occur in the presence of a robust response to romiplostim would be expected to enhance the risk of thrombocytopenia after discontinuation of romiplostim.

Thrombocytopenia after cessation of treatment may lead to an increased risk of bleeding, particularly in patients receiving anticoagulant or anti-platelet therapies.

In the Phase 3 trials, one subject developed a fatal intracranial hemorrhage after discontinuation of romiplostim while receiving anti-platelet therapy. However, the platelet count observed in the subject after termination of romiplostim treatment was similar to the pretreatment level in the same subject.

[Slide.]

An increase in bone marrow reticulin has been identified as a risk in romiplostim-treated patients, and several mechanisms were used to assess this risk during our

clinical studies.

A bone marrow study was conducted as an ancillary trial in patients participating in the romiplostim long-term extension study. Sites and patients were asked to participate and 10 patients agreed to the repeated bone marrow biopsies. In addition, adverse event reports included information on increased bone marrow reticulin in 10 out of 271 ITP patients in our overall ITP safety set.

We have asked a bone marrow expert panel to assess the bone marrow samples from Study 123, as well as from the spontaneously reported cases with reticulin information.

[Slide.]

The bone marrow expert panel reviewed all these cases and concluded that the underlying sample sizes were small and exposure to romiplostim may have been insufficient for observation of all long-term drug effects.

However, bone marrow effects of romiplostim in these samples seemed to include hypercellularity, increased reticulin and megakaryocyte clustering. Patients experiencing these findings tended to be exposed to higher doses of drug, usually above 10 mcg/kg/week.

Also, these findings appeared to be reversible

often soon after stopping the drug.

There was no evidence in those patients that romiplostim would cause a hematological neoplasm or chronic idiopathic myelofibrosis and no subject had an increase of bone marrow blast counts which also was assessed by the bone marrow panel on the same biopsies.

[Slide.]

Four assays were developed to assess antibody formation. Screening assays, so-called "biacore" assays were developed to detect binding antibodies to romiplostim and endogenous thrombopoietin. These assays are highly sensitive for both low and high affinity antibodies to TPO and romiplostim.

In cases with detectable binding antibodies to cell-based neutralizing bioassays were used, one, to detect neutralizing antibodies to romiplostim and a second one to detect neutralizing antibodies to thrombopoietin.

Amgen has considerable experience regarding immunogenicity analysis for thrombopoietic agents. In our preclinical experiments with MGDF, and you have heard about that earlier, administration of MGDF led to generation of antibodies to MGDF that cross-reacted with endogenous

thrombopoietin and led to thrombocytopenia.

In contrast, romiplostim administration in preclinical experiments and animal experiments led to development of binding and neutralizing antibodies to romiplostim only and these antibodies did not cross-react with endogenous thrombopoietin.

[Slide.]

In the overall ITP study population, 225 romiplostim-treated subjects and 45 placebo subjects were tested for antibodies to romiplostim and endogenous thrombopoietin. A total of 4 to 8 percent of subjects in both groups had pre-existing binding antibodies to romiplostim or thrombopoietin.

A similar number of patients in romiplostim and placebo groups showed post-dose binding antibodies to romiplostim or thrombopoietin. These binding antibodies to romiplostim did not cross-react with thrombopoietin and vice versa.

One subject in the romiplostim group developed neutralizing antibodies to romiplostim after dosing and these antibodies were present at the end of study time points and did not cross-react with thrombopoietin. Four

months later, after discontinuation of romiplostim, the neutralizing antibodies were not detectable anymore.

[Slide.]

Thromboembolic events are a potential risk for romiplostim treatment especially with thrombocytosis. In our Phase 3 studies, however, no imbalance for thromboembolic events was observed.

The rate of thromboembolic events was 2.4 percent in both romiplostim and placebo patients. We want to acknowledge, however, that thrombocytopenic patients may be protected from thromboembolic events and an increase of the platelet counts in romiplostim-treated patients may restore an underlying potential of thromboembolic events.

At this point, our data are based on a small patient number and limited exposure in this orphan disease. We are proposing further follow-up on this risk in the framework of our Risk Management Program, which Dr. Eisenberg will detail in the next part of the presentation.

[Slide.]

Romiplostim exerts its effects through binding to the thrombopoietin receptor as you have heard from Dr. Frucht. This receptor is expressed on hematopoietic cells.

The TPO receptor has not been detectable on solid tumor cells. The stimulation of existing hematologic malignancies is a potential risk for romiplostim-treated patients.

If we go back to our Phase 3 studies, there was no excess of neoplasms in the romiplostim group. Five subjects or 12 percent in the placebo group and two subjects or 2 percent in the romiplostim group reported adverse events that were categorized as neoplasms.

[Slide.]

Two patients in other ITP studies presented with potential myelodysplastic syndromes that were pre-existing but not diagnosed at the time of recruitment. Study 209--that is the study where these cases occurred--was an access study for subjects who did not qualify for the pivotal trials.

The first patient was a 63-year-old male who started romiplostim in January '06 and, after seven months, an adverse event of splenomegaly was reported and a bone marrow biopsy revealed fibrosis.

At this time, an earlier bone marrow biopsy that had been conducted in October 2005, prior to romiplostim exposure, was reassessed and revealed now positive reticulin

staining of sclerotic bone. Cytogenetics showed the deletion of the short arm of chromosome 20, consistent with myelodysplasia or myeloproliferative disorder.

In a second case, an adverse event of aplastic anemia was described after six months of romiplostim exposure, however, pre-existing macrocytosis at baseline would also support a diagnosis of hyperplastic MDS.

These cases do underline the need for accurate diagnosis of ITP and Amgen acknowledges the importance to limit the use of romiplostim to an ITP patient population. And we are proposing a controlled distribution which will be discussed by Dr. Eisenberg again in the next part of the presentation.

[Slide.]

Let me point out that we have also studied romiplostim in the setting of disease-related thrombocytopenia in patients with myelodysplastic syndromes. Forty-four patients with low or intermediate 1 risk MDS were receiving open label romiplostim.

The study had a treatment phase of 4 weeks and patients are currently being treated in the long-term extension phase. In the single-arm study, 54 percent of

patients had a clear treatment benefit with an increase in platelet counts and also reduction in platelet transfusions and bleeding events.

During the study, we received 11 reports of possible disease progression. Two subjects only had progression of the MDS to AML as defined by WHO criteria. This rate is in line with the population and expected progression rate from MDS to AML in a thrombocytopenic MDS patient population.

Three subjects showed an increase in MDS severity scores over time. Six subjects had a transient blast cell increase in their bone marrow or peripheral blood. It is not clear whether the increases in blast cells in these patients involve a normal blast cell population or leukemic blasts. However, none of the patients that had these transient blast cell increases showed cytogenetic changes that would be indicative of a progression to AML.

Further clinical studies in the setting of thrombocytopenia and MDS are ongoing or are planned. FDA will also speak to the MDS setting in their presentation and we are happy to answer any questions in this regard.

[Slide.]

Let me summarize the risk assessment findings in our clinical study program in ITP.

In the clinical studies in ITP patients, romiplostim showed a favorable safety profile and we conclude that benefits outweigh the risk of romiplostim in ITP.

The majority of adverse events were mild to moderate or transient. Bleeding events were analyzed and Grade 2 and above events were more frequent in the placebo group than in the romiplostim group.

Adverse events of interest, for example, neoplasm or thromboembolic events, were similar for placebo and romiplostim groups and present theoretical risks for the ITP patient population.

Identified risks include thrombocytopenia after cessation of treatment and increase of bone marrow reticulin.

[Slide.]

I want to now hand over to Dr. Paul Eisenberg who will detail our proposed risk management program for romiplostim in ITP.

Risk Management Program and Closing Remarks

DR. EISENBERG: Thank you. Clearly, the data you have seen shows the unique benefit for romiplostim for the treatment of patients with ITP. It has been developed as an orphan indication. The number of patients studied in the pivotal registration program are relatively small, as one would expect, and the goal of our risk management program really has to be twofold.

One is to assure that we can get this therapy to the patients who would benefit from it and at the same time we continue to learn more about potential risks that might occur with long-term exposure.

[Slide.]

I will be overviewing our risk management program, highlighting a few points. First, as you heard from Dr. Berger, we were able to identify risks in our clinical program. These were apparent both because they were looked for or they are related to the pharmacology, such as thrombocytopenia, or the reticulin finding that we have discussed.

There are also potential risks which were not identified in our program. But we acknowledge that we need to be considering as we monitor safety in the long term

could occur in a patient exposed to romiplostim.

So our proposed risk management program will focus on two areas. First of all is the additional risk assessment component and that will include both targeted studies, as well as you will see in the update of what we have provided in terms of risk minimization, an enhanced way of ensuring that we have complete capture of patients into what is essentially a safety registry. In addition, we will be proposing a risk minimization action plan and that is detailed and has evolved since the briefing book.

I want to take a moment just to highlight why it has evolved. We have had good feedback I think from FDA, as well as stakeholders, to understand how we can provide access and, at the same time, that the goals of the program, as I will detail, are to assure that patients who are appropriate for use of romiplostim, basically, the ITP patients, are the ones that are treated.

How one does that is something we hope and we see that there is a question to the panel in that regard this morning, is an area that has evolved and needs to be appropriate for both the practice of hematology/oncology, as well as access for patients.

Then, I will briefly summarize with an overall assessment of our perspective on the benefit-risk.

[Slide.]

Now, in terms of the risks that need to be identified in a risk management program, as we have described in our clinical development program, there really were two areas where we observed risk.

One is that, as you would expect, cessation of treatment with romiplostim will result in recurrence of thrombocytopenia. The extent to which it occurs, you heard that there were four patients who, in fact, had severe thrombocytopenia.

That would put a patient at risk of bleeding, so it clearly would be an area where we would want to acknowledge and advise around monitoring of patients should there be a need to discontinue therapy.

The increased bone marrow reticulin is a little more challenging. It is clearly an aspect of pharmacology that maybe have a background rate in ITP. It is not clearly pathologic. Nonetheless, it is an area where more knowledge is necessary as we apply the novel therapy, and we will talk about how we are going to approach that.

[Slide.]

In terms of the potential risks, these were highlighted. You saw some data in this regard. Thrombotic/thromboembolic complications are clearly an area we would have a concern about. When you increase the platelet count, certainly, there is the possibility that that would result in a thrombotic complication, thrombocytopenia, in some respects is a state of anti-thrombosis, if you will, but it is complex and we haven't seen clear data in that regard.

Neutralizing antibodies, the program as you have heard was designed to ensure that neutralizing antibodies, should they occur against romiplostim, would not cross-react with endogenous thrombopoietin and to date we have no reason to believe that would be the case.

Progression of existing hematopoietic malignancies or progression of reticulin, you have heard something about. Clearly, the number of patients exposed to date are insufficient to positively exclude that with 100 percent certainty, but it is something we need to consider. We have no evidence of it to date.

Finally, that really reflects into the bullet

about inappropriate use. We did observe medication errors in our clinical development program and I will just highlight those, because we focused a great deal in understanding the reason for that and it mostly related to complex dosing rules in the clinical development program and the protocol that had been addressed by simplification in the label's recommendations.

[Slide.]

Now, in terms of risk management, when we think about risk management in general, there are really two components that feed into each other, and they have to be considered also in terms of the broader context of what do we consider risk, both as practitioners, patients, society, regulators, and that is really reflected in this slide.

Risk management includes a component of risk assessment. Historically, we have done that through pharmacovigilance, collection of passive reports, adverse event reports. Many of you are familiar with that.

Obviously, that is always the cornerstone of what we do in pharmacovigilance. But we also have the opportunity when we have areas of special interest or need to acquire additional data, to think of risk management more

broadly--that is, doing targeted studies that will allow us to address specific questions, epidemiologic observational studies, or in this case even moving to a study in which you are gaining data on virtually every patient exposed to the product through a safety registry. That is, in fact, what we will be proposing, and the program is designed to facilitate.

Now, the beginning of risk minimization is labeling, appropriate product labeling, and that clearly is one form that can be enhanced by ensuring that labeling also guides patient information.

One component of that is something you will hear about, the Medication Guide. This is an FDA tool that utilizes patient-friendly language tool to deliver risk information in the labeling, important information that a patient needs to be aware of, that can be communicated to them through this tool called Medication Guide.

There have also been revisions to labeling by FDA to improve the quality of labeling in making it very transparent as to where benefits and risks are to practitioners, as well.

[Slide.]

Now, in terms of our risk assessment program, we believe there are really two components that have to be addressed, and I will highlight them here. The first is the natural history of ITP. Although you heard a lot from the presentations this morning about the disease state, the natural history of some of the components we are particularly interested in as we apply these novel therapies is not well know.

In specific, bone marrow reticulin or fibrosis or progression or misdiagnosis in an ITP cohort has not been extensively evaluated, and we have already initiated discussions and we will be taking the opportunity of a unique database that the Danish National Health Registry has as you may or may not be aware.

These databases actually have our medical records databases that are unusually comprehensive, and this database, based on discussions with investigators who manage it, contains data on about 3,000 patients with ITP collected over a decade and 600 patients who have had ITP and followed in the database for over six months.

Particularly unique and useful in this database is that they do have extensive bone marrow biopsy data that

will allow us to calculate or understand background incident rates of events that we will be looking for, and I will come back to that.

This is an important point to keep in mind since anytime we embark on a registry with a novel therapy, we don't have the control group advantage that we have in the clinical trial setting, so we need to understand the background rate.

We will also plan a prospective study. This is already in planning with a scandinavian cohort of patients. Again, the rationale for this is the quality of the medical record assessment that we are able to obtain from these databases, and we are going to be looking forward at longitudinal assessment based on criteria that we are putting in place, as well as the possibility of following that once romiplostim is introduced into Europe where we are hopeful the application will receive a favorable opinion later this year.

[Slide.]

In terms of more explicit evaluation, clearly, the passive collection of data may not be sufficient for bone marrow morphology assessments, and we propose approximately

a 200-patient study in which sequential bone marrow evaluations would occur.

Clearly, this panel needs no information as to the challenge of getting patients to submit to sequential bone marrows. We think it is possible. We have talked to investigators about this, and we are certainly committed to being able to do this.

We also think it will be tremendously valuable to understand the changes over time with exposure to romiplostim and would propose to do that over two years and five years, looking specifically at reticulin and collagen. This would also allow us to collect prospectively antibody samples in all of these patients, as well as our passive assessment for antibodies, which I will describe in a few minutes.

Any patients who are discontinued from treatment, we would have the opportunity to, in a control setting, specifically assess what the post-treatment incidence of thrombocytopenia, particularly severe thrombocytopenia, might be, and any incidence of hematological malignancies and thromboembolic adverse events would be captured in this manner.

[Slide.]

Now, I would like to turn your attention to risk minimization, which obviously when you introduce a new agent into the marketplace, is critical. Labeling, as I have described, is the cornerstone of risk minimization. It provides the information as to appropriate use of the product.

Recurrence of thrombocytopenia is one of the warnings we would include. Here, as I have indicated, we would be mostly advising for monitoring of the platelet count after discontinuation of romiplostim.

The increased bone marrow reticulin, while we cannot prevent it, we expect it to be pharmacologic and, in fact, as highlighted by Dr. Kuter, present to some extent in all of us, is important to note. If a biopsy is obtained, there needs to be certainly the information for a practitioner to know that he may observe reticulin.

We also think we can reduce the incidence. In our clinical trial experience, the cases where the bone marrow changes appeared to be most frequent were associated with higher doses of romiplostim. In general, we didn't see a benefit to higher doses of romiplostim, so when we looked at

the benefit versus this theoretic risk, we feel a maximum dose recommendation of 10 mcg/kg is appropriate.

[Slide.]

Now, I would like to turn to the potential risks. The first is obviously the appropriateness in the indication. I am pleased to see that FDA will ask your opinions as well as to how we frame the appropriate indication. Adult ITP patients, who we treated in the clinical trials, we have highlighted they had to fail therapy with at least a prior ITP-approved therapy.

We believe that is still the appropriate patients for treatment. That is the population, as I am sure many of you are aware who treat these patients, it is not black and white in terms of identification, and some discussion about that will certainly help guide us and FDA as to how to do this properly.

The neutralizing antibodies; here, the main component we include in the labeling, as with all our products, is that typically, a neutralizing antibody is heralded by the failure of efficacy of treatment, and what we provide information on is, first, to recognize that if there is failure of efficacy, to contact us.

We also provide actually a CLIA-certified program. We haven't instituted for this specific program but we have CLIA-certified laboratory support. We support that to assess for neutralizing antibodies and provide contact information and support that.

In terms of thromboembolic events, there is no clear relationship between platelet count and thromboembolic events, and I think most of you already would acknowledge that. It is important, however, to avoid excursions to very high levels of platelet counts, so we would have dosing information that will also focus on what the appropriate platelet count is.

The goal, and we want to emphasize this, is to maintain a platelet count around 50,000. That is the goal of therapy. There will be transient excursions and variability that need to be managed with appropriate dosing information to achieve that goal.

Progression to the irreversible fibrotic state, again, these potential risks clearly need to be warned against. We have not seen them but they do need to have an appropriate and highlighted warning which will be facilitated, as well, by this label being instituted under

the improved labeling recommendation, so-called physicians' labeling rule that FDA has indicated.

Medication errors, at least at the moment, we believe this program based on how it is administered and since it is a new program, should be administered by a health care practitioner. We recognize that over time there may be value in our providing kits or providing support for this, not to require administration in a clinical or physician's office. But that is not the intent at the time we launch.

[Slide.]

Risk minimization action plans I think are a particularly interesting area, and you will have the opportunity to hear more about this, this morning. Many of you may have seen or have experience with these programs. Thalidomide is an example, Tysabri, Revlimid, they have different kinds of structures.

It is important that the program be designed to meet the specific needs of the population in question that is being addressed. I think it is important, and each of the panel will be particularly important, as have our consultants, in informing what is the appropriate way to

manage risk for the hematologist/oncologist who will be treating this patient based on their practice and the extent to which they will recognize complications or adverse events that might be expected should they occur. That is key.

Secondly, we want to ensure that we have access and we do this in a way that facilitates the availability of this therapy since as you have heard, there is an unmet medical need here. We don't want patients to be denied therapy and to be exposed to therapies that are, in fact, either more dangerous or unapproved.

Finally, we want to use tools that are evidence based. In our enthusiasm to develop these programs both in industry and regulatory agencies over the last few years, we have learned some things work, some don't, and we need to continue to inform and improve, so that we have a meaningful impact on risk and have a meaningful benefit for society.

I will focus on three categories of tools that are highlighted in the FDA guidance. I believe FDA will also comment on these. These include targeted education and outreach, reminder systems and controlled distribution.

We are proposing to utilize each of these tools in the romiplostim risk minimization action plan.

[Slide.]

Now, the goal of our program, there are really two goals that we want to focus on. First, is that there is potentially a risk outside the ITP indication. We are carrying on clinical investigations in the MDS indication. There are other reasons for thrombocytopenia as all of you are aware and have been outlined.

We want to focus where we have studied the product, which is in patients who had idiopathic thrombocytopenic adults and who failed an initial course of a therapy that would have confirmed. As you have heard, it's a clinical confirmation of the diagnosis and a diagnosis of exclusion. So that is the population we believe is appropriate for use at this time of romiplostim.

We also want to ensure that we can identify any risks that emerge and that essentially means that we would like to have a registry of all patients who are exposed to romiplostim as it enters the marketplace, so we get that real world experience and are maintaining a regular update on safety that can be shared with FDA and obviously, transparently, with our stakeholders and public to ensure that the benefit-risk profile is appropriately understood.

So we will include both patient and physician education on the risk profile and specifically focus on physicians understanding the appropriate use. We will focus on identifying long-term risk by monitoring safety, And we will look to limit very explicitly, and this is the key component of the program, off-label use by controlling the distribution to patients in whom there is a confirmation by the prescribing physician that the patient has ITP--that is, an adult patient who has ITP.

[Slide.]

I have already commented on this. But these are the indications out of our clinical trial, adult ITP, both splenectomized and non-splenectomized patients who have had an insufficient response to a prior therapy or, if they are splenectomized, obviously, have had recurrence after splenectomy.

[Slide.]

Now, the program specifically includes the three components, the three tools I highlighted for you. I have already discussed product labeling and the development of the Medication Guide, the language of patient-friendly Medication Guide.

Again, ITP, as has been highlighted by the previous presenters, is a diagnosis of exclusion. There needs to be knowledge of how to make the diagnosis. So part of the education we believe should include providing guidelines, and ASH has developed a fairly robust set of guidelines to clinicians.

Not all clinicians may be familiar with those, so we certainly want to make those available and have them used in an ITP diagnosis checklist. The checklist, we also think is particularly useful that a provider go through the criteria prior to making a decision to prescribe.

I think checklists for many of us in all walks of practice are fairly routine these days and the use of a checklist I think is helpful to making certain. We believe in this instance that the practitioners consider any potential concerns that they should be considering based on product profile.

The Medication Guide is aimed towards the patient. We would use the FDA tool, as well as additional educational tools to ensure that it is in a patient-friendly language, and we are also proposing that at six months after initiation of treatment, there be reconfirmation of the

diagnosis of ITP explicitly, so we would solicit that through the program that the diagnosis is reconfirmed.

Again, the rationale for that is that we have seen that some patients--and we highlighted two examples--that entered into the program in the clinical trials, were subsequently found not to have ITP. We would want to reassess those patients and not include them in the controlled program for an ITP diagnosis. But we would consider other means if they are benefiting from therapy to providing that.

Now, controlled distribution I will go through in a moment and I will outline the system for you. It involves consent from both the patient and physician to enter the program. It ships romiplostim only to physicians who have enrolled patients who have consented to treatment and enrollment in the program and have ITP.

It involves a full tracking of all patients through a database and safety registry. I do want to highlight again we have put these components into the supplement we have provided. They are in evolution and we are committed to each of these components and look forward to your comments as to how we can enhance and make them most

appropriate for the hematology/oncology practice.

[Slide.]

The program schematically, I think it is useful to look at how this would work. Essentially, when the diagnosis is made by the hematologist/oncologist of ITP, the hematologist/oncologist would provide the education, would have availability of a guide or a kit to start patients on the program, so that they can inform them of what controlled distribution would involve, this would involve, as well, providing them a medication guide, discussing benefit-risk.

They then will be asked--and I will show you this in a moment--schematically, to sign an enrollment form, and the form then gets faxed to a case manager who enters the patient into the program.

[Slide.]

In terms of the Enrollment Questionnaire, we envision something like this. Again, not intended for you to read each of the components at a high level. It should be no more than one page to facilitate entry into the program. It will include a reminder of the appropriate use based on the label in ITP for romiplostim.

It will ask the prescriber to affirm that this is

a patient who meets the ITP diagnosis and appropriate use criteria. It will ask for some basic information. This is merely to facilitate romiplostim being provided to that physician's practice.

It will ask for the patient to consent to program participation since they would be sharing medical data and agreeing to provide a minimum of safety data.

I do want to emphasize that we envision the availability of this database and the consent allowing patients to be approached for other more detailed studies, but we do not envision that we are going to require every patient for entry into this to agree to bone marrow biopsy sequentially, for example.

Finally, we would ask that the patient affirm that they have read the Medication Guide and are aware of the risks.

[Slide.]

The program then provides for the case manager to release shipment to the physician's office, so that would be the controlled aspect of the program, and that the patient, at the time the case manager releases that shipment through the program, they will confirm the patient has ITP.

They will also solicit from the physician reconfirmation of the diagnosis of ITP at six months and they would work to collect the initial data for the safety registry. At the moment, we are envisioning that the data that would be necessary would be provided by the physician's office through a simple form that could be completed when the patient comes in for their treatment.

[Slide.]

So, to summarize, we are proposing a fairly aggressive and we believe comprehensive risk minimization action plan and risk management program that is appropriate for introducing a novel therapy with a novel mechanism of action and a relatively small clinical trial exposure into the market.

Obviously, the goals of this program should be to ensure this therapy which does have unique benefit-risks for these patients can be provided to them in a manner that facilitates access and that facilitates the practice in the physician's office of providing this therapy.

The components of the program, as I have highlighted, include each of the three tools that are typically cited as being appropriate. Others can be

envisioned. But certainly education, having a safety registry with full capture of every patient who receives romiplostim, and having a means of controlling distribution to reduce off-label use have been emphasized in our discussions with FDA and, in our thinking about this program, as appropriate, long term for management of this new approach to treating ITP.

[Slide.]

I would like to close with a few comments. First of all, I think all of us, whether in hematology/oncology or other practices of medicine, are aware of the risk of serious bleeding in ITP which can often be life-threatening and occur in otherwise healthy patients.

The safety and efficacy of the current therapies in general are inadequate. There are therapies currently used that have not been as extensively studied and are not approved for use in ITP. We believe romiplostim offers a novel and effective approach to treatment of ITP chronically, it has the potential to decrease the risk of serious bleeding. We have certainly seen evidence of that in our clinical trial program.

We believe that management of entry of romiplostim

into the armamentarium that hematologists/oncologists have for treatment of patients with ITP should be accompanied by robust risk management, which will include, as I have outlined, a risk minimization action plan.

We thank you for your consideration of what we think is an exciting program and hope that you will agree.

Thank you.

DR. ECKHARDT: Thank you. Now we will take a 15-minute break and reconvene at 9:55.

[Break.]

DR. ECKHARDT: We will now hear the FDA presentation. We will start with Dr. Jamali.

FDA Presentation

Romiplostim FDA Overview

DR. JAMALI: Good morning.

[Slide.]

My name is Faranak Jamali. I will present an overview of the major FDA review findings.

[Slide.]

Our presentation consists of three parts. First, I will summarize the major efficacy and safety data obtained from use of the product among certain patient populations

with chronic ITP.

Secondly, Dr. Steven Lemery will summarize important safety findings from a study conducted among patients with myelodysplastic syndrome or MDS.

Lastly, Dr. Suzanne Berkman will highlight the major features of the proposed risk management plan and various options related to risk management.

[Slide.]

The proposed indication applies to two subpopulations of patients with chronic ITP. The first consists of patients who have not undergone splenectomy but have had an insufficient response, or are intolerant to at least one course of corticosteroids or immunoglobulins.

The second population consists of patients who have had an insufficient response to splenectomy.

[Slide.]

The romiplostim database consists of data from 14 ongoing or completed clinical studies. Two exploratory studies enrolled healthy subjects while the bulk of the data are derived from 10 clinical studies conducted among patients with chronic ITP.

Two of these 10 studies were Phase 3 studies that

supplied the major safety and efficacy data. In addition to the ITP data, preliminary data were supplied from an ongoing study conducted among patients with MDS, as well as data from an ongoing study among patients with chemotherapy-induced thrombocytopenia.

Overall, the BLA consists of data from romiplostim exposure in 271 patients with chronic ITP and 121 patients in other settings.

[Slide.]

The two Phase 3 studies were almost identical in design except for the eligibility criteria. As noted on this slide, Study 105 enrolled subjects who had thrombocytopenia despite splenectomy.

Study 212 enrolled patients who had not undergone splenectomy but who had thrombocytopenia despite at least one prior ITP drug therapy as was exemplified in the protocol by the use of prednisone.

As noted at the bottom of the slide, subjects who completed either of the two studies were eligible to receive long-term treatment with romiplostim if they met certain criteria.

[Slide.]

The major design features for the Phase 3 studies are summarized here. Both studies were double-blinded and randomized patient in a 2:1 pattern to either romiplostim or placebo. The active treatment period was 24 weeks on medication followed by a 12-week follow-up period.

The starting romiplostim dose was 1 mcg/kg administered weekly that was titrated to achieve the platelet growth and not to exceed 15 mcg/kg/week.

The target platelet goal was between 50- and 200,000 with dose reductions for counts in excess of 200,000, and nonadministration of a dose if the platelet count exceeded 400,000.

Platelet counts were obtained weekly throughout the active treatment period along with standard laboratory tests and assessments of antibody formation to the drug, as well as antibody formation to thrombopoietin.

A number of patients reported outcome assessments that used a multi-component ITP Questionnaire were also performed at baseline and during the study.

[Slide.]

All major study outcomes related directly to platelet counts. The primary endpoint for both studies was

a comparison of the proportion of patients who achieved a durable platelet response which was defined as a count of 50,000 or more for 6 of the last 8 weeks of the study.

The four secondary endpoints consisted of comparison of the overall platelet response, a comparison of the total number of weeks with a platelet response between the two groups, a comparison of the proportion of patients who required rescue medication and a comparison of the proportion of patients who achieved a durable platelet count while receiving a stable romiplostim dose during the last 8 weeks of the study.

Multiple other platelet comparisons, as well as the PRO outcomes, were analyzed at supportive endpoints.

[Slide.]

Overall, 125 patients were enrolled in the two placebo-controlled ITP studies and the disposition is shown here. In each study, 21 patients were randomized to placebo while the number of patients randomized to romiplostim was 42 in Study 105 and 41 in Study 212.

Ten of the enrolled patients discontinued the study with a similar distribution among the treatment groups. The most notable reasons for study discontinuation

consists of 2 deaths in the placebo group and 3 deaths on 3 patients in the romiplostim group who withdrew because of adverse events.

These adverse events consisted of increased bone marrow reticulin in 1 patient, B cell lymphoma in another patient and a cerebral vascular accident in the third patient.

[Slide.]

As shown here, the major baseline characteristics were reasonably balanced between the study groups. The median age was approximately 50 years and as shown in the second row, most patients were female.

Compared to patients in the nonsplenectomized study, patients enrolled in the splenectomized study had slightly lower median platelet counts and slightly higher white blood cell counts.

[Slide.]

This slide illustrates the extensive history of prior medication use among the patient population. As you can see, a broad variety of ITP medications had been administered to these patients including predominantly prednisone and IVIG.

Importantly, only 11 patients out of the entire 125 sample size populations had received only a single prior ITP medication.

[Slide.]

The primary endpoint in the Phase 3 studies was a comparison between the study groups in the proportion of patients achieving a durable platelet response.

As shown here, the higher proportion of patients receiving romiplostim achieved the endpoint response than patients receiving placebo, the rate of 38 percent in the splenectomy study and 61 percent in the no splenectomy study. Only 1 placebo patient achieved a durable platelet response, a patient in the no-splenectomy study.

[Slide.]

All four major secondary endpoints related either directly or indirectly to patient's platelet responses. As shown here, statistical success was demonstrated in favor of romiplostim for all four endpoints.

[Slide.]

The Phase 3 studies provide the major comparative safety data and the next few slides will summarize these comparative data, as well as focus upon five major outcomes

of special interest including the risk for bone marrow reticulin formation and potential for marrow fibrosis, thrombotic risks, the potential for severe thrombocytopenia after discontinuation of romiplostim as may occur due to the drug suppression of intrinsic thrombopoietin levels, immunogenicity and finally the risk for neoplasia.

[Slide.]

Adverse events in the Phase 3 studies are summarized here with the placebo and romiplostim groups from each study pulled together. Any adverse event was experienced by all the patients receiving romiplostim and 95 percent of those receiving a placebo.

The rate of serious adverse events was also similar between the two study groups, 20 percent in the placebo group and 17 percent in the romiplostim group.

Four deaths occurred during the study, 3 in the placebo group and 1 in the romiplostim group. Within the placebo group the deaths were attributed to pneumonia, pulmonary embolus and an intracerebral hemorrhage.

The 1 death in the romiplostim group was attributed to an intracranial hemorrhage, an event that followed discontinuation of romiplostim when the platelet