count was approximately 5,000.

Any form of a bleeding adverse event occurred among similar proportions of the study groups, 61 percent for the placebo group and 57 percent for the romiplostim group.

Additionally, the rate of serious bleeding event was similar between the two study groups, 10 percent for the placebo group and 6 percent for the romiplostim group.

[Slide.]

The most common adverse events that occurred at the higher rate with romiplostim group compared to the placebo group are shown here. The most common adverse event was arthralgia reported at 26 percent in the romiplostim group.

Other adverse events occurred at rates of 17 percent or less and included dizziness, insomnia, myalgia, extremity, abdominal, or shoulder pain, dyspepsia, or paresthesia. Most of these reactions were of mild to moderate severity.

[Slide.]

The specific safety risks I will summarize are derived from the entire safety database which consists of

data from the clinical studies outlined here. The experience among chronic ITP patients accounts for exposure of 271 patients and is derived predominantly from the Phase 3 and other studies that were designed to examine romiplostim exposure for 6 months or less.

Especially pertinent to the safety review are the data from the long-term chronic ITP extension study that is currently ongoing, as well as the recently initiated Study 131 that will compare romiplostim to standard of care over a one-year period of time.

Data cutoff points, the median exposure in the chronic ITP safety database is approximately 37 weeks with 36 of the enrolled patients having an exposure of at least two years. Additional safety data are supplied by romiplostim exposure among 56 healthy subjects, 44 subjects enrolled in the MDS study, and 21 subjects enrolled in the chemotherapy-induced thrombocytopenia study.

[Slide.]

Reticulin formation and marrow fibrosis are the first major safety risks I will summarize. As noted in our background materials, excess reticulin in the bone marrow has sometimes been described as reticulin fibrosis. The

condition is identified with a silver stain and has been associated with benign as well as malignant conditions.

The condition is generally regarded as a potentially reversible process. In contrast, collagen fibrosis is thought to represent a more ominous condition. Collagen fibrosis is identified with a trichrome stain of the marrow and upon diagnosis is frequently cited as it correlates to myelofibrosis and blood cytopenias.

As noted in the last bullet, the overriding concern relates to any potential for long-term romiplostim exposure resulting in marrow fibrosis with subsequent cytopenia.

[Slide.]

An association between romiplostim and reticulin formation is based not only upon the clinical data but also upon animal data. In a repeat dose romiplostim study, bone marrow fibrosis developed based upon H and E staining of marrow biopsies.

Special stains were not performed to determine whether the fibrosis was predominantly reticulin or collagen. Nevertheless, the fibrotic changes were generally reversible after discontinuation of romiplostim.

The prior experience with another TPO agent is also informative. As described in the publication, repeat dose administration of the TPO molecules to rats also resulted in myelofibrosis, which was characterized as predominantly reticulin fibrosis.

These investigators also determined that marrow content of transforming growth factor-beta increased in parallel with the reticulin fibrosis. This observation led them to propose that the TPO molecule stimulated megakaryocytes to produce TGF-beta, which in turn resulted in reticulin formation.

[Slide.]

Within the clinical studies, increased marrow reticulin was detected in both the controlled and uncontrolled studies. Within the two Phase 3 clinical studies, one patient discontinued romiplostim due to an adverse event of increased marrow reticulin. No placebo group patient experienced a marrow adverse event.

Within the uncontrolled studies, the most recent safety update has identified a total of 9 patients who had increased marrow reticulin detected with most events reported as adverse events.

The available follow-up information indicates that 2 patients with baseline and follow-up marrow information had improvement in the reticulin deposition, while 2 patients were reported as having stable reticulin. Two of the patients remained on romiplostim, one following a dose interruption. Additional follow-up for other patients was not available in the 120-day safety update.

[Slide.]

At the time of the BLA submission, the sponsor had performed a detailed medical analysis of the marrow and patient features for 6 patients who had increased marrow reticulin reported as adverse events.

The major points from this review indicated that all of the patients had nucleated red blood cells detected in their peripheral blood. All had undergone splenectomy. All had received relatively high doses of romiplostim ranging from 7 to 18 mcg/kg and, finally, 1 patient had a positive trichrome marrow stain and, in this patient, the collagen deposition was assessed as "localized" and "inconsistent with chronic idiopathic myelofibrosis."

[Slide.]

As previously described by the sponsor, the ITP

database contains a report of one case of aplastic anemia that was recently submitted to the BLA as part of the safety update. This event occurred in a 75-year-old female with a history of diabetes mellitus, coronary artery disease and breast cancer.

Following six months of romiplostim, she was diagnosed with aplastic anemia with a marrow report of only focal erythropoiesis and myelopoiesis without convincing evidence of megakaryocytes.

A subsequent test for JAK2 point mutation was negative. The patient was receiving multiple concomitant medications as listed here including azathioprine approximately 6 weeks prior to the bone marrow biopsy and died 54 days following the aplastic anemia diagnosis.

[Slide.]

One of the concerns for a thrombopoietic molecule is an increased risk for the thrombotic events. Only 3 patients experienced thrombotic events in the Phase 3 clinical studies.

Specifically, one patient in the placebo group experienced a pulmonary embolus, while within the romiplostim group, one patient experienced a cerebrovascular

accident and another patient with atrial fibrillation experienced a peripheral arterial embolus.

Within the other studies, thrombotic events were reported among 12 other patients treated with romiplostim and mainly occurred as isolated events with no more than 3 subjects experiencing any single thrombotic events of deep vein thrombosis, pulmonary embolism, portal vein thrombosis, myocardial infarction, or unspecified thrombosis.

[Slide.]

The third major risk identified with romiplostim relates to the potential for romiplostim to suppress intrinsic thrombopoietin levels such that patients develop severe thrombocytopenia following discontinuation of the drug.

This potential was explored in the early phase clinical studies where 4 of 57 patients developed platelet counts below the pretreatment level. In all cases, the counts approximated baseline levels within 14 days after the onset of thrombocytopenia.

The last few bullets on the slide highlight a notable occurrence in the controlled clinical studies.

This was an 80-year-old man who received six

months of romiplostim and experienced a thrombotic cerebrovascular accident 3 days after discontinuation of the drug. At this time, his platelet count was 107,000 and aspirin was administered. Seven days later he developed an intracranial hemorrhage in association with the platelet count of 5,000. The patient received a platelet transfusion but died the next day.

This case illustrates the potential consequences of severe thrombocytopenia especially when combined with an anti-platelet medication.

[Slide.]

Antibody formation was assessed in 225 ITP subjects who received romiplostim and the major results are summarized here. Binding antibodies were detected through a biosensor immunoassay, whereas neutralizing antibodies were detected through a cell-based bioassay which tests for the neutralization of romiplostim or TPO activity on cell growth.

The sample with positive immunoassay results were tested in the cell-based bioassay. Overall, binding antibodies to romiplostim developed in 10 percent of the subjects while 5 percent of the subjects developed binding

antibodies to TPO.

In contrast, no subjects developed TPO neutralizing antibody and one subject developed a neutralizing antibody to romiplostim.

This patient chose to discontinue romiplostim and the neutralizing antibody was detected at the termination visit. The neutralizing antibody was not detected on a serum sample obtained four months later and no adverse events were detected during this time period.

[Slide.]

The final major safety risk pertains to malignancies. Adverse events due to neoplasia were uncommon in the Phase 3 clinical studies and were reported in two patients receiving romiplostim and five patients receiving placebo. Neoplasms within the romiplostim group were: B cell lymphoma and a basal cell carcinoma.

In the other supportive studies, neoplasms were reported among 13 patients with no predominant type of neoplasm.

[Slide.]

In summary, with respect to the use of romiplostim among patients with chronic ITP, the data indicate that the

product increases and sustains platelet counts in patients who have failed prior therapies.

However, long-term safety data are limited. For example, to date, less than 300 chronic ITP patients have been exposed to romiplostim and, for these patients, the median follow-up is only 37 weeks.

The limited available data suggest that the major safety concerns relate to various marrow events, such as reticulin formation and the potential for fibrosis, thrombotic events, the occurrence of severe thrombocytopenia after discontinuation of the product and neoplasia.

The neoplasia risks may be especially pertinent if romiplostim is used on patients who do not have chronic ITP, especially patients with MDS. Dr. Steven Lemery will highlight the preliminary findings from an ongoing MDS study.

Romiplostim Safety Review

MDS Progression

DR. LEMERY: Hello. My name is Steven Lemery and I am a medical officer in FDA's Division of Biological Oncology Products.

[Slide.]

Today, I will be presenting a safety review regarding myelodysplastic syndrome progression events that occurred in the clinical study 20050159. This study, referred to as Study 159 during the remainder of this talk, evaluated the platelet mobilizing activity of romiplostim in 44 patients with MDS and thrombocytopenia.

It should be noted that the applicant has not applied for licensure for the MDS indication, however, FDA believes that these findings are relevant to today's discussion regarding the overall safety of romiplostim and are relevant to the development of the product label.

[Slide.]

This slide summarizes why the safety review was conducted in a non-ITP population. C-Mpl, the thrombopoietin receptor, is expressed on certain hematopoietic progenitor cells.

Increased expression of c-Mpl has been detected using Northern blot analysis on the cell surface of blasts in some patients with AML or MDS.

A variable percentage of AML cells demonstrated in-vitro proliferation after exposure to high concentrations of thrombopoietin. Observations from Study 159 included

increased blast counts in some patients with MDS. Additionally, many of these patients experienced an elevation in their blast counts less than 3 months following the initiation of romiplostim.

[Slide.]

Note that Study 159 investigators enrolled patients with low or intermediate-1 risk of MDS according to the International Prognostic Scoring System.

Low risk MDS patients have an estimated 25 percent median progression rate to AML of 9.4 years and intermediate-1 risk patients have an estimated 25 percent median progression rate to AML of 3.3 years.

[Slide.]

Study 159 was an open label, dose escalation study evaluating weekly subcutaneous romiplostim at doses of 300 to 1,500 mcg/week. Patients were eligible if they had low or intermediate-1 risk MDS and a platelet count less than or equal to 50,000/mcl.

[Slide.]

This slide shows the demographics of patients enrolled in Study 159. Most patients were men and most patients had IPSS scores of 0 or 0.5. The median and mean

ages were both above 70 years.

[Slide.]

For this safety analysis, FDA reviewed narrative summaries provided by Amgen, serious adverse event reports and Study 159 data tables. FDA identified additional cases in the study data tables that were not presented by the applicant. These included 7 additional cases of increased blast count and 4 cases of cytogenetic progression.

During this review, 22 cases of MDS disease progression, cytogenetics progression, progression to leukemia or transient blast count elevations occurred among 44 patients with myelodysplastic syndrome who received romiplostim.

A patient was considered to have cytogenetics progression if he or she progressed from good risk cytogenetics to intermediate or poor risk cytogenetics, or if he or she progressed from intermediate risk cytogenetics to poor risk cytogenetics.

Other cases of MDS disease progression are defined here for the purposes of this presentation as an increased blast count that resulted in an increased IPSS score. Increased blast counts or cytogenetics progression occurred

in all-dose cohorts evaluated during the conduct of Study 159.

The following slides describe the cases of AML progression, MDS progression, or blast count elevations identified during the safety review.

[Slide.]

At least 4 cases were suggestive of AML progression. One of these 4 patients was considered to have MDS progression and not AML by the applicant. Amgen's central blast count reading was 19 percent versus 25 percent at the investigational site.

If the blast count average at the two sites is calculated, this patient would be considered to have AML by WHO criteria. An additional patient was considered by the applicant to have experienced a transient increase in his blast count differential from 4 percent prior to treatment to 24 percent by week 3.

The blast initially decreased to near baseline after romiplostim discontinuation, however, this patient developed AML requiring treatment with Myelotarg and arsenic about 6 weeks after stopping romiplostim.

[Slide.]

This slide describes additional cases of rapid MDS progression or potential AML. Two patients who were deemed as experiencing MDS progression by the applicant died after experiencing rapid disease progression and these cases may have portended the development of AML.

One of these two patients developed myelofibrosis, a rapid increase in his white count, cytogenetics progression and blasts in the peripheral blood less than 3 months after beginning romiplostim. He died of his disease 3 months later.

The other patient experienced an increase in her blast count from less than 5 percent at baseline to 12 percent less than 1 month after beginning treatment. She began treatment with azacytidine but died before an end-of-study visit in the setting of worsening MDS.

Finally, a 72-year-old man with fewer than 5 percent blasts at screening developed a blast count percentage of 36 percent by morphology. He began treatment with azacytidine on day 51. He died of MDS-related causes approximately 10 months after beginning romiplostim treatment.

Of note, 5 out of the 7 potential AML or rapid MDS

progression and death cases initially presented within 4 months after beginning romiplostim treatment.

[Slide.]

This slide describes additional cases identified during this review. Four patients developed blast counts greater than or equal to 20 percent while receiving romiplostim.

All blast counts decreased off treatment, however, at least 1 patient progressed to a higher IPSS score compared to their baseline status. This patient died of unknown causes approximately one year after starting romiplostim.

Three patients developed blast counts between 10 percent and 19 percent while receiving romiplostim. One of these 3 patients also experienced cytogenetics progression. This patient's blast counts improved off treatment but he died of MDS 7 months after romiplostim treatment began. A second patient experienced MDS progression and died of unknown causes 15 months after beginning romiplostim.

Four additional patients experienced increases in blast counts while receiving romiplostim. Among these patients, one woman with an IPSS score of zero and who was

considered to have a transiently increased blast count, developed AML one year later. One man developed an increase in peripheral blasts up to 2,400/mcl. He died of a CNS hemorrhage with thrombocytopenia prior to undergoing a repeat bone marrow aspirate.

Additionally, one woman with an IPSS score of zero experienced a transient elevation in her blast counts during week 24 of therapy. Her blasts increased again after 16 months of therapy and she died of MDS after subsequently receiving decitabine.

Finally, 4 patients had cytogenetics progression alone without a notable increase in blasts. One of these patients who progressed to poor cytogenetics at week 36 died shortly thereafter with a cause of death determined to be related to myelodysplasia.

A second patient had a bone marrow biopsy and became moderately positive for the trichrome stain indicating the presence of collagen fibrosis.

[Slide.]

The previous slides described the cases of romiplostim-associated increased blast counts or cytogenetics progression identified during this review.

This slide shows important limitations that should be considered regarding these events. Because Study 159 was uncontrolled, the possibility that this cohort of patients may have been at a higher underlying risk for MDS progression or AML could not be ruled out, for example, due to older age or other unknown variables.

Secondly, the risk of progression due to myelodysplastic syndrome should be differentiated in this population versus immune thrombocytopenia, the indication for which the applicant is seeking licensure.

Patients with MDS have an abnormal hematopoietic clonal population and defective hematopoiesis. The theoretical stimulation of this abnormal hematopoietic clonal population with acquired genetic abnormalities may increase the risk for disease progression in patients with MDS.

This potential risk of MDS progression does not necessarily encompass the ITP indication because ITP is an immunologic disease as opposed to a clonal stem cell disorder.

Third, it is unknown if the rate of progression to AML will be more rapid for patients who experience a

transient blast count elevation. As discussed, one patient with a transient increase in her blasts and an IPSS score of zero developed AML approximately one year later.

[Slide.]

In summary, at least 7 of 44 patients developed acute leukemia or rapid MDS progression and death during or shortly after romiplostim administration. At least 7 additional patients died within 19 months of beginning romiplostim albeit 1 was due to a CNS hemorrhage.

Additional long-term follow-up information was not available to determine if more cases of AML or death occurred in patients who were not found to have blast count elevations while receiving romiplostim.

Fifteen of the 22 events noted in this review initially began withIN approximately 3 months of beginning romiplostim. All of the 22 events initially began within approximately 9 months of beginning romiplostim.

[Slide.]

As a final reminder, this should be taken in the context that low-risk myelodysplastic syndrome patients have an estimated 25 percent median progression rate to AML of 9.4 years and intermediate-1 risk patients have an estimated

25 percent median progression rate to AML of 3.3 years.

Thank you.

DR. ECKHARDT: Dr. Berkman will present risk management considerations.

Risk Management Considerations for Romiplostim

DR. BERKMAN: Good morning.

[Slide.]

I am Suzanne Berkman, an analyst with the Division of Risk Management. I will briefly review the sponsor's risk management proposal, then, highlight two particularly important components of the program for the Committee to focus on, appropriate patient selection and patient monitoring.

I will provide an overview of the current risk management program for natalizumab as an example to draw upon for romiplostim.

[Slide.]

As Dr. Eisenberg illustrated, risk management encompasses risk assessment, as well as risk minimization activities. Both of these components are equally necessary to develop a sufficient program for romiplostim.

Routine risk management in the postmarketing

setting relies on two main components: the package insert to communicate the drug's benefits and risks, as well as spontaneous adverse event monitoring for continual risk assessment.

Additional risk minimization measures are considered when these routine measures are not considered sufficient if the drug is believed to offer a meaningful therapeutic benefit or fulfill an unmet need for patients.

These additional measures may range from educational campaigns to programs linking product distribution with the completion of certain tasks to assure safe use.

Further risk assessment for various types of studies are particularly important if the risks are not well characterized.

[Slide.]

To minimize the identified risks associated with romiplostim, the sponsor recently informed us of plans to create a controlled distribution program.

Many of the details have yet to be worked out, but the basic proposal includes education and a system that required prescriber and patient enrollment for drug access,

completion of a safety questionnaire every six months of treatment and a one-time patient reauthorization form completed after six months of treatment.

Certain aspects of the program, such as appropriate patient selection, monitoring requirements and discontinuation procedures need more development.

In addition to risk evaluation through the program, the sponsor has proposed concepts for three studies to further assess the risk of bone marrow abnormalities, thrombotic events and immunogenicity. The sponsor has also proposed not to market directly to consumers.

[Slide.]

I would like to spend some time focusing on two important aspects of the program: the possible criteria for appropriate patient selection and parameters for adequate patient monitoring.

[Slide.]

Much of the effectiveness of this program will depend on targeting use to the appropriate patients. Identifying these characteristics raises many questions:

Should the duration of idiopathic thrombocytopenic purpura be specified?

Should romiplostim use be limited to splenectomized patients?

How should "insufficient response" to or "intolerance" to corticosteroids or immunoglobulins be defined?

Should a particular platelet count be specified?

Should a bone marrow biopsy be documented?

Should patients with a known history of bone marrow stem cell disorder be considered for treatment?

Should patients with active malignancy be considered for treatment?

Should certain concomitant medication use be discouraged?

Finally, are there other factors that we need to consider?

As part of enrollment, a number of risk management programs require attestation by the prescriber that the patient meets the criteria for safe use set forth, or that the prescriber understands the indication and criteria set forth.

The degree to which romiplostim access depends on meeting these criteria versus the use of an attestation

needs further discussion, however, at minimum, the program should collect this type of baseline data regarding the patient's disease state and possible risk factors for adverse events.

[Slide.]

Once the target population is determined, the next step in assuring safe use is to develop an appropriate monitoring system. What to monitor, how often to monitor, and how to collect the data needs to be discussed.

Because there are several major risks identified by both the sponsor and FDA, coupled with the need for more long-term safety data, a robust monitoring and data collection component to this risk management program is essential.

[Slide.]

To give some perspective as to how a risk management program might work for romiplostim, I will review the main features of the natalizumab risk management program as an example.

[Slide.]

Natalizumab is a monotherapy treatment for relapsing forms of multiple sclerosis. More recently, it

was approved to treat moderate to severe active Crohn's disease, however, my example will focus on the MS indication.

Three cases of progressive multifocal leukoencephalopathy were reported in the clinical trials, so a risk management program titled Tysabri Outreach Unified Commitment to Health or the TOUCH Prescribing Program was developed to minimize and further assess this risk.

I use natalizumab and the TOUCH example instead of thalidomide S.T.E.P.S. program, which you may be more familiar with, because the S.T.E.P.S. program addresses a single identified risk of birth defects, a risk with known outcomes and straightforward methods for pregnancy detection and pregnancy prevention to prevent fetal exposure.

Romiplostim risk management is not nearly so straightforward, encompasses concerns of off-label use, and will require different strategies that are more similar to the natalizumab program that manages PML, a risk that cannot necessarily be managed or mitigated.

[Slide.]

The TOUCH prescribing program strives to minimize the risk and health consequences of PML, promote informed

risk-benefit decisions and to further assess the safety profile of natalizumab and the indications and risk factors for PML.

To accomplish these goals, the program reinforces appropriate patient selection, risk communication to health care providers and patients and requires close patient monitoring and data collection for further risk assessment.

The program is an integrated computerized database that captures enrollment, patient tracking and drug distribution data.

[Slide.]

The TOUCH program requires enrollment of every prescriber, patient and infusion site. This slide will walk you through the process that requires initial authorization, monthly evaluation before each infusion and a reauthorization requirement every six months while the patient is on treatment.

The prescriber/patient actions are in yellow, the infusion site actions in light blue, and the TOUCH prescribing program in dark blue.

The process begins when the prescriber and patient complete an enrollment form. This form is sent to the TOUCH

prescribing program, which authorizes the patient to receive natalizumab and assigns the patient to an infusion site.

When the patient presents for treatment each month, the infusion site confirms that the patient is authorized, completes a pre-infusion checklist to determine if the patient should receive natalizumab that day, and sends the completed checklist to the sponsor regardless of whether the patient receives the infusion.

The TOUCH program tracks the responses to the checklist for every patient monthly. The prescriber is required to complete a reauthorization form every six months while the patient is on treatment.

If natalizumab is discontinued, the prescriber is responsible for completing a discontinuation questionnaire at the time of the last dose and six months later as a final measure of follow-up.

[Slide.]

It is important to remember that risk management is not a "one size fits all" approach. Each existing risk management program is unique and customized to the risk, the patients and the prescribing population. Just as there is utility in finding similarities to draw upon with the

natalizumab program, there is utility in pointing out the differences.

Romiplostim is a weekly subcutaneous injection. Natalizumab is a monthly infusion. The difference may affect the frequency of monitoring. Romiplostim will most likely be distributed to and administered in physician's offices. Natalizumab is distributed and administered in infusion centers.

This difference may require nursing and staff education at the physician's office, as well as possibly the need for different methods to monitor drug distribution. Specific laboratory monitoring requirements may be outlined for the romiplostim risk management program. If so, the sponsor may consider the utility of contracting with laboratories and exploring different approaches for data collection to determine what would work best.

Romiplostim has multiple risks, some of which have yet to be fully characterized. Romiplostim has one risk identified through its risk management program at this time. Monitoring and data collection for romiplostim will need to be more extensive.

The potential off-label use for romiplostim is

largely within the same prescribing population, whereas, the off-label use for natalizumab is outside of neurology.

This difference makes an attestation based on understanding the disease state more effective with natalizumab than it would be limiting use with romiplostim.

[Slide.]

In summary, the risk management program for romiplostim should employ tools to assure safe use through mandatory enrollment of prescribers, patients and any other stakeholder necessary for administering or distributing this drug. Clear criteria to identify the target patient population are essential.

Along with mandatory education, patients need to be monitor appropriately and a system must be developed to accommodate the necessary long-term data collection.

This sort of comprehensive program is feasible to implement with romiplostim because you have a limited patient population, a limited prescriber population, and a close patient-prescriber relationship established because of the nature of the disease.

Thank you.

Questions to the Presenters

DR. ECKHARDT: Thank you.

We will move on to the question session. I just want to make a couple of comments. One is among the panel, make sure to turn on your microphone when you are speaking and, in particular, when we do ask questions, I would ask that if it is a question regarding the primary data set of these studies, to potentially address those towards Amgen, and then certainly any questions regarding the FDA presentations, to them.

I think we will get started. Dr. Perry had a question?

DR. PERRY: Yes, ma'am.

My question is for Dr. Eisenberg, please. It has several different parts and I will just list them all at once because I think they will link.

Do you propose to restrict this drug to hematologists alone, and, if so, how do you identify those?

Two, what are the medical-legal implications of signing a document that says I have this patient that has ITP when there is no specific diagnosis for ITP, no tests that we can do, in contrast to Crohn's disease, for example?

Three, who is going to pay for all this? Amgen is

going to make millions from this drug but, it seems to me, that the burden for collecting all the data is shifted to the physician's office.

If this were a clinical trial, you would be paying me and my data managers to collect this data for you. What is the likelihood that you are going to reimburse us for doing your work?

DR. EISENBERG: Those are very fair questions and ones that certainly have come up, and I think I will take them from the top and just let me know if I am not answering the question. I will stop after each one.

First, in terms of what is the target physician audience for prescribers. Clearly, our intent initially would be to focus on the education and marketing only to hematologists/oncologists broadly speaking. As you know, there are some differences in practice. We would want to identify physician practices and physician groups that focus on hematology more than strictly medical oncology.

Clearly, that would not encompass all physicians who might be interested in prescribing in this population, and I think one component that we considered is certainly to have material around information for this program available

for other physicians. But it would not be our intent to have professional education focused outside the hematology/oncology specialty.

So, that may be less than satisfactory in terms of full access but I think that initially is appropriate.

Does that answer the question in terms of how we would identify physicians?

DR. PERRY: Not very satisfactorily. For instance, a rheumatologist who is treating somebody for what he thought was lupus and now thinks is ITP, he could use the drug?

DR. EISENBERG: I think in that circumstance, they would have to agree to participate in the program. We are not requiring a medical subspecialty certification to participate in the program if that is what you are asking.

DR. PERRY: Yes, I was. Thank you.

DR. EISENBERG: With regards to the second question, which really was focused -- I am sorry, I lost the train on that.

DR. PERRY: The second one, the medical-legal implications, testifying this patient has ITP when there is no diagnostic test for ITP.

DR. EISENBERG: I think that is a very fair concern and one that we have thought about, I think. In fact, the proposal is that the physician indicate that the diagnosis is ITP, I don't believe that is any different and that, in fact, we don't believe we can create, for example, as has been the case in some of these other systems, a checklist that has specific criteria associated with it.

We believe it is more appropriate to simply remind the physician of the indication in which the romiplostim was used in clinical trials, which was ITP patients who failed a prior treatment and we would simply trust that the hematologist making that diagnosis makes the appropriate diagnosis.

I don't know, and I think that is one of the challenges when you look at some of these other programs, that we can given that it is a diagnosis of exclusion, begin to create a checklist that confirms the hematologist's diagnosis. I think that is one of the challenges here, and it is one of the areas I think that FDA wants some guidance on in terms of how to think about that level of ensuring appropriate use.

In terms of collection of safety data and ensuring

that we get this information, we have not specifically addressed that at this point in the program. We agree and certainly have heard the concern that since the data we need here are more specific than would typically be the case for routine practice of some of these other programs, we are going to have to have a way to ensure that we can get that information and facilitate that at the physician's office in a manner that doesn't promote in any way, you know, an inappropriate incentive, so it would be through a third-party program and there would have to be--and I am certain you have been involved in some of these activities--there would have to be some appropriate manner to support the acquisition of that data. It can't be charged to the patient or be the responsibility of the physician simply because they are participating in the program and that clearly would be addressed.

DR. PERRY: I can foresee a nightmare of having prescribed tyker[?] for one patient, lenalidomide for another patient, this drug for a third patient and not having my nurse available for the rest of the afternoon.

DR. EISENBERG: I understand and I think each of those components are obviously the feedback that we and FDA

need to ensure that we can get the important safety information at the same time and understand the long-term benefit and risk.

DR. PERRY: Thank you.

DR. ECKHARDT: Dr. Harrington.

DR. HARRINGTON: Thank you. I also have questions about the risk management action plan. Some of them may be for both the sponsor and the FDA, so they go from the statistical to the increasingly sociological.

From the statistical, one piece that seems to be missing from the plan after the data is collected is what to do with the data. I realize that it's early, you still are fleshing out the details, but I think we are all aware of the problems of monitoring relatively rare events in small populations.

So, I guess I am curious about whether the plan will include some sort of boundaries which say when we see X, this will be a safety signal, when we see Y, this will be a danger signal, and when we see Z, maybe we are seeing that the drug is not working long term because you will get long-term data, so there is that.

The second is understanding the selection effect

of people who will be or not in the risk management plan and I am trying to understand the extent to which your patients are different from the population that might get the drug once the aggressive safety monitoring ends.

I understand that the Denmark registry will help, but not completely, because the populations are not different, the medical management is not the same.

The third is how will you ensure that the risk management plan, which looks terrific in its initial form, does not limit access to, for instance, low literacy patients, patients without access to a hematologist, patients for whom they go relatively longer without the right diagnosis.

DR. EISENBERG: Let me have the last question first and FDA may have some additional thoughts based on their experience with other programs.

I think access is an important component that is actually stated as one of the key objectives in the FDA guidance around thinking about minimization action plans as you probably know.

I can't answer in detail. I think as you add each of these components, certainly providing information to

patients in a patient-friendly way has to be a component of the program and the Medication Guide alone doesn't solve that problem.

Access--and I think it is reflected in Dr. Perry's question, access to physicians outside of the targeted initial subspecialty is something that we are not really considering at this point in an effort to initially focus on most of the prescribers. I think having this kind of program, by definition, limits access outside of targeted subspecialties even if you don't require that someone be certified in a subspecialty to prescribe.

So, you are absolutely correct. I mean there are some limits to how broadly access is applied anytime one of these programs is mandated and implemented, and we will need to think about that to ensure that we do provide access.

The first question I wouldn't say is easier, because you understand the methodologic and statistical challenges to doing this. We have had a lot of experience with data bases based for rare events--for example, PRCA with ESAs is a very rare event--and we have looked at similar kinds of databases and clearly the intent is to inform the database from the Danish studies, from the other

epidemiologic studies.

We have looked at other access, you know, other databases we can access that have medical record fidelity that would help us. As you know, United Health Care, managed care providers, others have such databases. Whether they would have enough patients who would be prescribed romiplostim remains to be seen and whether they have enough ITP patients.

We have actually probed this through a number of sources and the Danish scandinavian registries seem to be more rich in terms of the specific bone marrow data we are looking for, so that helps.

But certainly the intent in terms of the quantitative approach is to establish boundaries that would begin to give you a sense of what the expected background rate is.

I think that fact is the particular problem when you consider the MDS issue clearly and the uncontrolled data is that you have a certain rate of progression of disease and when is too much going to occur. It is going to be challenging in this disease data. I think it requires a commitment, as we are prepared to make, to fully understand

the available data.

DR. HARRINGTON: One follow-up question. One thing that was embedded in my questions, but maybe have separated out, will this aggressive monitoring also include long-term efficacy monitoring?

DR. EISENBERG: Yes.

DR. HARRINGTON: You have very limited data on exposure out at 100 weeks, the effect of the drug may be quite different.

DR. EISENBERG: Absolutely. The intent would be to have an explicit evaluation every 6 months. As Dr. Perry highlights, we need to ensure that can happen in a way that facilitates acquisition of data in a manner that is appropriate to the practicing physician but also has to include basic information as well as any safety information.

To your middle question, which was obviously any patient who is entered into this, we would be asking that they agree to long-term follow-up even after the drug is discontinued.

DR. ECKHARDT: Dr. Pazdur, a comment?

DR. PAZDUR: Yes. I just want to answer some of the questions that were raised by other people.

Here again, I think the granularity of this program is going to be worked out after this meeting, so the specifics, I really don't want people really to focus on. Our major issue here in proposing this program, and the central issue here is that we have a very limited database on the safety of this drug with important safety signals. we have less than 300 patients treated with this drug. The median follow-up of patients is only 37 weeks of the data set that was given to us.

I think that is why we are interested in looking at this added degree of scrutiny of this drug after it is -- if it is, I should underline that word -- if it is approved for this indication.

As far as issues of cost, et cetera, in administering the program and how much this drug will cost, I would like people to remember--and we have stated this numerous times, we are not looking at the cost of the program, we are not looking at the cost of the drug, et cetera. We really need to focus on the safety and efficacy of this drug.

I think from FDA's perspective, we truly believe that this drug raises people's platelets. Our major concern

in bringing this drug here is really the safety. We are looking at this program really to help us address that question, however, underlying that question is, is this drug ready to be approved with the safety database.

DR. ECKHARDT: Dr. Kulkarni.

DR. KULKARNI: I had a bunch of questions. A couple of them related to the drug. In your romiplostim continuation study, were there differences in the placebo patients who started romiplostim later on versus the romiplostim group which continued to have elevated platelet counts?

Also, were there any baseline CTs, MRIs, or interleukin levels obtained which showed a difference in the different groups?

DR. BERGER: We looked at--the first question I think was, was there any difference in response in the long-term extension study for previous placebo patients versus previous romiplostim patients, and the answer is there was no difference between the two. Both of them responded rapidly and adjusted the dose of course weekly and adjusted to the platelet counts, about 50 x 10^9/liter.

The second question was regarding any kind of

cytokine analysis. We did not look at interleukin levels, for example. The only cytokine analysis that we did was we looked for thrombopoietin levels, and they were not different.

DR. KULKARNI: Because one of the causes of morbidity or mortality was intracranial hemorrhage, were there any baseline MRIs or imaging studies done prior to instituting this drug?

DR. BERGER: No, there were not.

DR. ECKHARDT: Dr. Link.

DR. LINK: I just have a couple questions about perhaps the confusing diagnosis since there is not an acid test for this disease.

Has the drug been tested in patients with destructive thrombocytopenias of other causes, so lupus, Evans syndrome, hemangiomas, something like that, to indicate (a) that it might work in those indications by the same mechanism, whether there are any dangers?

DR. BERGER: We have not conducted studies in those indications. The key studies that we did were in the indications mentioned, also, in the FDA presentation were the studies in ITP and then the ongoing studies or the

studies in MDA or chemotherapy-induced thrombocytopenia.

DR. ECKHARDT: Dr. Mortimer.

DR. MORTIMER: I have a few quick questions for the sponsor probably reflective of my hematologic lack, but I understand that side effects were not related to the platelet count. Were they related to age?

My second question is about the paresthesias, if you could talk about those perhaps some more.

My third question relates to platelet function. Is there a change in platelet function with this drug as opposed to not?

DR. BERGER: Let me again take one question at a time. You asked about the age relationship of the adverse events. We have, of course, a limited number of patients in our clinical studies and especially if you look at different age groups, the number gets even more limited.

On the basis of the limited sample that we have, there was no impact on age on the adverse events.

The second question was regarding--excuse me, can you repeat that?

DR. MORTIMER: Paresthesias.

DR. BERGER: The paresthesias, there is a limited

number of paresthesias. Most of these paresthesias or all of these paresthesias, as discussed, were mild to moderate. They did not require any intervention. Most of them occurred early during the studies, resolved actually during the studies.

We had a total of 5 cases in the romiplostim group. We had no case in the limited placebo group, and, of course, there are a lot of potential confounding effects, for example, in the romiplostim group. We saw a higher number of patients who discontinued corticosteroids which sometimes can also lead to these kinds of events.

DR. MORTIMER: So what do you think that is due to?

DR. BERGER: I cannot speculate regarding that. There is no biological reason why romiplostim would cause paresthesias.

DR. MORTIMER: Unless it's platelet function.

DR. BERGER: Yes, we do have studies regarding platelet aggregation. We actually do have two studies. One study is with 30 patients in healthy volunteers in Japanese subjects where we looked at platelet function both in the placebo group, as well as in the romiplostim-treated group

at various time points, and the platelet function was not increased or decreased in those healthy subjects after dosing of romiplostim at three different doses.

We also have one study in ITP subjects which actually was conducted recently and which was conducted by Dr. Kuter, which indicates very similar results.

DR. ECKHARDT: Dr. Richardson.

DR. RICHARDSON: While we have Dr. Berger up there, I have a question regarding his Slide No. 35, if we can show that.

DR. BERGER: Slide up.

[Slide.]

DR. RICHARDSON: It looks to me as though the platelet counts, the curve goes upward for the first 80 weeks or so, after which the general trend is downward and, as a matter of fact, if you look at the first quartile, the lower hash mark there, clearly, those folks seem to be decreasing over time.

I am wondering, two questions in this regard. One is do you have any information now on these platelet counts beyond 150 weeks and do these patients need higher doses to maintain their platelet counts?

DR. BERGER: The long-term extension study is a study where the patients entering that study are coming from different initial studies. They are coming from the Phase 1 and 2 study program and they are also coming from the Phase 3 pivotal studies.

The effects that you see on the platelet counts over the course of time are an effect of selection from those individual studies if you plot the platelet counts over time for the individual studies, then, you do not see the same pattern. You do see a pattern that is actually more flat over time, so we think it is a selection effect.

Also, I want to point out that, throughout the end of the study, the patient number actually does go down, so again this underlines the potential that this is a selection effect and, in the end of this curve, we will basically have 11 patients whereas we started with a much higher number of patients.

We do have some data beyond 144 weeks. We are currently out to 156 weeks and we see that the platelet counts go up during the additional 12 weeks that we have observed this.

DR. RICHARDSON: Let me ask one other question

then. This gets to Slide No. 41.

DR. BERGER: Slide on, please.

[Slide.]

DR. RICHARDSON: You discussed 4 patients out of 57 who developed thrombocytopenia following cessation of treatment. On page 49 of your background information, and you didn't present a slide on this, but there were 7 patients described in whom the drug was stopped who had maintenance of their platelet counts without further therapy.

DR. BERGER: That is correct.

DR. RICHARDSON: Do you have any further information on those patients, number one and, number two, in view of the fact that there were--I don't know what the denominator is, if it is 7 out of 57, as well--but is it reasonable to consider a trial off therapy after patients have been on this for a certain length of time?

DR. BERGER: We are discussing two very different effects. Now we are discussing thrombocytopenia after cessation of treatment, which actually, the Phase 3 studies were not designed to observe. The Phase 3 studies, we observed the platelet counts and as soon as platelet count

dropped below 50 x 10^9/L, patients were allowed to go into the extension study.

The observation of thrombocytopenia after cessation of treatment is therefore coming out of the Phase 1/2 study where we had actually 4 reports of thrombocytopenia in those patients.

We also developed criteria to describe thrombocytopenia after cessation of treatment and again saw that 4 out of these 57 patients satisfied those criteria, so really, thrombocytopenia after the drug was stopped.

The 7 patients that you are referring to--slide up, please--are 7 patients, 7 subjects who maintained their platelet count after discontinuation and those 7 patients are out of the Phase 3 studies, so the denominator there is the 84 romiplostim-treated patients in those studies.

[Slide.]

Out of those 7 patients, 5 were coming out of the non-splenectomized, 2 were coming out of the splenectomized study, and they were able to discontinue romiplostim during the treatment period.

All basically had platelet counts above 50 x 10^9/L at the end of the treatment period, at week 25, and did not

fall below this threshold, so did never qualify for the long term extension.

It is important to note that those patients did not require, for example, a high dose of romiplostim at the end of the study. Those patients were basically tapered off drug following the dose adjustment criteria pre-defined in our study during the treatment period and all patients came off drug prior to week 25.

DR. RICHARDSON: And how long have they stayed off, how long have their platelet counts been maintained?

DR. BERGER: We followed those patients for some time. They never entered the long-term extension study. But then, of course, later on they were lost to follow-up.

DR. ECKHARDT: Dr. Curt.

DR. CURT: I have two questions for the sponsor. The first is a follow-on to Dr. Pazdur's comments on safety. The two pivotal Phase 3 studies allowed dose modulation between 1 and 50 mcg/kg with the bone marrow changes being seen at the high end of that curve, in fact, your proposed label proposes to cap the dose at 10, so the question is, in the two, Phase 3 pivotal studies, were the clinical effects seen at the lower end of the 1 mcg, or the higher end of the

15 mcg?

The other is more of an industry-related question. In your risk management program, you propose to use sales representatives for education and, given the expertise of the physicians likely to use this drug, would medical science liaisons be a better group to do the education?

DR. BERGER: Let me answer the dosing question first. We did, of course, a dose analysis in our studies. The median dose in the pivotal studies, in the pre-splenectomy, the median dose used across the 25-week period in our patients was 2 mcg/kg. The median dose in the post-splenectomy study was 3 mcg/kg.

We did a dose analysis during the study, and you are right, initially, a dose was allowed up to 15 mcg/kg. We then did that analysis and we saw that patients do not have an additional benefit at a dose above 10 mcg/kg, and following that analysis we actually kept the dose at those 10 mcg/kg, which is also, interestingly, a comment that the bone marrow panel made, that most of the changes that they saw in the bone marrow were actually in patients with a dose above 10 mcg/kg.

The second question was regarding the sales rep

versus RMLs. The think as Dr. Pazdur mentioned, all the details of the program are not fleshed out at this point, and we are definitely happy to take further guidance from the panel. We felt that this is the broadest group and, of course, there is a variety of physicians that we need to reach.

DR. ECKHARDT: Dr. Link.

DR. LINK: I also have a question about stopping the agent. I guess I would have seen that if you stopped the agent and the platelet count drops, it sort of confirms that the thing actually works. I wouldn't have thought it was an adverse event.

We heard two explanations for why that would have happened. One was, you know, that these patients had stopped their ancillary agents or gone down on their ancillary medications. And so when you stop this, they sort of were left high and dry.

The alternative is that giving this stuff sort of suppresses endogenous TPO, that was FDA's version. That is an answerable question. So, do you have any data that would--

DR. BERGER: Yes, I have data that answers that

question. Let me go back to the TPO physiology and it is very important to note that the liver produces thrombopoietin and the liver produces thrombopoietin at a constant level.

The regulation of platelet count is actually that the thrombopoietin is bound to components of the thrombopoietic cascade and is then bound to platelet and is then eliminated, so high platelet counts leads then basically to a reduction in the circulating thrombopoietin level.

We looked at thrombopoietin levels in our clinical studies--slide up, please--and this is an analysis of the thrombopoietin level now, for example, in the pre-splenectomy study, and we have a similar analysis for the post-splenectomy study, which is very, very similar

[Slide.]

What the slide basically is there to illustrate is that if you look at thrombopoietin levels before entry into the study and then, at week 25, they are absolutely comparable, so the thrombopoietin levels were stable.

We feel there is a strong impact of the reduction of concomitant therapies and also it is very important to

note that platelet counts are very hard to measure especially at those lower levels and there is some variation in platelet counts simply in the measurement, of course.

DR. ECKHARDT: Mr. Petosa.

MR. PETOSA: In all the literature that I was going through, I believe I read that there was rescue medicines used for placebo and for the ones taking the drug, but I haven't really heard any interaction when you start.

It's bad enough we are taking one medicine and we are mixing medicines. Is there any data being collected to see if there is any integration of problems between the medicines? That is one question.

The second question, I am really pleased to hear about the risk management and the long-term collection of data because my daughter is 17 years old, and a lot of this mean age, 52 and in other cases are 70, it is a different animal, and that is probably more related to the FDA mandating that this safety register and the collection of data is firm.

I will just tell one instance we have been through WinRho and the IVIG and the second time on the WinRho she was put in the hospital with very bad side effects and, as

far as the patient knows, that information went nowhere, it just didn't go anywhere, so here we are talking about long-term collection. I want to see what that is and validate that it is happening, so we can assess this for the long term because I would like to see my daughter reach 70 years old at least.

DR. BERGER: I can answer I think the question on the rescue medications. As you saw in the presentation, rescue medications were used far less in the romiplostim group than in the placebo group, so the data itself is limited in the setting. Slide up.

[Slide.]

This shows you the rescue medication used across the two studies, across the two pivotal studies, and I just wanted to show this slide in order to show that there are data for use of romiplostim with different rescue medications.

We have done a safety analysis, we have compared those patients that had a rescue medication to other patients that had romiplostim only.

We didn't see any signal, we didn't see any increase in any adverse events, et cetera, so that part is

done. But I want to point out that, of course, the data here is limited especially as rescue medications are reduced in the romiplostim-treated patients.

DR. ECKHARDT: I have a question with regards to the rescue medications and that is, was there a set threshold for institution of that? For instance, what proportion of patients had platelets, say, below 10,000?

DR. BERGER: The criteria in the clinical study for use of rescue medication were following clinical practice. Slide up.

[Slide.]

The criteria were that rescue medication is basically allowed following clinical practice when the investigator feels that a subject is at immediate risk. It was not linked to one specific platelet count but, for example, bleeding or wet purpura would have been incidents that would have triggered rescue medication.

DR. ECKHARDT: But do you have the data on the platelet counts for when it was instituted or not?

DR. BERGER: We have data on the platelet counts when it was instituted. The vast majority of rescue medication was used at platelet counts below 30 x 10^9/L and,

if you looked at those rescue medication uses, they were exactly the same in the placebo groups and in the romiplostim groups.

DR. ECKHARDT: Dr. Katzen.

DR. KATZEN: Thank you. Two questions, one for Dr. Berger and one for I think Dr. Berkman.

The first one is in reference to Dr. Pazdur's concern about the safety. I would like to know a little bit more about the patient who died of a cerebrovascular accident who was on the drug. If I am not mistaken, I think the patient had a platelet count of 107,000--and I may be incorrect--and then was given an anti-platelet agent aspirin.

I don't know how much thought has gone into the propriety of that management with an anti-platelet agent, and did we convert a non-hemorrhagic into a hemorrhagic stroke. I just want to be certain that as we think about that case, is it or is it not a drug-related death or possibly a management-related death.

DR. BERGER: That was a 80-year-old male patient who had various risk factors for thromboembolic events, hypertension, hyperlipidemia, type 2 diabetes mellitus.

The patient in study week 21 on romiplostim presented to the emergency room with some left arm numbness and tingling and had a CT scan at that point in time which was initially negative and had a platelet count of 107 on that study.

The patient was not presenting--and I think that is an important point here--the patient was not presented to the study site but was seen at another site which was not the clinical trial site and, in that site, was put on aspirin then at that time.

Then, romiplostim at that time, at that other site, was discontinued and the patient was basically discontinued with anti-platelet therapy. There was an MRI done of the brain two days later which showed some hyperintense areas.

At that time, the platelet count was still 113. The patient was then discharged at a platelet count of 132 two days later but then was readmitted to the hospital roughly one week later with a platelet count of 5, and then the intracerebral hemorrhage. That is basically the clinical history.

DR. ECKHARDT: Dr. Pazdur, did you have a

question?

DR. PAZDUR: Yes. One of the issues that we have is the labeling of this drug, and we generally don't go over labeling issues. But in order for a drug to be approved, there has to be the requisite information for the safe use of the drug.

I want you to go through the important components of any proposed labeling and let me walk you through some of the questions that I have.

Number one, who should receive this drug with ITP? Generally, when we have a major safety issue with a drug or unresolved safety issues, the therapy is held for only patients that have generally been more refractory to other forms of therapy, in other words, have gone through standard therapies.

So, one of the questions that I have is if you could please justify to us in light of your safety information your proposed patient population.

Secondly, when should this drug be initiated? I think that is an important question that needs to be answered here. We have seen from the presentation earlier in the morning that a platelet count bleeding doesn't occur

until platelet counts sometimes go below 10,000, where it is stated here in your proposed labeling, 30,000, how did you get that?

Thirdly, what is the target platelet count you are going after? In your clinical trial, it was 50- to I believe 150,000. Do you need a 50,000 platelet count to ensure that bleeding isn't going to be a problem?

Fourthly, what about the upper limit of this dose, are some of these patients really hyporesponders to this therapy similar to what we see with the ESA agents? There is indication that people that get 17 to 18 mg are the ones that get into problems with reticulin formation.

I would just like to emphasize we have had a lot of discussion about this. Some of these major issues that we are facing here are very, very similar to issues that we will be talking about tomorrow with the ESAs. Here again, we would like to make sure we don't repeat history here, that we have a very clear understanding of where we are going with this drug before it gets approved.

DR. EISENBERG: If you could put up the slide I presented on labeling, that will help, and then I actually would like to ask Dr. George, who has been involved in the

diagnostic guidelines for ITP to make a few comments on the appropriate population because I think these are important questions. They are not easily answered because this is a state in which there is a need for clinical judgment regarding the appropriate patient.

Slide up, please.

[Slide.]

First of all, in terms of the indication, this is the indication as it currently stands in the proposed labeling. It highlights the need for chronic therapy in adult patients with ITP.

It recognizes efficacy in both the splenectomized and nonsplenectomized population and the criteria, specifically to answer your question, is that there has to be an insufficient response to at least one other prior therapy. That would have been consistent with the entry criteria in our study.

Slide off, please.

In terms of how long one would need--slide off, please-- I think we can come back to the dosing in a moment.

I will ask Dr. George in a moment to answer the question of when do you make this decision. I think that is

a fair point and I would prefer to defer to an expert in that regard.

But I do want to clarify the last two questions very explicitly because I think you raise important points. First, it is not the intent of dosing to target a specific range of platelets. We don't believe that the appropriate use of romiplostim is to find a specific target platelet range.

We do believe, as we have outlined, that most clinicians and most of the data support achieving a platelet count of 50,000 and that when romiplostim is administered to achieve a platelet count of 50,000--if we could put the last slide that you showed me up, before this one, please, slide up--

[Slide.]

If you look at dose adjustment, that is exactly what the labeling would focus on--that is, to adjust the dose to get the platelet count into the 50,000 range, and then to have dose adjustments that would prevent the platelet count, since to achieve 50,000, as you saw, you want to get that--to prevent bleeding, you want to get most of your patients into that range, that you would have dose

adjustments.

The dose adjustments should be incremental. Certainly, there is absolutely no question that if the dose has gotten above 400,000, as in the clinical trials, the dose should be held.

Whether dose adjustment can be provided based on the data we have when you get, for example, over 200,000, which is what we are considering, we think that is reasonable and we will propose to do that. But we don't believe one should target--slide off, please--we do believe that it is appropriate that the range be defined simply by the need to achieve that threshold level of 50,000, which I believe in clinical practice certainly, most clinical practice we believe prevents severe bleeding.

Dr. George, I think has a few thoughts as well as to when we select the appropriate patient.

DR. GEORGE: Dr. Pazdur raised key numbers for physicians who deal with ITP, the 10,000 number, the 30,000 number, the 50,000 number.

When we developed the ASH guidelines, published now 12 years ago, these numbers were loose in practice and our attempt was to try to establish some consistency even

though the evidence was very minimal. We chose a number of 30,000 to give a margin of safety for initiation of treatment.

Subsequent to the publication of the ASH guidelines, there have been data on patients with thrombocytopenia from other etiologies, chemotherapy-induced thrombocytopenia, hospitalized patients, indications for platelet transfusions with a trigger level of 10,000, and that was emphasized in the initial presentation as a risk level for severe bleeding.

We didn't choose that level because we didn't want to operate on the precipice. We wanted to operate with a margin of safety and therefore 30,000 was discussed, established in the ASH guideline, and I am pleased and always proud to see that, 12 years later, the ASH guideline continues to be accepted and commented on.

The 50,000 is out there in clinical practice. I am sure every hematologist in the audience has this 50,000 mind-set for safety for procedures, safety for trauma, safety from bleeding with any external risk, so that was assumed to be a very realistic margin for achieving a goal for the safe platelet count with this agent.

If I could go back maybe to the initial question that Dr. Pazdur asked, what would be an appropriate indication in terms of prior history of the patient, the clinical trials required failure of at least one therapy. In most instances, this is the initial therapy which is given to adults with ITP, which are corticosteroids.

In our experience and practice, and I think the experience of most hematologists, corticosteroid toxicity is underestimated by physicians, not appreciated to the extent that toxicity is experienced by patients. And so I think that limiting the duration of corticosteroids is a reasonable goal.

Beyond corticosteroids, effectiveness of treatments is less predictable and side effects are greater.

DR. ECKHARDT: Dr. Kulkarni, you had a question?

DR. KULKARNI: Not for--well, maybe I could. I was just wondering, as you say correctly, as hematologists we do go by platelet count although sometimes it may not mean anything, I was just wondering about mean platelet volume, whether that has anything to do with the bleeding.

But before I ask that question, I just wanted to make a comment and then ask those questions. A comment is

about postmarketing surveillance. I note currently at the CDC, we are involved with the FDA and with Pharma for postmarketing surveillance of a hemophilia drug at 13 pilot sites through the hemophilia treatment centers, which calls for detailed data abstraction.

The idea there was to look at inhibitor development and complete gene sequencing of the hemophilia gene in these patients, currently have about close to 600 patients in that population.

I was wondering if the company had any plans to do postmarketing surveillance because that is where the ball gets dropped. I mean one can educate and all that, but I think one has to keep track of these patients, who they are, what they are, and what happens to them long term-wise.

So that is a comment I want to make. The question I have is in this drug, were there any racial, gender differences noted? Number two, are you planning any studies in adolescents, because I see just adults and a 19-year-old can fall into an adult group.

Maybe that is a better group which may not have all these baggages that a 70-year-old--I am sorry, I am getting there, but--and also if there are any plans to

develop pegylated or a long-acting drug.

DR. GEORGE: I will go back to the very beginning with mean platelet volume, and then I will sit down.

Mean platelet volume, of course, was not around when I was in training, and I feel that I am too old to understand any relevance of mean platelet volume. I don't know of any clinical importance of that measurement and there was no change in mean platelet volume during the course of these studies.

DR. LINK: A follow-up question while you are up there. But those of us, certainly pediatricians feel that patients with immune thrombocytopenia and therefore rapid platelet turnover tend to bleed at much higher platelet counts or tend to be more protective at low platelet count, so a child with ITP and 10,000 platelet count rarely bleeds, whereas, a patient with leukemia, who has a production defect, often bleeds at that same--I think that is what you were probably getting at.

DR. KULKARNI: Correct.

DR. GEORGE: But I am not sure that is reflected in the MPV.

DR. LINK: The question for the actual thresholds

that you have developed, you know, is it really fair to say that somebody with 30,000 platelets, who has an increased platelet turnover, is really at such high risk of bleeding as compared to, let's say, somebody with aplastic anemia.

DR. GEORGE: Sure, and I think this is standard accepted knowledge and practice in hematology, that patients who can't produce platelets are at greater risk, the assumption being that patients who can produce some platelets, a normal amount, slightly increased. But at least some, are always injecting platelets into the circulation even if the count is not high, so there is always access to some platelets to prevent bleeding.

In children, the diagnosis of ITP is usually a self-limited disease and there is often an issue of whether to treat or not to treat children because the natural history is one for spontaneous recovery.

In adults, the disease is chronic. The assumption is that there will be no spontaneous remission, therefore, treatment is always initiated.

The issue again, as I stated before, is what is an appropriate threshold for initiating treatment, assuming a persistent disease, assuming no clear understanding at the

diagnosis of what the risks may be in terms of comorbidities, hypertension, older age, menses, et cetera, 30,000 has been accepted as a reasonably safe threshold for initiating treatment.

DR. BERGER: I just wanted to briefly respond to the second part of your question, which is whether the studies are ongoing or planned in the adolescent or let me call it pediatric patient population. It is an orphan indication, so it is not required, but we have started a study in the pediatric population, which is a dose escalation study.

We are not focusing on the acute ITP. We are focusing on those children that then develop the chronic ITP are those adolescents. That study is ongoing, so no data are available.

DR. KULKARNI: Any racial or gender differences involved?

DR. BERGER: We looked at our data. We cut them various ways by gender, by race, by age. There were no differences in both response on the basis of the limited data population in both response or safety.

DR. ECKHARDT: Dr. Perry.

DR. PERRY: Just a comment. In this enlightened audience, I think we can all agree that 30- to 50,000 may be a sufficient endpoint. But to a less intelligent group that might include orthopedic surgeons or neurosurgeons, for instance, they might want a platelet count of 100,000 before they would venture into somebody's brain.

So I think we need to have some sort of exclusion that says there may be circumstances in which you need for practical purposes to exceed the 50,000 limit even though most of us feel that 50,000 is probably sufficient. But, if you are going to get the surgeon to operate, you have got to be able to get them in the OR.

DR. ECKHARDT: Dr. Katzen.

DR. KATZEN: Yes, I wanted to address a question to Dr. Berkman in terms of the accessibility and the vetting of how you get the drug--I mean I am in private practice and I think there is a practical point to this in that if you have a patient who requires this medication, it is probably going to be a medication that is required fairly quickly.

If you have to go through a process of approving the physician and then approving each individual patient, first of all, I think that may be time-consuming.

Dr. Perry indicated, and I totally agree, that to register a patient in the S.T.E.P.S. program or whatnot, I definitely lose a nurse doing something on the computer for 30 to 45 minutes. We have to address practicality here.

You may be limiting, you know, if we decide that this is a medication that helps patients, I mean from a practical standpoint if I have a patient in front of me, I may elect another treatment if I know that I am going to be down an hour or two hours or maybe tomorrow.

The other part of the question, which I know many around the table might not have to face, but I do, is do I keep this--first of all, from you, am I able to keep this drug in stock for immediate use if I haven't vetted the patient yet.

If not, that means there is probably a minimum of a 48- to 72-hour turnaround for me to receive the drug for the patient, so I am very concerned about overlimiting the access.

As a suggestion, and I have really not understood why we haven't been able to do this with the other medications that you alluded to, is I think there is a point at which someone has the obligation to vet the physician and

say the physician is qualified to give the medication. At some point, I think there are methods, whether it's through the MLA, or whatnot, to evaluate the physician's use, you know, retrospectively.

This is an urgent situation and for me, I would be a little unhappy if everybody approves me after an hour's work for this patient and, 48 hours later when the drug comes, the patient has had a catastrophic event. I think that would be a tragedy.

DR. ECKHARDT: Dr. Berkman, did you want to make any comment to that?

DR. BERKMAN: Dr. Katzen, I think that your point is very well taken, and I think a lot of these things are certainly things that we are going to have to consider while we are developing the program.

I think based on my understanding of what the sponsor has proposed at this time, physicians wouldn't be enrolled until they had a patient that required the medication.

Now obviously, there are other programs that you can enroll as a prescriber ahead of time, and whether or not you actually have drug available in your office or whether

or not they are going to be enrolling hospitals and that sort of thing, I think all of those are very valid points that we need to continue to consider.

I don't think that the timeliness of delivery has really been addressed yet.

DR. ECKHARDT: Mr. Petosa.

MR. PETOSA: Just to validate what Dr. Perry said on the doctors out there and what the safe range is for surgery, my daughter still has all her organs. We refuse to take them out until it is absolutely necessary.

You know, what is safe as far as walking around the streets and spontaneously bleeding, and being in a car accident, on a moment's notice, and the platelet counts need to be in a safe range--and all these studies are, as we saw in the charts, 50,000 to 75,000, is that really a good range to put it in. All the data collection is based on that level, so that really needs to be scrutinized, what is really a safe level, not just to walk around and not be spontaneously bleeding, but really be in a safe condition in case something extraordinary happens.

But the doctors do feel 100,000 out there is what they want if they can get there. My daughter still responds

to any of the treatments, side effects are one thing, which she still responds to, so if we had to have surgery, a planned surgery, she can take steroids and can get the counts up and that could be done.

But as far as the normal individual just walking around, are they really in a safe condition for what may happen on any given day.

DR. ECKHARDT: Other questions?

DR. RIEVES: I would like to emphasize from the FDA perspective, as well as from Amgen, too, this risk management proposal has only come to us in the last few days, so I want to encourage the committee members to be very vociferous in offering opinions here because you are witnessing a process in the development, so, please, do not hesitate to ask questions, to offer suggestions.

The logistic aspects are very important to Amgen to developing this proposal to us, so not only is the fundamental question, is the short term benefit worth perhaps a long-term cost, for example, associated with marrow fibrosis, we would prefer not to be two to three years down the road to find out that we have a generation of patients, if you will, with marrow fibrosis.

We would like to avoid that. But, on the other hand, we do have at least relatively solid six months' data in a reasonable population. The risk management program, though, we would like to emphasize is very nascent, so, please, speak up, raise these issues. We want to hear it because we have a relatively short time frame.

Thank you.

DR. ECKHARDT: Thank you. We will be having quite a bit of discussion this afternoon. Are there other panel members that have questions that will help in that discussion?

DR. LINK: How long does this RiskMAP go on, in other words, how long do you keep the study under this kind of control before it's then more widely --

DR. PAZDUR: We would evaluate the program in periodic fashion, for example, after 18 months, after 24 months, et cetera, to see what is going on and is there a need for it, et cetera.

Here again I think one of the reasons why we are looking at this program here is because of the limited safety data that we have for a drug that is supposed to be used on a long-term basis.

It is not the same type of program as the S.T.E.P.S. program where we have this known defect that we want to prevent pregnancy, et cetera. The issue here is it is basically to get to be a plan to further examine the safety but to reevaluate it I think also.

I don't want anybody to feel that just because we are instituting it, that that means this is now and forever if that is the route that we go.

DR. LINK: So, at some point you are going to be able to diagnose ITP without a checklist and maybe not even being a hematologist?

DR. PAZDUR: It doesn't have anything to do with the diagnosis, it has to do with the safety of the product, that is what we are interested in, in ensuring that people that have the right diagnosis, as well as other features that adhere to the product label are getting the drug.

DR. ECKHARDT: Dr. Richardson.

DR. RICHARDSON: Getting back to the specifics I guess of the RiskMAP, with respect to the collection of bone marrow samples, it provides for sampling at two years and five years and I guess, in view of the limited follow-up on these patients, is this something that should be done

earlier than two years out concerning this kind of treatment? How did you come up with the two-year figure?

DR. BERGER: This is a proposed prospective study where we would basically look at around 200 patients. We would collect bone marrow samples after two years and five years and this was based really on the concern around the long-term risk because we do have the earlier bone marrow samples from our clinical studies.

Then, we would look at really the reticulin end of the collagen staining in those samples basically in order to collect long-term data in those patients.

DR. RICHARDSON: But why not six months, why not a year rather than exposing people to two years of this treatment before you see what is going on in the way of reticulin deposition?

DR. BERGER: We have to remember that repeated bone marrow biopsies, that bone marrow biopsies at all in these patients are not standard of care. We tried to collect bone marrow data in our ongoing studies and this was very, very difficult.

The key question we are trying to ask in this study is really the long-term effects of the drug. Of

course, those subjects will be monitored on a more frequent basis. We are actually collecting, for example, peripheral blood, and we are looking at peripheral blood smears. We will collect cytopenias and other parameters more often. But we need to balance here the feasibility of the study with the objective that we have, which is really long term analysis.

DR. ECKHARDT: Dr. Perry.

DR. PERRY: If you pay people to have bone marrows, you can get them done at any interval you want if you pay enough. Let's be realistic here. If you paid me a million dollars, you could do my bone marrow today.

I think Dr. Richardson's point is well taken. In five years, there may not be many of the original population left for whatever reason, particularly if you are doing an older population. So do it at six months, a year, then two years, et cetera. But I think you run the risk of missing an early safety signal for being penurious.

I think if you simply say to people, you know, you don't have to volunteer for this and be uncompensated, we will pay you to get a bone marrow done. You can do it. People undergo bronchoscopies for scientific purposes, which

to me is much more invasive.

DR. RICHARDSON: But even if you do the same number of marrows, I am just saying you might want to look at it earlier rather than waiting two years.

DR. BERGER: We are very happy to take that into consideration and develop the study in a way to do one bone marrow sample earlier, like, for example, after six months or a year and a second one then after the long term.

I think I have to -- I don't have to point out to this audience that we cannot pay patients for the participation in clinical studies.

DR. ECKHARDT: Dr. Kulkarni had a question.

DR. KULKARNI: Yes. I am not too familiar with this RiskMAP tool but I was looking at it and would it require IRB approval because it says patient consent for program participation. And then is there a confidential agreement, does that data go to Amgen, or where does it go?

DR. EISENBERG: There are really two components. Participation in these programs, since it is for a marketed product, typically is not considered investigational, so it is not an IRB but there is access to the medical records which requires patient consent as it would to participate in

any program where any health claims database or other circumstances where you are providing medical information.

If there were specific studies, a bone marrow study, a specific registry that required additional information that the patient didn't consent to, that would be considered investigational and would have to be managed separately under those circumstances.

DR. ECKHARDT: Mr. Petosa.

MR. PETOSA: Getting back to the bone marrow, my daughter has had a bone marrow done. How do I know that you have got that information? We talked about communicating and there is information out there. How are we going out there collecting that? Everything we do, I am in nuclear power, the thing that makes it better is communicating, communicating, all different directions.

So, you don't even have to pay me. I mean you can go get that information at a younger age to start getting some more data. How do I know that is happening, or are we even trying to get that information?

DR. EISENBERG: No, I agree. I think transparency is an important part of these programs and clearly, you know, again, to answer the question, the goal here is

actually surveillance and following every patient who gets romiplostim once introduced to the market and making certain that information is available through reports to FDA that we have external consultants doing this, in fact, proposing to have this monitored externally, as well, so that all of this is information that is publicly available at FDA, is updated regularly.

We think transparency is obviously the most important way to understand whether there are safety issues.

I would have one last comment.

MR. PETOSA: Excuse me just one second.

DR. EISENBERG: I am sorry.

MR. PETOSA: But has the company gone out there soliciting those bone marrow tests that have already been done to put into the studies?

DR. EISENBERG: In the studies in which patients have participated, yes, where we can have access to medical information because the patient allows it, yes, at least where it is available to us, so that is exactly the studies in Europe we can do.

In the U.S., it is more challenging for just the reasons that we were talking about, that you would have to

provide access to that information and we would have to know where it is to be able to acquire it. Those circumstances right now, at least in the U.S. databases, are hard to accomplish.

So the answer to your question very specifically is no, we wouldn't know unless your daughter participated in a database in which we would be able to have access because she gave information, permission for her medical information to be accessed.

DR. ECKHARDT: Dr. Richardson, last question.

DR. RICHARDSON: One final question. This is for Dr. Berkman. It has to do with kind of the logistics of the RiskMAP and that is, if the patients are going to be signing some sort of informed consent, as new toxicities are brought to the fore, does that mean they have to be reconsented?

DR. BERKMAN: Not necessarily. The RiskMAP program would focus on--the consent for the RiskMAP program would focus on the identified and potential risks that the sponsor and FDA have come to agreement on, so if something changed with that, or we felt that we found out that there was liver toxicity associated with this drug, for example, and we wanted to monitor or that, then, that would be added

to the consent.

Does that answer your question?

DR. RICHARDSON: And the patients would have to sign another consent.

DR. RIEVES: The logistical aspects of this, many of the details have to be worked out, potentially not, potentially not. In fact, conveying that information could just be done through the Mediguide and communication and interaction with the physician, that sort of thing.

There are many avenues for updating new information that conceivably would not involve constraints by signing documents.

DR. ECKHARDT: Thanks.

This will wrap up the question session. Our plan is to take a break for lunch from 11:50 to 12:50, after which we will promptly go into the open public hearing. Thanks.

[Whereupon, at 11:50 a.m., the proceedings were recessed, to be resumed at 12:50 p.m.]

AFTERNOON PROCEEDINGS

[1:00 p.m.]

DR. ECKHARDT: We are going to start the Open Public Hearing.

Open Public Hearing

DR. VESELY: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decisionmaking. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of

your statement, to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

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

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

Therefore, please speak only when recognized by the Chair. Thank you for cooperation.

DR. ECKHARDT: Our first speaker is Valentine Santos.

MR. SANTOS: Good evening. My name is Valentine Santos. I am a patient with ITP for 10 years, 10 years ago. I will be pretty fast.

I started like in Robert Wood Johnson. I woke up

in the morning and I went to take a shower and, after I take a shower, I was starting to rub with my towel and half of my body comes like black and blue. I look to the mirror and I said something got to be strange with my body, you know.

I run directly to my private doctor and I take my shirt and I show him my body and right away he said you have a big problem, we have got to take you to the hospital. He called an ambulance. I went inside of the ambulance, I went to Robert Wood Johnson.

After getting into Robert Wood Johnson, I saw doctors all over, nurses and, for the first 10 minutes, I know I passed out, I don't know where I am, you know. I wake up like 45 minutes later with all machines on me, blood draws taken from the nurses, you know.

An hour and a half later comes one doctor to me and they said to me you have a blood disorder, we don't know yet what kind it is, but your blood is very low. Right now at this time is 500. I don't know what is 500, 500 is very dangerous, I can die right away, you know. Okay.

We are starting fighting with this disease. I went like to a clinic. Dr. Claire Phillips [ph] take care of me for like 3 1/2 years, getting some IVIG, Decadron,

prednisone, WinRho, nothing comes through. She said to me, I can do nothing for you but I have a friend in Maryland, in NIH, and I go send you to him, maybe he help you. I said that's fine, I will go, you know, I can lose nothing, maybe he can help me.

I come to NIH on Rockville Pike, very nice hospital, and Dr. Patrick take care of me. And he said to me, I go do stem cells on you, because you have no brothers, no sisters, nobody can match you, I will take your own cells, run them in a machine, and I will give you back, and we hope everything comes like true, and you are getting your platelets back.

Everything is fine. The first week comes like 320,000. I am like I have got my life back, you know. I used to play soccer and I want to play soccer. You know, I am happy, and doctor said, but relax because we have got to keep like seeing like the blood work for next week and next week, because I stay six months in Maryland.

The second week it drop, drop 3,000. I said that's fine, nothing we can do to you, but send me back to New Jersey. I went to Robert Wood again. Dr. Claire Phillips took care of me again, and last chance, she said I

have one doctor maybe can help you in New York. I said that's fine, let's try. His name is Dr. Bussel, a good doctor on that disease ITP, and let's see if he can help you. I said go for it.

She make me an appointment with him. I call him and he take care of me. After three months he said come in and we go see if we can do something for you, because you are a young kid, you need to get your life back. I said thank you, Doctor.

We are starting with a protocol called AMG-531. I do for the first month, second month, third month. Nothing comes through, 9 months, 11 months, nothing. The 12th month the doctor come to me, he said, Valentine, I want to say something to you, but this medicine not working on you, maybe you finish with this and starting you on another protocol with a new medicine.

I said, Doctor, can you just finish this last dose to try like starting the next medicine, and he said I give you the last dose. Next week I went and I draw my blood, and it's like 378,000 platelets. After that for the past year and a half, my blood is running for 300 to 350 to 400 with no shot six months ago, no shot.

I want to just say thank you to AMG and thank you, Dr. Bussel. That bring my life back and I want to say don't give up on ITP, please, fight.

Thank you very much.

DR. ECKHARDT: Thank you.

Our next speaker is Barbara Pruitt from the Platelet Disorder Support Association.

MS. PRUITT: Hi. Good afternoon. My name is Barbara Pruitt and I am a member of the Platelet Disorder Support Association but I am speaking solely on my own behalf. I have no financial relationships to disclose.

I have chronic refractory ITP. Several months ago my platelet count was very low and I had an episode of bleeding. My hematologist could not get me into the Amgen study because it was filled, so he appealed to them so that I could receive the drug for compassionate use.

Every one of his patients that were in the study had an increase in their platelet count. He and his staff were very encouraged and optimistic about this drug, and I was very excited to get started.

I even, for the first time, started dreaming about the things I could do when my counts went up - would I

remember how to ride a bike, what about roller skating. I could finally maybe go back to the gym and start working out again.

I found myself smiling just thinking about it and thinking about the other prospects of things that I could do. It took about a month before I got my first shot. That morning my platelet count was 3,000. The shot stung but I really didn't care because I knew it was going to be worth it.

The dosage started at 3 mg/kg, and it could be increased by 1 mg/week to get to the maximum of 10 mg. During the next six weeks my dose was increased every week until I hit the maximum dose of 10 mg. My weekly platelet counts bounced back and forth between 1,000 and 8,000. It obviously wasn't working for me.

I can handle disappointment, I have had plenty of practice with it. You see, I was diagnosed with ITP in 1961. I was 4 years old. After my splenectomy at age 6, I had four months of remission and that was the last time I had a normal platelet count.

Through the years I have tried every treatment available, some of them with horrible side effects.

Unfortunately, none of them have worked for me.

When you are faced with a life-threatening disease like ITP, you search. You search for solutions, you search for treatments, you search for answers. Ultimately, the patient has to make the decisions about their treatments.

You weigh the side effects of a treatment against the chance that it might work. I knew all about Amgen-531 before I took it. I had read the papers on it, I had read the documents, I had spoke to many different hematologists about it.

I knew the risks, I knew the side effects, and I still made the decision to take it. For me, for those 8 weeks, it didn't work, and that is unfortunate. I will continue my search. My counts remain under 10,000. I might look cool and calm but, honestly, it can get very scary. For the hundreds of thousands of patients out there with ITP, who are searching for treatments, they need choices, they need safe choices.

They should have the opportunity to choose this treatment. There are risks in everything we do in life, and choosing a treatment is no different. Some of the treatments I chose in the past had horrible side effects but

that was all that was available to me.

The risks and side effects of Amgen-531 are so much less than the other options. We do need choices. Please give the patients with ITP the opportunity to choose this treatment.

Thank you.

DR. ECKHARDT: Thank you.

Our next speaker is Pamela Ford.

MS. FORD: Good afternoon. My name is Pamela Ford and I have no financial relationships with anyone involved in this matter.

I have no medical degree, but I have learned more in the past few years than I ever thought I would know about blood and medicine. I am the mother of an ITP child that will be 8 in May. My son was diagnosed with ITP nearly four years ago and since that diagnosis, has endured numerous treatments that have failed to control his severely low platelet counts.

While I am aware that this meeting is to address the adult use of Nplate, please allow me to state my case regarding why this drug is needed for adults and children alike.

My son received his first IVIG 12 days after his initial diagnosis, to which he had a severe reaction. The second infusion was less than two weeks later, pre-treated to ease the side effects. This form of treatment has continued throughout the 3 1/2 years as his standard emergency treatment. He responds for 2 to 3 days, then, drops back down to what is considered his normal count of less than 10,000.

High-dose steroids failed next, followed by a short therapy of vincristine with cyclosporine and steroids, short because after the second dose he suffered a life-threatening paralytic ileus reaction to the vincristine. This information is relevant because it shows his limits for future types of treatment.

Seven months after his diagnosis, his spleen was removed. We were moving down the list of treatments almost in clinical order. The splenectomy resulted in a recovery of counts in the 40- to 60,000 range for about a year before plummeting back to this normal range again.

This particular year was a blessing for the mere reason that our son, who is an excessive, frequent, and spontaneous bleeder, was free from his 2 1/2-hour nosebleeds

for that year.

Once the year of somewhat peace was over, we were in what seemed to be worse condition than before. His body seemed to be rejecting all treatments. In the past year, we have tried rituximab, 6MP, Dapsone, and CellCept.

His current treatment is a combination therapy of high-dose infusions of prednisone, IVIG and WinRho injections supplemented by daily oral meds of Decadron and azathioprine. He is receiving the infusions every Wednesday, holding his counts above bleeding level for 2 to 4 days before they drop dramatically. We are on week 14 of 16 with no results.

Each Wednesday's appointments, his counts are less than 10,000. We go to a large children's hospital, one of the best in the U.S. Our doctors have told us on numerous occasions that this is the worst case of ITP they have seen at their hospital. The mix of persistently low counts with the excessive bleeding and the side effects of standard treatments has been a challenge for all of us.

The doctors have been reaching out to leading specialists. Their recommendations have all turned to the new treatments like AMG-531, which has given us renewed

hope. We are now stuck between point A and point B. While we are aware of the great results of the clinical trials, we are so excited about this drug, we can't get it. We have to watch and wait for the process to take its course.

The pediatric trial filled in my son's age group very quickly. We have been told there is no compassionate use or individual use program available since the drug is so close between clinical trial and possible FDA approval.

I am also a member of the Platelet Disorder Support Association and communicate daily with other parents of children, as well as adults, that are currently in or were in these clinical trials. We are excited and anxious for this desperately needed drug to become available.

There are not many others that are in the exact same situation as my son, but there are definitely many of us that will benefit from the use of this drug.

In closing, I will tell you this. I am just a wife and mother of one very sick child and three well children. I am just a Christian who has faith and hope, faith that a cure someday will be discovered but, more importantly, hope for some relief for my son. This drug gives us that hope.

I am a passionate friend and a representative to the many other chronic refractory ITP children and adults who can't be here today to speak for themselves. While your jobs require you to do this on a regular basis, this is a very important day for me, for my family, and for my friends in faith.

For me to travel 580 miles, leaving my son's side on a clinic day should be evidence of how very strongly I feel about this particular drug. My hope is that it will be available soon. There is a need.

I thank you for your time.

DR. ECKHARDT: Thank you.

Our next speaker is Joanne Moriarty.

MS. MORIARTY: Good afternoon. My name is Joanne Moriarty and I am from Medfield, Massachusetts. I am 61 years old and I have had ITP for over five years.

No one can say for sure how this happened to me, but my platelet count began to drop rapidly after having pneumonia. My lowest platelet count was 11,000. At that point, the first thing my hematologist did was a bone marrow test, and as we all know, diagnosing ITP is a process of elimination, and what one has to go through even to find out

that you have ITP can be amazing.

The first treatment I had was with high doses of prednisone. My numbers climbed quickly. But the side effects are ugly and dangerous. I suffered extreme sweating, high blood pressure, mood swings, and swelling. I didn't recognize myself in the mirror.

I can easily say that I would never want to resort to that treatment again. I understand that some people have a positive result from that drug but most of the patients that I have spoken to agree that this therapy is just terrible.

My next treatment was with WinRho, which did not raise my platelets enough but reduced my hematocrit to very low levels, so much so that I had to receive other drugs to raise my blood count. I was exhausted all the time, I was getting very depressed, and I didn't know if they would ever find a solution for me.

The next drug was IVIG. That had some success, but only lasted about two weeks. The infusion took so long that I had to invest an entire day for each treatment. At that time, my hematologist told me there was a shortage of the drug. He scheduled me for surgery, hoping that a

splenectomy would solve the problem. At this point, I had to receive all sorts of inoculations because I would no longer have a spleen.

I did not have a splenectomy. I sought out a second and third opinion. These doctors did not recommend the surgery because of the low percentage of success in people over 40 years old. I began treatment with a different doctor at Beth Israel Hospital in Boston.

The next drug, Rituxan from which I got a good result. I had treatment weekly for four weeks, then monthly, bimonthly, then three months after that. As you know, this requires infusion. This left me exhausted and unable to carry on with my regular daily activities.

I did maintain a decent platelet level for more than a year after my last treatment. In my case, Rituxan was not without its negatives. Besides having to sit for so many hours for each treatment, I developed blood clots in my legs for which I had to be hospitalized to have a filter put in, so that the clots cannot move to major organs. I now take coumadin, as well.

This balance can be a very slippery slope. Also, I must add that the cost of Rituxan is huge. Even with my

insurance, the co-payment was for thousands of dollars every year. My life has changed drastically. I cannot travel as I used to. I traveled here to Washington by train to speak to you today, and I did not say I have no affiliation with anyone. I am an ITP patient and that is why I am here today.

Also, I have to say I cannot fly with low platelet counts. Also, flying can cause more blood clots. My life has never been the same, I have to say that, since I developed ITP.

I do hope that this board will recognize that more research has to be done to find new treatments for ITP. So few people are even aware of this disease. I certainly had never heard of it until it happened to me.

Drug companies must be urged to move forward to develop these treatments so that so many of us can return to our normal lives, so that adults and afflicted children will be able to participate in their normal activities without the fear that an injury could end their lives.

My doctor tells me, Joanne, go out there and live your life; but don't bang your head, drive carefully, don't have an automobile accident, and don't fall down on the ice.

So I know we all have to be careful of these things, but ITP patients have to be extremely, extremely careful of this.

Thank you for your time.

DR. ECKHARDT: The next speaker is Joan Young.

MS. YOUNG: Hello. My name is Joan Young and I am the founder and president of the Platelet Disorder Support Association, or PDSA. Our organization represents more than 20,000 families with ITP worldwide.

I was diagnosed with ITP in 1992, so I am speaking both as the president of PDSA and also from personal experience.

PDSA receives grants from several companies that hope to market thrombopoietin mimetics, as well as companies that market other treatments for ITP. This far-reaching corporate support has enabled us to broaden our scope of services and reach more people afflicted with ITP and other platelet disorders.

It is the policy of PDSA to not endorse the approval or recommend any particular treatment. I will therefore speak to the general approval of thrombopoietin mimetics in treating people with ITP, and not the specific approval of Nplate.

Each week I talk to people diagnosed with ITP who have exhausted their current treatment options. They may be resistant to steroids, have failed splenectomy, are intolerant of IVIG or have a myriad of other reasons why they have reached the bottom of the treatment list.

I find myself telling them about the thrombopoietin clinical trials or giving them a hopeful message that these new treatment options will be available soon. In 1993, I had reached the bottom of the treatment list in dealing with my ITP. The only things that were left were very toxic, and were not very effective.

For several months, my platelet count was below 5,000. It would have been wonderful to have other treatment options to try. Many of the current treatments for ITP suppress the immune system. We have heard from several families where the person with ITP died from opportune infections, and not from bleeding.

One of the benefits I see from the thrombopoietin mimetics is they do not suppress the immune system. When I was being treated for ITP, I developed tachycardia, a seizure disorder, was bald from vincristine, and was so weak from the side effects of the treatment, so that I could