There's a fair number of individuals who, excuse me, there are a fair number of individuals who don't make it to six weeks of therapy because they attained, I guess, greater than 200K in the platelet count. My question is twofold. One is, these individuals were taken off the drug. By the end of six weeks, what was their platelet count? Were they counted as successes and then the value of 200K was used for the rest -- they made it as a success and so they were continued to be successes all the way to week six -- do we actually know what their platelet count was after they were taken off the drug? And these individuals who were sort of rapid responders, do they have a different safety profile than those individuals who may have improved their platelet count but did it at a slower pace? Is my question clear?

DR. RIEVES: Yes, it is clear. And we're very interested in that subject. And

I'm sure GSK has multiple slides on what is referred to as the observed platelet database. But you're correct. These rapid responders counted as meeting the primary endpoints.

You're essentially asking what did the data show on platelet responses after that time.

DR. SANDLER: Did they go back down? Because in terms of the chronic question, I mean, would you stop them? And then what happened to them? Would they continue? And then also are they more prone to adverse events if they rapidly climb?

DR. RIEVES: They're good questions. Madam Chairman, if I may turn it over to GSK to go through the details -- the anthology of the platelet count responses.

DR. HUSSAIN: Sure.

DR. ROYCHOWDHURY: We did have patients -- to answer the questions with regards to were they counted as a responder.

Yes, they were counted as a responder. Their platelet counts decreased in the same manner as a patient whose platelet counts had not gone up beyond 200,000 during treatment.

DR. SANDLER: So by week six --

DR. ROYCHOWDHURY: It had the same profile.

DR. SANDLER: By week six many of them could have been back to where they started.

DR. ROYCHOWDHURY: Absolutely. Their adverse event profile is the same between those patients, as well as the patients that had the platelet elevations of 200,000 earlier than six weeks.

DR. SANDLER: There's a small number. There's only about 27 or 28 of these individuals.

DR. ROYCHOWDHURY: That's correct.

DR. SANDLER: In terms of their adverse events, can it be said that we don't have enough subjects to really understand

what's going on with them?

DR. ROYCHOWDHURY: Of course, the numbers are small, but the adverse event profiles look very similar among those patients versus the other patients. And finally, I think you had one other question with regards to a prolonged response. We did see some patients in our clinical trials who did have a response beyond a two week time period where most of the patients have their platelet counts come down. But they were small numbers. About 8 percent of our patients had platelet counts beyond the two weeks that were still above 50,000. And they lasted about 6 weeks.

DR. SANDLER: Just one more question, please. What's the implication for long-term use? There's no long-term use that we can pull out of this. What's the implication or long-term use if they rise quickly to 200K. What would be done with them?

DR. ROYCHOWDHURY: Right. In EXTEND study, we were able to -- in Part A and Part B, we, of course, asked the patients to stop the medication when they go above 200,000. But in EXTEND, we allowed those patients -- we followed those patients and we made changes to their dosing such that the platelet counts could then be kept in the range between 50,000 and 200,000. And that was quite possible in EXTEND.

DR. SANDLER: Thank you.

DR. HUSSAIN: Dr. Sandler.

DR. SANDLER: I have a question for the sponsor, specifically Dr. Bussel.

Dr. Bussel, in your presentation you chose to show us pictures of an intracranial hemorrhage and wet purpura, which would be situations where the short-term indication would be urgent. And the data that we saw showed that it takes 8 days to go from 20,000 to 30,000 platelet count, and a median of 15 days to get to

70,000. My question is, a lot of us would think of a short-term treatment for something like surgery, dental care, or an intracranial hemorrhage, but I didn't see data that would relate to the urgent indications, which would be most of the indications.

So the proposed indication reads that it would be intended for the short-term treatment, etcetera. Do we really mean for the non-urgent short-term treatment? Because I don't think we mean for the urgent treatment.

DR. BUSSEL: I think your point is well taken, Dr. Sandler. I may have misspoken in that someone with wet purpura, I don't think their treatment is so urgent that if it took, let's say, a week to increase the platelet count, that that would be insufficient. But certainly for an intracranial hemorrhage or major bleeding that we would count as truly urgent, I'm unaware of data that suggests that this

should be the treatment. And I think the way you phrased it was quite fair. Dr. Roychowdhury, do you want to --

DR. ROYCHOWDHURY: Dr. Sander, our studies, of course, had our first platelet count check only on Day 8. So we cannot give you the kinetics before Day 8. But you're correct that most patients, we see the elevations starting Day 8 and Day 15. In our highly volunteer studies we did see platelet elevations start even at Day 5. But in our label -- proposed label to the FDA -- we have suggested that if there is an urgency to elevate platelet counts within, you know, one or two days, or three days, or four days, then eltrombopag should not be the drug that should be used.

DR. HUSSAIN: Dr. Perry?

DR. PERRY: Thank you. I have several questions for the sponsor, and I'm not sure who wants to take them.

The first is, how is the 50 mg dose

picked? In at least one graph I've seen the 75 mg dose had a higher response rate, and I didn't see any data on anything beyond a 75 mg dose. Nothing to indicate that a dose limiting toxicity had been achieved.

DR. ROYCHOWDHURY: So the dose of 50 mg was picked after we completed our Phase II where we had 30, 50, and 75. And what it showed was, yes, 75 mg patients, most of them -- more of them did achieve the endpoint. However, can I have the slide please? However, if you see the number of patients who achieved platelet counts beyond 200,000, you can see that more patients actually had -- during the 6 week period, or before the Day 43 period, had platelet counts beyond 200,000. And also, there were patients who had platelet counts beyond 400,000. So we felt that the dose of 50 mg allowed us to have patients -- allowed us to have platelet count elevations greater than 50, but keep more patients beyond the 200,000 mark. So

that was -- it was sort of an optimal dose to keep them in that range.

DR. PERRY: There was not a toxicity question with a higher dose?

DR. ROYCHOWDHURY: There was no --

DR. PERRY: Okay. In the repeat study where patients got cycles of therapy, the number of patients dropped by about 50 percent from the first course to the second course to the third course. Why did that happen?

DR. ROYCHOWDHURY: Actually, at the time of data cutoff, that was the data we had. We have since then completed the study and we did do a final analysis of the REPEAT data. I can share with you this analysis which has not been -- this data has not been shared with the Agency. But just to prove the point that we had patients go through the cycles, can I have the slide?

So, here, as you can see, there were 66 patients who were enrolled on REPEAT,

of whom 52 had response in Cycle 1. Those are the patients that were moved into Cycle 2. And 45 of those patients then subsequently had a response in Cycle 2 or 3. And in Cycle 2 and 3 were 48 patients. So a large majority of the patients who did have a response in Cycle 1 went onto Cycle 2 and 3.

DR. PERRY: Okay. And at the risk of revealing my ignorance in a large group, what is Hy's law?

DR. ROYCHOWDHURY: I will ask one of the world's leading experts to talk about Hy's law, Dr. Maddrey.

DR. PERRY: Dr. Hy is here?

(Laughter)

DR. ROYCHOWDHURY: He, unfortunately, is not around with us anymore, but Dr. Maddrey had worked with him and can give you that.

DR. MADDREY: Over a number of years of studying drugs of a whole variety of types Hy made the observation that those

patients who had elevated aminotransferase of some significance, a floor really around three to five times the upper limit of normal, was of interest to us as far as hepatotoxicity. But those patients who in addition developed clinical jaundice, a rise in the serum bilirubin in the initial statement to three times the upper limit of normal, this combination separated out a group of patients who are at a special risk. We studied this in isoniazid. We studied this in methyldopa. We studied this in tienilic acid. So that Hy's rule or Hy's law says that in a non-confounded patient who does not have evidence of a colostatic injury, an elevation of aminotransferases and an elevation of serum bilirubin puts the patient in a special group of risk with a mortality for the several drugs we've studied from somewhere around 7 or 8 percent to about 14 percent. So that is a good guideline for us to identify a group of individuals at

special risk of hepatotoxicity. But I want to mention that it's for hepatosaliandry in non-confounded cases.

DR. PERRY: Thank you. One other question for the sponsor. If someone had an intracranial bleed as exhibited on the slide, what -- whose scale would that bleed be on? Would that be gross? Debilitating? If it's a small bleed, would that be a Grade 2?

DR. ROYCHOWDHURY: Can I have the slide on the WHO scale please?

DR. PERRY: It's a little confusing to me applying that particular scale to a clinical situation. That seems to deal with the amount of blood loss. To me it's often where the blood is being lost, particularly if it's being lost in the brain.

DR. ROYCHOWDHURY: Yes. Of course, as you can see on the WHO bleeding scale, it's great for if you have an intracranial hemorrhage. Minor bleed confirmed by a CT or MRI would be a Grade 3 gross blood loss. And

then this also outlines what Grade 1, and Grade 2, and Grade 3, and Grade 4 are with regards to different other types of bleedings. So this was the scale that was utilized in our study. We did go through a training process or an education process with the investigators around the scale as they were using it in our clinical trials.

DR. PERRY: Thank you. Then I have one final question for the FDA.

It seems to me that if you were a non- responder, or put it this way, if you're on placebo, got no response in your platelet count, ended the study and bled, then that bleed was attributed to the disease. Is that correct?

DR. RIEVES: Right, right. The logic.

DR. PERRY: And if you got treated with the drug and didn't get a response or had a suboptimal response, a platelet count of 5,000 or 10,000, stopped the drug and then

to a bleed, that was attributed to the drug. Is that correct?

DR. RIEVES: I think it is impossible to exclude a potential drug effect in terms of worsening of the thrombocytopenia, if you will, compared to baseline. I guess what I would like to emphasize is that following that initial drug exposure, I think we have to be very careful about slicing and dicing the data based on whether you're on or off the drug since the pharmacodynamic effects can actually extend beyond the --

DR. PERRY: I understand that but I want to make the point that the risk factor for bleeding is a low platelet count. The drug may also contribute to that, but having a low platelet count of 5,000 is harmful to your health regardless of whether or not you received the drug.

DR. RIEVES: Yes, sir. We agree with that. And that mechanism we will

follow.

DR. PERRY: Okay.

DR. RIEVES: Madam Chairman, if I may make two points to follow up on before we get too far along in the discussion. One is to follow up on Dr. D'Agostino's comment -- question there -- which we think is a very good one in terms of this long- term exposure. Because here today we're not talking about the drug in terms of yes or no -- is it safe and effective, especially with respect to the long- term usage. We need to know the dosage regimen. In the short-term studies, essentially there was almost no dose adjustment. It's these ongoing clinical studies that actually provide the information for the clinician whether -- on how to adjust the dose.

So in terms of risk benefit assessment for the long-term usage, it's not simply the drug, is it safe and effective? The question of the drug regimen comes in

there, and that's why we're looking forward to getting those data because the clinician obviously needs to know how to adjust that dosage.

And the other point I would like to emphasize with respect to this moniker of Hy's law, which is sort of a misfortune if it's misinterpreted. This is a reviewer's tool. This is a screening tool. It is not a threshold test, if you will, of tolerability. It's not a yes or no. So I think we have to be very careful. It's very useful -- the construct of that nominal law -- is useful for us as regulators and for drug developers because it does help us explore the databases.

But on the other hand, we have to place it in the context there. It's open to interpretation.

This question of confounding is in the eye of the beholder. So we look at the totality of the data and do our best to not

focus on the adornment, if you will, of the cases themselves.

Thank you.

DR. HUSSAIN: Dr. Rieves, I have a question for you. Just so I understand. I know Dr. D'Agostino and you repeated the issue of long- term use. As I read it, it reads to me that what is requested is a short-term use. Is it the fact that it's going to be in the market and people can just use it willingly?

DR. RIEVES: That is among our concerns. And we've also been challenged in particular -- at FDA these days we're talking a lot about risk management plans. And the development of a particular risk management plan, as you can imagine, could be a formidable, formidable challenge in this situation for a drug oral tablet as exemplified by the patients in these studies. These patients were largely refractory patients. And the logic of discontinuing

that drug as shown by the data, if one were to place some clinical meaningfulness upon the WHO bleeding scores. For example, at baseline, 60 percent of the patients were nominally bleeding if we believe that score. That proportion seemed to decrease. By the end of the score though, by the time the drug was stopped, patients went back to bleeding. So you catch yourself thinking if there is clinical meaningfulness to this logic, then the appropriateness of drug discontinuation at that time is a challenge, if you will. So, yes, we do have concerns regarding the ability to effectively use the drug, especially in severely ill patients who need a long-term therapy. It presents a formidable challenge for us all.

DR. D'AGOSTINO: Can I add -- in terms of my question, can I add something? I was concerned, or also concerned, even within the six weeks if you rise rapidly with your platelet count, then you're taken off, do you

fall rapidly? And then how do you manage even within the six weeks? Because it seems like they took them off and then they were considered successes and followed for bleeding, but not followed for what would you actually do in clinical practice. And then from the six weeks to the long-term, obviously the implication gets even more confused.

DR. HUSSAIN: Sir, if I may just follow up one more. So how do we balance the interest of the patient who needs it and will benefit from short- term use with the bigger concern, which is real, of potential abuse and not enough known about its safety in the long-term. I mean, there's got to be a way that the language can be worked out, but supposing I have a platelet count of 20 and now I urgently need my gallbladder out, how is my interest served in that situation by not having that drug available? And can the language be worked out so that, you know, I

mean, there's got to be other examples potentially out there of oral agents that may be of need only for short-term, but they're certainly available there and the potential for long-term use is there by physicians?

DR. RIEVES: Right. I think we all recognize there is potential benefit for certain patients who need the short-term therapy. And your point is well taken.

If controlling its use or regulating its use -- regulating its safe use after that period of time, especially in the severely chronic ill patients -- is going to be a real challenge to the development of a risk management plan. And those details have yet to be worked out. As you can tell, we did not present a discussion of a risk management plan, in part because of the complexity that will need to go into that sort of situation. We have also requested that the sponsor develop an expanded access program even as we're sitting here talking

about this such that patients under the IND, if need be, can have access to the drug for these specific indications.

Your points are well taken though. I think we're all faced with a dilemma here of a subset of relatively refractory patients who actually direly need long-term therapy. It's those patients we would all like to benefit. And the data ultimately may be very, very informative for the use of the drug in that situation. At the present time though, our database is focused upon the short-term.

DR. HUSSAIN: And if I may push my luck one more time and then I'll stop asking -- so why couldn't this be given sort of an accelerated-type approval pending definitive trials being completed?

DR. RIEVES: That subject is on the table, yes, and it is an option. There's multiple options.

That is among the options. Your

point is well taken.

DR. HUSSAIN: Dr. Harrington:

DR. HARRINGTON: So this is I think a follow up to that line of questioning, and it partly came from Dr. Perry's earlier question. So a question first for the sponsor.

Two studies which I think will shed light on some of the longer term toxicities, although not over long extended use or REPEAT and RAISE, and so we just found out that REPEAT now has more mature data on people who moved through the study, and we saw the response data. But do you have the safety data for those?

DR. ROYCHOWDHURY: Yes, we do have the safety data. There are absolutely no differences in the safety data that was presented by Dr. Arning in the subsequent cut or the initial cut, which is the final cut. With regards to EXTEND, we've given all of the data that was available at the 120 day

safety update. With regards to RAISE, we have given nearly all -- I would say nearly three-quarters of the data that we have as blinded safety data, of course, for review in the application. So there is only a small amount of data that remains still -- that is beyond the 120 day safety update that has not been provided with regards to RAISE.

The only data piece that is missing from RAISE is the efficacy data which is blinded.

DR. HARRINGTON: So blinded safety data means you've given the data to the Agency. That doesn't break the treatment codes? It just gives overall rates?

DR. ROYCHOWDHURY: That's correct.

DR. HARRINGTON: So let me just press on this for a second though. So maybe this is for the sponsor or for the FDA -- how much longer do we need to wait or does the FDA need to wait before it can do a detailed analysis of the safety analysis by treatment

in RAISE? If the data aren't available yet, when would they be available?

DR. ROYCHOWDHURY: Well, the study is ongoing and we will most likely have the first analysis of the data by the end of the year. That's the first time we can provide the unblinding of the treatment codes.

DR. HARRINGTON: The reason for my question is while there is substantial uncertainty here about the safety data for extended use, I guess, the length of time that we're going to have that uncertainty is important. If it's a matter of weeks it's worth waiting. If it's a matter of many years, then obviously one needs to make a slightly different decision.

Question for the FDA. This is a question that comes up in this presentation, but I think it's a more general one as well. So, on slide 20 of the FDA's presentation where the numerically elevated adverse event rate was shown -- it was the NESAE 66 percent

versus 52 percent, I guess -- so I understand the reason for being cautious with safety data as opposed to efficacy data, but do you have precision figures on that? Do you have confidence intervals for the difference or confidence intervals for the odds ratio of those?

DR. RIEVES: We did not apply statistics other than just the display. No, we did not -- I don't think we developed confidence intervals. Although, I suspect GSK may have that hand.

DR. HARRINGTON: So I guess I would urge that it's fairly hard -- I understand the value of the raw numerical summaries, but it's hard to interpret them without knowing the precision. I'm not asking for a formal test, but just to get a sense if, you know, that difference of 14 percent is plus or minus 3 percent, or plus or minus 20 percent, or plus or minus something that would give me a sense of whether that's data that is

actionable or not.

DR. ROYCHOWDHURY: Dr. Harrington, we can show a slide. I don't know if we have done any specific statistical analysis, but if I can have slide S361, please. No, that's not -- do we have a comparison slide? 852 maybe. That might show it. Yes, can you put that up please?

So these are the numbers that are available in Part A and Part B which are comparable to placebo. We do not have statistical analysis or testing around 48 percent versus 57 percent.

DR. HARRINGTON: I don't want to seem obsessed about a test here. I'm not actually looking for a test. I'm just looking for some indication of the precision of that difference so that we have a sense. But, okay, I won't press the point. But I guess I would urge FDA and others when you do numerical tabulations of side effect data you at least give us some sense of the precision

of that estimate of the difference.

I think that's all for now, thanks.

DR. ROYCHOWDHURY: Dr. Hussain, if I may follow up on just one answer.

DR. HUSSAIN: Sure. And then Dr. Curt afterwards.

DR. ROYCHOWDHURY: I'm sorry. Okay. It's just that I wanted to just follow up on the issue of long-term data. You know, we have, of course, given data in the randomized setting with short-term -- with Part A and Part B. In long-term, yes, the RAISE data is still not available, but we do know that if one gives placebo to patients with chronic ITP, and that was seen in the romiplostim dataset from March ODAC, very few patients actually achieve platelet counts beyond 50,000 for any reasonable period of time. And we have seen an extent that many of these patients are achieving platelet counts, as Dr. Arning has shown, for a fairly lengthy period of time. And so we expect

RAISE to have long-term efficacy data that is probably most likely going to support the user -- the activity and the effectiveness of Promacta.

So we feel that EXTEND gives a very good idea of the effectiveness of Promacta in the long- term setting. So I just wanted to make that clear in terms of the efficacy data that is pending from RAISE.

DR. HARRINGTON: So I understand and it's a point well taken. I think it is the safety data over extended use though that is perhaps the most valuable thing that RAISE will provide.

DR. ROYCHOWDHURY: Yes, unblended safety data.

DR. HARRINGTON: Unblinded safety data.

DR. HUSSAIN: Dr. Curt?

DR. CURT: Questions for the sponsor. Two on the drug's pharmacology, and one on its biology.

Do the effects of Promacta on platelet count track with the drug's known pharmacology, particularly the attainment of steady state concentrations and half life as the platelet counts decrease when patients are taken of drugs? And is there any relation of individual patient response to achieved systemic drug levels, particularly in responding patients. And the biological question is did you see any effects on bleeding time or other measures of coagulation, particularly in responding patients?

DR. ROYCHOWDHURY: So, the answer to the first question is yes, it does track the pharmacology of this drug.

With regards to -- I think your second question was around -- I'm sorry, individual differences in PKS. We have seen that in Asian population patients there is an increase in exposure for the same dose. Dose for dose against non-Asian patients. And

that's one of the reasons why we had in our briefing document, as well as in the package insert that we proposed to the FDA, have suggested a lower starting dose for Asians.

And finally, with regards to the -- you had one other question. I'm sorry, Greg?

Oh, bleeding, yes. I'm going to ask Julian Jenkins actually to give a brief summary of the studies that we have done to address this.

DR. JENKINS: Can I have slide S291, please? Show the slide, please.

We didn't measure bleeding time. It was something that we considered when we first designed the studies. However, we did look at platelet function during the program. And in vitro studies and platelets from normal subjects we showed that we had normal aggregation and activation based on simple aggregometry and also facts analysis using P selecting, which is a well known surface marker on platelets for platelet activation.

And in both our healthy volunteer studies and in our ITP program, patients administered Promacta, we looked at aggregation and activation. In the healthy subjects we did aggregometry and again we did P selecting, and also Pac1, another marker for activation. And in our ITP programs in collaboration with Dr. Bussel and Dr. Alan Michaelson in UMass, we did facts analysis including platelet leukocyte aggregates, P selected markers, and GP1B. And in all these cases we showed normal aggregation and activation.

DR. HUSSAIN: Dr. Link?

DR. LINK: I just have one question -- two questions, but one, I guess, for the Agency in terms of if this is going to be approved for chronic use, which is obviously, you know, you're driving at, but this is how it would be used. How much data would you need? In other words, so we're going to have some data for a year of exposure, but that

won't tell us what happens if you take it for three years.

And these patients have a disease which is likely to be lifelong. So what would -- where would the bar be set and what kind of dataset would you need in order to approve it for chronic use. That's my first question.

DR. RIEVES: I wish I had a simple answer. A simple numeric answer, if you will.

I think one could say the bottom line is we just have enough data to write a label. The drug usage label.

Here in the context, as I've mentioned earlier, one of our challenges in the description of how to use the product is the dose adjustment. Now, EXTEND data will importantly inform that, as well as RAISE. Because EXTEND, in particular, not only has dose adjustment in the eltrombopag, but there's also modulation of the concomitant

medication use. So it's really proposed to help inform the actual market use of the drug as it will be used in practice. Those data will be very important. We recognize that. And conceivably, those data may be in, listening to the timeline, within about a year or so. So I don't think we can give a single number of how large a database or how long of an exposure database on this usage. As you know, from aromaplastin we recommended a six month exposure time to give a reasonable approximation, if you will, of acceptable long-term support, along with extension data.

Here, though, one of the overriding concerns is the dose adjustment -- how you actually use the drug. So I don't have a simple answer for that. But the bottom line is we need to know how to write a label for the clinician to use the product.

DR. LINK: But it would be used in getting sort of in an interim (?) fashion

chronic patients that are getting chronically exposed to the drug to sort of get the toxicity profile that you would need in terms of safety. Basically, you have to have the drug out there being used in order to have people -- right?

So let me just ask a second question. There seemed to be some -- I don't know, some concern that these patients didn't have any hemostatic challenge, you know, to sort of prove that they could do it. But it's kind of -- you know, the surgeons are already telling you they're not going to do a surgical procedure that's elective on somebody with less than a 50,000 platelet count.

So you're not going to get that. You know, the surgeon is going to say, okay, if you can't get the platelet count above 50,000, use something else. And they're going to say -- and that's why all the placebo patients got something, because they

needed a procedure.

So you're not going to get that data as far as I can tell. I mean, I know that there was some sort of beating around of, well, we'd have liked to see that it actually happened, but you know, you're not going to get surgeons to do it because it's too risky. So I don't think you're going to get that data. I mean, you got it in patients who got the drug and had their platelet counts at 50,000.

And I think more to the point, people are telling you something here -- that in clinical practice, whether it's got the right kind of supporting data, we know that people above 50,000 don't bleed and can safely undergo invasive procedures. It might be 60,000 or 70,000 for some people, but most of us taking care of patients sort of know that. And if you've got a patient with 10,000, they bleed. And so you're not going to get a surgeon to a tonsillectomy on

somebody with a 10,000 platelet count even if it's an elective procedure.

And obviously, if it's an emergent procedure, you're going to have to have something that raises the platelet count, like stat, if you're going to get the patient to the operating room safely. So I think some of those things -- you know, you want that data, but I don't think it's achievable in patients that are receiving, you know, this drug versus placebo.

DR. RIEVES: Your points are well taken. There's a number of design considerations we could get into, but we won't go through. But part of our point was not so much to bemoan the design of the study with respect to hemostatic challenges because we all look at these data and they're clinically useful. My point is with the scale though. We have concerns about use of the WHO scale as a precedent for grading bleeding in this fashion. We're still

concerned about its quantitative incremental use. So that's the point.

DR. LINK: Let me put it another way. I think most of us sort of take that the platelet count is a sufficient enough surrogate that we're willing to look at the platelet count. You know, those of us who practice and do hematology, I mean, there is differences if it's immune thrombocytopenia versus a production defect and all that kind of stuff. But basically we know when patients start to bleed. And each patient has a different sort of thermostatic bleeding point. But I think that most of us actually would more look at the platelet count as a useful endpoint than actual bleeding. You know, somebody walking around -- as we said, somebody walking around with a 2,000 platelet count, if they get hit in the head they're going to have a serious hemorrhage. If they're lucky enough not to -- I mean, our kids, our toddlers are walking around in

bicycle helmets ridiculously enough because we know that if they bump their head they're going to bleed. Whereas, somebody with a 50,000 platelet count, they don't have helmets on. So that should tell you something about our own where we assess. We don't look for bleeding scores. And I don't think we ever record it. We just put helmets on patients with low platelet counts.

DR. HUSSAIN: So just because we're going to go slightly over time, I'm going to ask -- and we'll go through the list of people that I have right now, but I'm going to ask that you make your comments briefly please. Dr. Gull?

DR. GULL: I'm one of those patients with years of ITP.

DR. HUSSAIN: Please speak into the microphone.

DR. GULL: I'm one of those patients with years of ITP and my focus is on this drug of long-term exposure. Some of the

things I see missing in this study is the anecdotal information of the patients that are in the study.

One is number of years since ITP diagnosis. I think that's a very important factor, and probably coupled with that is the different treatments that have been administered to the patient, even possible cause. Is there any correlation? Because we know ITP is caused by different sources here.

Specifically, steroids, I think, is something that we should be concerned about. And when you start talking about bone degeneration, or cataracts, or that, is it necessary that this drug is the cause or is it just simply that is the effect coming from previous treatments? That needs to be sorted out here, and I think we may have a cleaner picture of what's going on here.

I am concerned that there was not information of liver or bone abnormalities at the beginning of the treatment. I understand

bone marrow studies are very painful. Very few patients want to go through it.

And then a fourth question is body mass. That doesn't seem to be a factor that's being brought into this picture also.

Can somebody answer those questions?

DR. ROYCHOWDHURY: With regards to the anecdotal information on patients, I might ask Dr. Saleh and Dr. Bussel who have participated as investigators on this trial, to give some idea of the kinds of patients that they put on the trial and maybe that might help a little bit. But you're right. We did not collect extensive anecdotal information that was prepared to present in this forum. But Dr. Saleh or Dr. Bussel?

DR. BUSSEL: Relative to the anecdotal information that you mention, many of the patients that I at least entered on the study had had the disease for a long time, and many of them were relatively

advanced in years. Not 20, 30, healthy.

Some of them certainly, but many of them 60, 70 year olds who might have had more problems with the side effects of other treatments as well. Is there more you want to hear about them?

DR. GULL: Well, I mean, are you able --

DR. BUSSEL: About the courses?

DR. GULL: -- to sort out some of the bone marrow studies? Is that correlated with age or number of years of ITP treatment? Or --

DR. BUSSEL: I don't think anybody knows that. I don't think that's been systematically studied. I think there's now, because of the concerns of reticulin Fibrosis, studies are ongoing. It's clearly a part of ITP having nothing to do with therapy. How much, how long, age, etcetera, hasn't been worked out.

I can't comment on the body mass

issue, but as far as ideologies, there are clearly ideologies of ITP. I think most of the patients -- almost all the patients on this study is idiopathic immune and is -- I think you know, outside of patients who are kids who have an acute viral infection and seem to develop an acute ITP afterwards, we're not really very good at causes in terms of, oh, this patient had their ITP because of this. And this patient because of that. So I don't think it's easy or possible to really answer that part of your question.

DR. PERRY: As a clinician, let me just add I put about 10 percent of patients on A & B combined together. And all of these were chronic patients with debilitating side effects from the current therapy, be it steroids, IVIg, rituxan. All of them had a life-threatening and life-debilitating quality of life. And to me on study, at least 70 percent of those who responded did very well, were able to go and play with the

kids, did not have bleeding every morning. To me this is a life altering treatment. At least in the patients I treated.

DR. ROYCHOWDHURY: We're trying to pull up a slide that can help with the body mass index, but I've just been told that the slide is not available, but the analysis was done and there was no difference in efficacy with body mass index.

DR. HUSSAIN: Dr. Vose?

DR. VOSE: Yes, I had one question for the sponsor. Specifically on the EXTEND study, you showed data about the reduction and the bleeding with respect to Grades 2 to 4, but I think everybody would say that the really extensive bleeding, maybe Grade 3 to 4, is the most important. So I just wondered if you had specifically data in the EXTEND study on that since that's probably how it'll be used in the long run.

DR. ROYCHOWDHURY: Yes, I believe we do. Do we have one that shows Grade 3 to

4? Okay, one of the things -- I think one of the reasons we have not shown much of the 3 to 4 -- I'll just go back to the FDA briefing document. There's one slide on the FDA briefing document, and I'm trying to pull out the figure. Michael, do you remember the figure?

This is on page 19 of the FDA briefing document. It doesn't have a figure number, but it shows the patients who had Grade 3 bleeding during the study. And you can see that patients on Promacta -- yes, please pull up the slide. I didn't realize that we already had the slide up. So, the bottom plot shows that in pink patients on Promacta 50 mg, none of them had Grade 3 bleeding between days 15 and 43, or 57 actually. And then on the placebo arm there were some patients -- and these are very small numbers, so they need to be cautioned that they're very small numbers. But on the placebo arm these are Part A and Part B

studies, you see that there are patients who did have Grade 3 bleeding during that period of time.

DR. VOSE: I guess my question more was to the later time points as a concern for the chronic long-term use. That's the question.

DR. ROYCHOWDHURY: Can you go back to that previous slide with EXTEND please? Yes, the bar graph with bleeding. Please show this.

We will be -- hopefully after the break we can tell you exactly how many of these patients in the blue bars beyond Week 18 had Grade 3 bleeding. But you can see the numbers are very small. And so it's very hard to really tell you how many patients had Grade 3 or 4 in this.

DR. VOSE: Yeah, I understand. I guess the question just goes to, again, clinical relevancy. And that's the issue in the long-term use.

DR. ROYCHOWDHURY: Michael, do you want to add something more?

DR. ARNING: I monitored many of those patients, and the results, Dr. Vose, is exactly what is already proposed. If the platelets are high, patients do not bleed. There is, as we all know, a small group of bleeding occurs regardless of bleeding code. So we had patients who had bleeding about 50,000. We had hemorrhoidal bleeding. We had a case of epistaxis. But in principle, we can say patients with Grade 3 or 4 bleeding did not occur when the platelets -- occurred very rarely when the platelets were up. Strictly an inverse relationship is maintained. When the platelets are up, bleeding is down.

DR. VOSE: Certainly in, you know, clinical practice that is in general true, but it's just nice to be able to actually see the data.

DR. ROYCHOWDHURY: We will do that.

DR. HUSSAIN: Dr. Syzmanski?

DR. SYZMANSKI: I had something similar to these questions. And I found it a little bit problematic with the FDA analysis of the bleeding data. Because I think it's difficult to analyze the bleeding, stoppage of bleeding, in absence of platelet count. I think since it has been shown that these platelets generated by Promacta are functioning normally, therefore, when the platelet count is increased the bleeding is fairly, you know, stopped. And it's effective data. So I find this table on page 9 is a little bit confusing.

DR. RIEVES: One point I would like to make, and I think it's coming out. We are not questioning the usefulness of platelet count data. Our situation here is that the sponsor has made a proposed indication statement that specifically says -- and this has marketing implications as you all can imagine -- it specifically says it not only

treats the thrombocytopenia, but the proposal is that it also has been shown to reduce or prevent bleeding.

Now, some of this gets into some nuances of regulatory considerations and marketing, that short of thing. But we respect the utility of increases in functional platelets as we discussed at our advisory committee a few weeks ago from a sponsor who did not propose that specific claim. Here the sponsor has actually made the proposal to make a claim of reduction of bleeding. The example is like the anti-hypertensive drugs. They're marked and approved to treat hypertension. They don't, in general, have a claim to decrease incidence of heart attack, or stroke, or make you live longer, unless the manufacturers have shown those effects.

DR. HUSSAIN: Dr. Pazdur, do you want to say something?

DR. PAZDUR: I just wanted to

reiterate this. We've had this discussion in the last ODAC about the usefulness of platelet counts and bringing them up from a low level. And that can be an endpoint for approval. And here again, some of the issues of a bleeding claim, as Dwaine has pointed out, has implications for labeling of the drug and what type of data one would actually want to see if one is actually going to say this actually reduces bleeding. And the example is a good one of, you know, you could control hypertension and have a claim for hypertension, but we wouldn't say it controls hypertension and reduces the risk of stroke unless somebody actually demonstrated that convincingly. And that's a higher bar.

For example, with the statins. You know, we say it lowers cholesterol or other lipid profiles, but we don't say that it reduces heart attacks unless somebody showed that basically in very well designed trials.

DR. HUSSAIN: Dr. Alving?

DR. ALVING: I wanted to ask just a couple of quick questions. One, with the finding of increased reticulin, are these participants still continuing on with the drug? Was there any change to their receiving Promacta?

DR. HUSSAIN: Sponsor?

DR. ALVING: And secondly, while sponsor is coming, can't there be central adjudication with bone marrow findings? I would think that would be a rather simple thing to set up, and that would be certainly very valuable.

DR. AVADO: I'm Manuel Avado. No, as of the 120 day safety update, no patient was stopped on the drug because of bone marrow findings.

And of note, these bone marrow findings were not associated with clinical findings. No WVC increases, no evidence for organomegaly, no new created red blood cells in the peripheral blood.

DR. ALVING: So I guess the FDA has to consider when is increased reticulin important. And maybe you don't want to wait till you find peripheral blood findings.

The last question is in talking about the decrease in the platelet count after repeated administration, I know that today we heard the criteria by Dr. Bussel's criteria, and that was 11 percent had less than 10,000 than baseline and a platelet count of less than 10,000. But if you read in the report, 30 percent had less than 10,000 from their baseline and a platelet count lower than 20,000. So, what criteria will the FDA use? Or are you thinking about this in terms of labeling and what's going to be most useful for the clinician?

DR. RIEVES: Yes, we are thinking along those lines, as well as GSK. You're exactly right.

The hypothetical risk and some signals of worsened thrombocytopenia after

drug discontinuation, that can tie into labeling considerations. Also, how to monitor patients.

DR. ROYCHOWDHURY: Dr. Alving, just to add to what Manuel had said. We do intend to have an independent panel that will adjudicate the bone marrows.

DR. ALVING: Have you informed the participants of this finding?

DR. ROYCHOWDHURY: No, not yet.

DR. ALVING: Do you plan to?

DR. ROYCHOWDHURY: Yes, of course.

DR. HUSSAIN: Dr. Sandler?

DR. SANDLER: Question to the Chair. I have questions that would follow up on your question to Dr. Rieves on what mechanisms are available to make the drug available to those few people who might fit the indication without opening up the flood gates to a lot of thrombocytopenic people who wouldn't fit that narrow indication? Do you want to take that now or would you rather

defer it to the further discussion?

DR. HUSSAIN: Let me just do this. We are already 15 minutes over. We may have time in the afternoon, and I was going to ask the FDA to perhaps comment on that in the afternoon. I'd like to go through the questions first today if that's possible.

Dr. D'Agostino, I think you had the last question. You're done. Okay.

I think we have taken all the questions that we have. We will take a 15 minute break. I'm going to ask you all to come back here at quarter to so we can resume our discussions. Thank you.

(Recess)

DR. HUSSAIN: So we'll start with the rest of this morning's session with a statement that Ms. Vesely will read.

DR. VESELY: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. 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, it's product, and if known, its direct competitors.

For example, this financial information may include a 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 hearing process. The insights and comments provided can help the Agency and this Committee in their consideration 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 your cooperation.

DR. HUSSAIN: Thank you. I have here that we have only one public speaker. I'd like to invite Ms. Joan Young to present.

MS. YOUNG: Hello. Is this on? Hello, my name is Joan Young and I'm the founder and the 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'm speaking both as the president of PDSA and from personal experience.

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 Promacta.

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 service and reach more people afflicted with ITP and other platelet disorders. PDSA has paid my way to this meeting, and I was not reimbursed by any particular pharmaceutical company for my

attendance.

ITP can be difficult to treat. Often the first line of treatment, a short course of corticosteroids, usually prednisone, offers only a brief reprieve from a dangerously low platelet count. But also, most patients are then left to deal not only of the return of their low platelet count, but also the side effects of the corticosteroids. These side effects can include significant weight gain, cataracts, muscle loss, diabetes, osteoporosis, and steroid psychosis. Five minutes is not enough to describe the havoc this drug creates in a person's life. One person told me, "I'd rather die than take prednisone again."

When I was reducing my high dose of prednisone prescribed for my ITP, I experienced a seizure and tachycardia that required additional medication for nine months. This was in addition to a myriad of

other health issues exacerbated by the drug, some of which still haunt me.

After prednisone, many people with ITP have a succession of other treatments, most not approved to treat ITP. Some have minimal toxicity, except in very rare cases, and provide short-term relief. Others compromise the immune system, sometimes permanently, or are high toxic carrying a black box warning. An often cited research study from just a few years ago concludes that as many people with ITP die from the treatments as the disease.

In 1993, when I had reached the bottom of the treatment list in dealing with my ITP, I felt it was a toss up whether the treatments or the disease was going to kill me. For several months my platelet count was below 5,000 with only minimal relief from increasingly devastating treatments. At one point I was bald from vincristine and too weak to walk up stairs. Needless to say, it

would have been wonderful to have other options to try.

Our organization is very sensitive to the balance between safety and efficacy for all of the treatments for ITP. I believe it is important that the thrombopoietin mimetics are available to those patients who would benefit from that choice. My hope is that they will be approved and become available in a manner that considers the safety of these new treatments while assuring the privacy of patient data. I believe it is important that any program minimize the incremental time and cost for the prescribing physicians, manufacturers, and third party payers, all of which may reduce access for those patients who might be helped by this new treatment approach.

I also hope that the safety profile of the thrombopoietin mimetics will be considered in light of the safety aspects of those treatments currently recommended and/or

widely used to treat ITP.

Thank you.

DR. HUSSAIN: Ms. Young, thank you on behalf of the Committee for sharing your thoughts with us.

The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. The Committee will now turn its attention to address the task at hand -- the careful consideration of the data before the Committee, as well as the public comments. Dr. Curt.

DR. CURT: Question to you and to the Agency. In the questions, would it be possible to start with the second question first? It's more general to specific as opposed to specific to general. It's sort of a meeting policy change, but I'm wondering if that makes sense.

DR. PAZDUR: That's fine. Because I wanted to address the issue that you had

discussed.

The question of long-term use versus short-term use and what would be the regulatory mechanisms that we would have available to try to ensure that people are aware of the existing information and limit the use.

There's a variety of mechanisms that would fall under a risk management plan here. They could be simply labeling of the drug. And by labeling I mean specifically in the indication section that this drug is not intended for the use of -- long- term use of the drug and safety and efficacy has not been demonstrated. And that could then be removed when data is presented to the agency which would suffice it.

That's one possibility. Another possibility could be some type of even restricted distribution of the drug where prescribers and patients -- the prescriber would have to be registered and the patient

would have to be registered. And then every period of time, whatever that period would be, six weeks, two months, whatever the company and the Agency would agree to, that the authorization be renewed for that patient giving pertinent laboratory evaluation of the patient. His platelet count, liver functions, etcetera.

So, you know, there are mechanisms here. So it's not an either or. Obviously for labeling, you know, people don't have to adhere to the labeling. Off label use is frequently used. However, I think if something is stated in the indication, that it's not indicated for long-term use, I think that there would be a great deal of trepidation about just kind of a random use of the drug.

DR. HUSSAIN: Dr. Perry.

DR. PERRY: I'd just like to go on record as saying that while I'm very much in favor of pharmacovigilance, I'd like to see

that done not on the backs of the physicians who prescribe the drug.

Every time I have to fill out another two or three page questionnaire or have my nurse call to get permission from a drug company or an intermediary pharmacy to get a drug, it uses up a lot of time that nobody's paying for. It does, at least in the immediate term, no significant good. Long-term it may do great good, but if we're going to have a pharmacovigilance system, I'd like to see it not as an unfunded mandate on the backs of physicians.

DR. HUSSAIN: So with that I think we could probably, Dr. Curt, proceed as planned and make the vote -- we will first discuss the first question and then move to the second question.

I'm now going to read the first question. It's a long statement. If we can have them be put up please. And I'll ask the Committee members to read it.

So I'm going to just read the question right now. And we can begin a discussion and then take a vote afterwards.

Eltrombopag is proposed for use in patients such as those undergoing a surgical procedure who have a specific need for short-term therapy. The patients in the completed controlled studies did not have the specific need, and some experienced serious hemorrhage when eltrombopag was discontinued. Since ITP is generally a chronic condition, long-term therapy is anticipated. Given these observations, should the FDA delay marketing authorization until it has reviewed final data from the ongoing clinical studies, specifically RAISE and EXTEND.

Anyone want to -- I'm sorry, go ahead, Doctor.

DR. PAZDUR: And again, people should be cognizant of my previous statement that we would try to have a risk minimization plan in effect, either labeling or some other

restricted distribution that needs to be discussed.

DR. HUSSAIN: Okay, so -- yes.

DR. ECKHARDT: Yes. So my question then is whether it's really delay or modify. Yes, no. Because I think that's the question.

DR. PAZDUR: The indication would be for what the company is asking for, and that is the short-term use of the drug. It wouldn't be just a chronic -- I mean, by broad term this drug is used for ITP.

The question here is do people feel that these plans would be sufficient to mitigate against the outstanding questions on this drug through some type of risk minimization strategy, such as labeling where it's not indicated or the more kind of conservative approach of actually restricted distribution.

DR. HUSSAIN: So anyone from the Committee would like to have a question posed

discussion about this specific issue? Dr. Link.

DR. LINK: Somebody brought up the issue before about an accelerated -- and you commented that that was on the table. That's really not what you have on the table.

DR. PAZDUR: It could be, but the issue here is this is a safety issue and these probably would be more germane of addressing the safety issue. We could do that also.

DR. HUSSAIN: Just so we are clear --

DR. PAZDUR: You have to demonstrate safety and efficacy for an accelerated approval and, you know, as we stated before, this drug does increase the platelet counts and we've accepted that as an endpoint.

DR. HUSSAIN: So if I understood you correctly, Dr. Pazdur, what you said is that the delay of marketing or not delay of

marketing, or the vote, ought to take into account what you commented, and that is should the vote be not to delay. That the FDA can indeed write up a package insert that will give directives to the physicians. That's what I heard you say. Correct.

DR. PAZDUR: Or other risk minimization program. Will that enable us to proceed forward?

DR. HUSSAIN: Okay. Any comments or issues? Dr. D'Agostino.

DR. D'AGOSTINO: I'm sure I know the answer, but all of that would focus -- was only talking about the short-term here, so all these warnings and what have you --

DR. PAZDUR: Correct.

DR. D'AGOSTINO: -- would say long-term is not --

DR. PAZDUR: Correct.

DR. HUSSAIN: Yes.

DR. LESAR: Tim Lesar. I just have one concern. It relates to the fact that

everybody is talking about indications that may or may not exist to any great extent in terms of how to use this drug. It would be marketed with everybody's idea that this drug will be used longer term and in other patients. And whether or not there isn't the alternative way of changing the indications such as simply an increase in platelets and present the data in such a way as to show the risks and benefits and what the data is, and not avoid short-term, long- term as part of the indication.

DR. PAZDUR: Generally, we don't get into the specifics of labeling. I just want to emphasize that what has been -- the indication has to reflect what has been studied and reviewed. And short-term studies have been submitted. So I think as the proposal and not the entire indication we're not talking about here, but the short-term use is something that I think we would consider given the appropriate caveat of some

type of risk management program where it's specifically stated that there are not long-term data.

DR. HUSSAIN: Dr. Rieves, do you want to say something?

DR. RIEVES: I was just going to reiterate again the concern about the dose adjustment, our nominal short-term program, if you will. We have dose adjustment information there. There basically is no dose adjustment. But in the long-term though, those data -- the adjustment data are pending. So developing that label would be a challenge at this point in time. So we're really voting on the short- term, if you will, since that's the type of label we can work with.

And tying into this first question also, it's essentially the feasibility. Is it practically and logistically doable to set up a risk management program that may be somewhat challenging, if not burdensome, to

ensure safe use of the product.

DR. HUSSAIN: Would that require then the sponsor's help, obviously? And is the sponsor -- please.

DR. ROYCHOWDHURY: Dr. Hussain, we have submitted a risk management plan that tries to address the potential concerns, both from a safety perspective as well as distribution perspective.

In terms of dosing recommendations, I would just like to make one comment with regards to how we dose Promacta in EXTEND. In EXTEND we also dose Promacta where the dose modifications are made based on a very clear PD marker which is platelet counts. And patients do receive -- they get a platelet count and then the physician makes an adjustment to the dose. In RAISE, which is the blinded study, that same paradigm is followed. Essentially, dose adjustments are made based on the platelet counts. So, in a follow up label that we provided the Agency,

we did have some dose adjustment recommendations based on what we found in EXTEND or what we did in EXTEND.

DR. HUSSAIN: Thank you. Any -- Dr. Harrington.

DR. ROYCHOWDHURY: The question of Dr. Link.

DR. HUSSAIN: Yes, can you please speak in the microphone?

DR. LINK: I was just curious if there was a starting dose adjustment for Asian patients based on your pharmacokinetic data.

DR. ROYCHOWDHURY: Yes, we recommended an initial starting dose of 25 mg as opposed to 50.

DR. HARRINGTON: So this is a question of clarification. I apologize if it's naïve. I guess I'm not sure I know the definition of short-term here because the test was for six weeks. So would the label be as specific as saying that controlled

clinical trial data indicate that the drug is safe and effective for six weeks, or will you use the three cycle data that's going to come in relatively soon? The other thing I'm wondering about is the physicians will know that, but patients -- someone who is suffering with chronic ITP lifelong, a year is short-term. Maybe five years is short-term. Six weeks is infinitesimally small.

So I don't know what short-term will mean here in practice. I'm a little bit confused whether that can be sorted out in the label.

DR. PAZDUR: It should reflect what was studied. Now, here again, part of this risk minimization program, you know, we're not here to deny people therapy that could benefit beyond six weeks. So perhaps there could be a restricted distribution so then after six weeks if the patient needed it, the physician would call and give the appropriate

laboratory parameters and have that renewed again. But what is short-term is basically what has been studied in the trial.

DR. RIEVES: Six weeks.

DR. HUSSAIN: Dr. D'Agostino, then Sandler, and then Lyman.

DR. D'AGOSTINO: The studies that are positive haven't really played with the dosing. I mean, you withdraw after you reach 200K and so forth. So, I'm not so sure how you can use REACH and RAISE, or excuse me, RAISE and EXTEND in this. But I'll leave it to the FDA to worry about it. It's not where we really have dosing data that we can, you know, fall back on.

DR. RIEVES: Your point is well taken, Dr. D'Agostino. From our -- as reviewers, it's presented special challenges because these are ongoing studies. And as you can tell, the data are dynamic. They're changing almost daily, if you will. And so it's difficult.

We can get a handle on the completed studies, and that's really where the safety and efficacy should be weighed here. We're cognizant that there are accumulating data, but using those data without a through vetting for labeling has its own challenges.

DR. HUSSAIN: Dr. Sandler.

DR. SANDLER: Question to the FDA. With regard to what's up your sleeves -- with regard to controlling the use off label. I'm a gatekeeper for drugs similar to this where people on committees like this have spent a lot of time wordsmithing indications, but in real life clinicians come and say I want to use it off label and get out of my way because I've got a sick patient. I don't know of a way to stop that. What do you have up your sleeve to stop it?

DR. RIEVES: Well, Dr. Pazdur can elaborate on this because it comes up all the time.

We understand there is appropriate use, off label if you will, of many products. And we expect that. And it's not our intent to reign that in, if you will. In this situation there may be patients who do not have chronic ITP who could benefit from this drug. We recognize that. What we're more interested in in the risk management plan is to track. To find out who is using the product and to try to optimize safe use of the product, meaning monitoring liver tests, if you will. Some of the other considerations there. It's not necessarily to reign in off label use.

DR. HUSSAIN: Dr. Lyman.

DR. LYMAN: Perhaps to the sponsor, although the risk management strategy is obviously a negotiated process between the Agency and the sponsor.

I think that I would want some assurance about the details of that strategy, and particularly whether we are going to see

out of this as well additional data on some of the unanswered questions that we've all addressed. I'm particularly concerned about the hemostatically challenged population. The data is very sparse. And I think on the efficacy side we are all pretty satisfied that the platelet count goes up. That's protective.

But I think on the safety side, it would be nice to have more targeted data in that population in terms of whether they're -- for instance, their thrombosis risk was higher if the platelet count was higher because of the drug as opposed to transfusion of some other mechanism.

The data is just very sparse in that category. The dosing question we've talked about. And I think also whether there's going to be some central adjudication of the marrow follow up on these patients.

DR. ROYCHOWDHURY: So we are committed to collecting data not only from

the patients who will receive this drug off study, but also to conduct further studies to understand many of these potential risk issues. So the risk assessment will not only be just a routine pharmacovigilance, but also active pharmacovigilance. And to be able to do that, as Dr. Pazdur suggested, some way by which we can get patients and physicians to enroll onto this program and then following those patients with questionnaires so that we can follow with what kind of adverse events they had. And then following up on those adverse events literally, and then discussing those with the Agency and analyzing that to see what is the long-term effects or what other effects are seen as this drug is used in patients in a large population. So we are totally committed to doing that.

I don't know if I've answered your question.

DR. LYMAN: I guess, again, are you anticipating that the usage will be heavily

oriented towards those hemostatically challenged patients or patients with particular acute needs as opposed to just the ongoing platelet support?

DR. ROYCHOWDHURY: Our hope is that through the labeling, through the target education, as well as the acknowledgement during the enrollment period, or during the enrollment time, we will be educating the physicians to use it in the manner the prescribed -- the prescription -- the prescribed USBIAs. However, there will be some patients who may receive this on the long-term. And, you know, as we have shown you in our dataset, we do have data to suggest that it does benefit patients long-term. And so there is a potential that patients will receive it long-term.

DR. HUSSAIN: Dr. Alving.

DR. ALVING: Could we maybe ask some of our resident experts who are sitting behind me, maybe Dr. Bussel or Dr. Doug Cines

about, you know, let's say we put it out for short-term use but we know there will be other people just breaking down the door to get it. And it's going to be really difficult not to give it to them. So could they kind of envision who these patients are and give us an idea of what they ideally would like to see, and how could we do that surveillance. I mean, let's figure out what is the reality and then how do we capture what we need to capture. And it goes along with a whole idea of post-marketing surveillance. Could maybe one or two of them speak just very honestly, because I know it would be very hard as a physician to deny it to somebody who has had very low platelet counts. That's probably a very small -- well, you see all the complicated ITP patients, but I mean, for the general hematologist, most of them can be handled fairly well with a whole lot of reassurance and say you can live with a platelet count of

30,000 and you'll need this when you, you know, get your molars removed or something.

DR. BUSSEL: I'm not sure if I'll answer this exactly correctly, but I think that many general hematologists do "some amount of therapy" whether that's prednisone or something else, or go to anti-D, IVIg, whatever they go to. And then at some point rituximad, decide on splenectomy. So I think there will be patients who will get their six week course of this and see what happens to their platelet counts and see if their platelet counts remain more elevated afterwards or anything like that, and may be relatively restricted to this in addition to the list of indications that we had, which are pretty specific and individually not that common.

I think that people like Doug Menser or myself who are going to see very refractory, chronic patients, who either may have failed splenectomy or may have a good

reason not to have splenectomy are, yes, going to need ongoing therapies. And there are people who I've entered on these studies who failed literally everything else and I was forced to leave them at a count of 5,000 or 10,000 and hope that nothing bad happened. And some of them have been on romaplastin or eltrombopag for long-term periods and it does seem to be the only thing that will help them. And I think there will be some of those patients. I think, fortunately, there's not that many. And to be honest, I think that sufficient additional data will be forthcoming soon enough that some of this will be less of an issue going forward. But I don't know what Doug would say.

DR. CINES: No, I agree with what Dr. Bussel said. I think that the prudent physician looks at the patient and assesses what's the patient's bleeding experience? At what platelet count? What medicines have I used? What toxicities have accrued to this

patient? How much data is known right now in the public domain about this drug that I'm making a decision about? And they would then factor that into their decision. Because it's not free not to use the medication in a very old patient. And it's not free to use other medications with their toxicities in some patients.

So I think the prudent physician integrates the information that's available. And there will be some patients, undoubtedly, for whom this has been an extraordinary breakthrough in their medical management.

DR. ALVING: And we recognize those patients, or those types of patients -- you could probably define them and say these patients can go into a registry so that you can -- it's part of the risk management, but I think it's more like the data capture to ensure that you capture that data. So you identify those right up front. And you could probably come up with who they are and then

say wherever they are, they could get it if they go into a registry and you define what you need -- the data you need to get. And that could be most helpful for every other kind of patient. And I think linking the short-term to say to anticipated, you know, hemostatic challenges would be, or like surgery or events could really be very clarifying and really emphasize that we don't know the long-term effects with respect to bone marrow fibrosis reticulum.

DR. PERRY: I agree with my esteemed colleagues. I just want to be sure that as a physician I don't have my hands tied behind my back and cannot use it in a clinically managed way whereby it's prescribed in such a tightly mannered way where I, the clinician, have to give up my own independent judgment. And I think that should be important in the discussion.

DR. HUSSAIN: Dr. Link.

DR. LINK: Can I just ask what the

dosing regimen is going to be? It's going to be 42 days and then sort of mandate that it be stopped at that point. Is that how it's sort of going to be recommended?

DR. RIEVES: What has been proposed is for the short-term use. And that's what has been proposed to us. Perhaps GSK wants to talk about their construct for ultimate long-term dosing. That information has not been vetted by FDA yet.

DR. ROYCHOWDHURY: In the risk management plan, what we proposed is that patients will receive a 42 day course initially. And then if the physician chooses to give the drug for a second course later on or continue the drug following that 42 day period, they have to re-enroll to enter the plan or at least re-register the patient. And then a second dispensation is made of 42 days. So it's a very similar manner to what Dr. Pazdur had suggested in his opening remarks with regards to a risk management

plan.

DR. LINK: So is there a mandated amount of time off between courses?

DR. ROYCHOWDHURY: No, it's up to the physician. It's up to the physician to make that judgment. If they feel that there is a need for time off, they will. If they don't, then --

DR. HUSSAIN: Can I ask a question about -- Dr. Roychowdhury, if you don't mind -- when the studies were designed, if a patient hits a platelet of 200,000 then they stop pills. Why not if they hit a platelet of 100,000. I'm just curious as to if indeed reaching a level of 50 is what you need, why do you need to keep pushing higher?

DR. ROYCHOWDHURY: It is difficult to actually ditrate that platelet count to such a narrow number between 50 and 100. Normal platelet counts can be up to 400,000 with no adverse consequences. Since it's normal, all of us have platelet counts up to

400,000. So we stopped it at 200 because it is possible that if you stop it at 200 for the next week there is a possibility that it could still rise because the drug is still in the system. And it could go up to 400. That was the reason we chose 200. And that allowed us to have very few patients that went beyond the 400 and million mark.

DR. HUSSAIN: Dr. Bukowski.

DR. BUKOWSKI: For the sponsors. Do you have in place or do you plan an expanded access program? That was mentioned previously as something that was discussed.

DR. ROYCHOWDHURY: Yes, we've been very fortunate actually that the agency has allowed us to have an inpatient program, and we are working towards having treatment protocol under RIND that will allow patients to get the drug. But that's right now being written and discussed with the Agency.

DR. HUSSAIN: Dr. Perry.

DR. PERRY: I'd like to suggest

that the FDA and the company consider using a different term rather than previously treated. Previously treated to me is a pretty expansive term. Maybe somebody had a single dose of prednisone and decided I didn't want to take prednisone and I didn't want to take anything else. Perhaps a better wording, or at least different wording would be refractory or intolerant. Refractory and/or intolerant of other therapies that, to my mind, encompasses better the patient population.

And I would not want to see labeling that said somebody had to have a hemostatic challenge anticipated like a surgery in the near future. If your platelet count is 3,000, every day is a hemostatic challenge. Walking down the street is a hemostatic challenge, and I don't think any of us are smart enough to anticipate when bad would suddenly go to worse. And so to my mind a low platelet count is sufficient

indication to treat on this if they've already exhausted other sources.

DR. HUSSAIN: Dr. Gull.

DR. GULL: Just a second question. I just have a question on the monitoring. What is the plan for blood CBC? Is this going to be weekly, continuously, or after six weeks as this gets stretched out? I'm concerned about over response of a patient.

DR. HUSSAIN: Sponsor.

DR. ROYCHOWDHURY: In our label that we have proposed, the monitoring of platelets, of course, our patients do get platelet monitoring often on a weekly basis, but we proposed liver function monitoring every other week during the time that the patient is getting eltrombopag.

DR. HUSSAIN: Will there be any criteria for discontinuation based on LFT abnormalities?

DR. ROYCHOWDHURY: Yes, absolutely. There are criteria that we've used in our

clinical trials that are actually more concerted than what often is used that is in the label that we proposed on our label.

DR. HUSSAIN: And are the LFT abnormalities reversible upon discontinuing the drug?

DR. ROYCHOWDHURY: Yes.

DR. GULL: But in the long-term you don't really mean weekly monitoring after a year or even six months?

DR. ROYCHOWDHURY: For LFTs?

DR. GULL: Yes.

DR. ROYCHOWDHURY: No, we don't. And in our studies with EXTEND and RAISE we've allowed monitoring to be done on a much less frequent basis up to four to six weeks, yes.

DR. HUSSAIN: Okay, if there are no more comments we can go to the vote. Any comments or questions or concerns or issues? Dr. Alving.

DR. ALVING: In a way we're not

really voting on short-term. You know, because this is immediately stretched into long. We still haven't defined short-term because it could be 43 days, and then another 43 days, and then another 43 days. So, we have not -- we're really voting on long-term. Because one just sort of bleeds into the other, if you will.

(Laughter)

DR. HUSSAIN: No pun intended.

DR. ALVING: I mean, does anyone else have this confusion? If I vote for short-term, I don't know really what that means. I know I'll get 43 days worth of, you know, I can treat someone for 43 days. But then the rest of it is just maybe I want to do it another 43 days and another 43 days.

DR. HUSSAIN: It is recurrent short-terms. I mean, it's multiple terms with no term limits. I mean, it's just one after the other.

DR. ALVING: No term limits. We

know where that leads.

DR. HUSSAIN: I mean, no, I agree what you're saying is that there is an open-endedness. And I think that's what probably the FDA is struggling with.

DR. ALVING: Well, if we do that we're going to have to say -- and then we trust the FDA and the sponsor to fix it. I mean, we have to realize what we're voting on.

DR. HUSSAIN: So, the FDA.

DR. RIEVES: That is correct. And that's part of our major angst here. In essence, given the practice of medicine, we're probably looking at long-term exposure. So it gets, at this question of realistically, is it feasible to construct a risk management plan that would involve fairly intensive liver test monitoring for these situations where there is long-term use. And that is the question. Is it feasible to develop such a relatively

demanding risk management program at this time until the other data mature.

DR. HUSSAIN: I mean, to be honest about it, none of the studies I've heard are really, really long-term. I mean, everything that is being done is really slightly longer-shorter term-type thing. And when we're talking about long-term, you're talking, exactly as was pointed out, this is a 10, 15, 20 year event potentially. And there isn't going to be any kind of information there.

So, I don't know that there's an ideal way to vote on things. I mean, you know, there are people who need it, as was pointed out. It's a challenge if your platelets are 2,000 and you need it. And you don't worry about six months from now because you may not be alive six months from now. I mean, that's really where the balance -- Dr. Curt.

DR. CURT: That's why it may be

better to consider voting on the second question first. Because there your judgment is really being directed at the short-term use.

DR. PAZDUR: Do you want to go to question number two?

DR. PERRY: Please, yes.

DR. PAZDUR: Okay. Because I think we've heard your problems with this. And here, again, I think without having basically dug down into the details of a risk management program it's going to probably be impossible to answer question number one.

So, let's just go to question number two. And given the studies that have been presented for short-term use, i.e., the six weeks of treatment, does the clinical data demonstrate a favorable risk benefit relationship? So, the indication would be for short-term use, and there would be a risk management program institute that would ensure that patients are aware of the lack of

information regarding longer use, such as a patient registry, such as an indication statement. You know, these things have to be worked out. But, the bottom line is for the short-term use of the drug, is there a favorable risk benefit relationship?

DR. HUSSAIN: So, may I point out that whichever way the vote goes, if the vote goes in favor, the net effect is going to be the same. Is that people will end up using it. It doesn't matter that we voted on it first as opposed to the first question. Right? I mean, it's going to be out there if, in fact --

DR. PAZDUR: That's kind of a practice of medicine situation.

DR. HUSSAIN: Yes.

DR. PAZDUR: Which is difficult for us to --

DR. HUSSAIN: No, I understand. What I'm saying is I think the sequence of the vote -- I mean, I don't mean to -- I

don't see the point. The point is if the end result was a yes and somehow the FDA decides to approve for a short-term use, it's going to be recurrent short-term use. It doesn't make a difference.

If you noted no. That's -- exactly. That's why I think maybe voting on the first question is more important. But -- because then things would follow.

DR. PERRY: Whatever you wish. You're the Chairman.

DR. HUSSAIN: No, that's okay. Yes.

DR. HARRINGTON: So, you know, as I hear the discussion then, the vote for short-term use is really -- there's an appendix on that vote for short-term use which says that there would be some sort of risk management program -- really a surveillance program. And so I guess my question to the agency is do you have experience with long-term surveillance and

chronic use of a treatment where you really can examine a database to understand long-term adverse effects and act on it fairly quickly? Because this really will require -- as I understand the situation, it's unlikely that there will ever be a control trial over long-term use that will give the kind of data that you would be comfortable with to show adverse effects of long- term use. So your best bet here to get the possible adverse event rate and long-term use is through a risk management plan or surveillance system, whatever it's called. So, have you done that in the past? Do you have confidence you can do that?

DR. BERKMAN: We don't have a risk management program at this time that is quite as comprehensive as what we're looking at for Promacta.

But we do have experience with a number of risk management programs. There's currently 16 products.

I believe there are 16 unique chemical entities that are recognized with risk management programs at this time. And some of those have been on the market for years. Most of those products have risks though that are much more specific than what we're looking at for Promacta considering that there's a number of unknowns.

Does that answer your question at least? Most of these programs are extremely comprehensive, even though -- it's just that most of them have a risk that is much more specific. So, for example, I think some of you were on the Committee when I spoke about Tysabri which has one very specific risk, whereas we're looking at multiple risks with Promacta.

DR. HUSSAIN: Dr. Vose.

DR. VOSE: I don't see any reason that a very comprehensive risk management structure can't be just slightly modified from what is already in place for a number of

different drugs. I mean, all of us deal with these drugs every day that we do have to fill out a lot of forms for and do have to do a lot of information. But obviously, it's very important for patients to be able to get these medications who really need them, and yet we need to capture this information. So I think all of us who manage these patients would be very willing to do that sort of a risk management structure.

DR. PAZDUR: And in answer to Dr. Perry's queries, you know, here again we're not trying to burden people with additional paperwork. And once additional information would come out, this would be a more flexible program where we would then revise it pending on the comfort level that we have with the drug and the longer term data that comes out with these studies that are ongoing. So, it's not a program that is going to be in place and never changed.

DR. VOSE: No, I think given that

information that that would be modified as more information comes in, and not wanting to withhold a very important medication from patients who truly need it, that we need to balance those items.

DR. HUSSAIN: Dr. Szymanski.

DR. SZYMANSKI: Is this vote for adults only that use this drug?

DR. HUSSAIN: Sponsor.

DR. ROYCHOWDHURY: Yes, at this time we have only evaluated this on adults. We are planning studies in children.

DR. HUSSAIN: Dr. D'Agostino.

DR. D'AGOSTINO: I just want to be sure I know what I'm voting for here. I would have said no to number one because I think there is positive data. When we move to number two and we talk about the short-term, are we automatically -- are we all agreed that we're talking about multiple short-term?

DR. HUSSAIN: I think it would be

implicit.

DR. D'AGOSTINO: I was going to say because it seems like from the discussion and from reality there's no way out of it. So --

DR. PAZDUR: This is the same dilemma have discussed internally. It's like which came first, the chicken or the egg here in the Agency. And this is why we brought this really specific question because it is like going around, and around, and around. And that's why one of the issues that we were thinking of is a risk management program that would have, you know, some type of registry or some type of call in where somebody would have to give if they're going to give multiple courses, you know, the laboratory values of the patient. Make sure that people weren't getting --

DR. D'AGOSTINO: So keeping the multiple short-term as implicit, explicitly there's a risk management going to be attached to it if we say yes to this.

DR. PAZDUR: Yes.

DR. HUSSAIN: Just a clarification, both from the FDA and the sponsor. Supposing you decide to approve it under whatever umbrella. When is it anticipated that the drug will be actually in the market for patients to use? And when would the results from the recurrent use trials become available?

DR. ROYCHOWDHURY: The marketed product would be available very shortly after the drug -- after we get an approval. Usually within a few weeks we can make the marketed product available. As I had mentioned, the RAISE study -- the data on that will be available to us probably towards the end of the year. And we can share that data with the Agency very soon thereafter.

DR. PAZDUR: And the approval would be contingent upon a successfully negotiated plan of risk management. This is not done after the approval.

DR. HUSSAIN: So then we're not talking about years and years before you actually have information. From when the drug hits the market and it actually begins to be used until you get your data, we're talking a few months.

DR. ROYCHOWDHURY: Yes, and we will also have, you know, ongoing analysis of EXTEND data, etcetera.

DR. HUSSAIN: Okay, thank you. So I guess I'll have to go back to the FDA and say do you really care to hear our vote on number one?

(Laughter)

DR. PAZDUR: Let's go to question number two.

(Laughter)

DR. HUSSAIN: Okay. I kind of sensed you made up your minds somehow.

Okay, so the question for vote for the Committee is -- before I read the question -- so what's going to happen is

this. When we vote I'm going to ask those who are voting yes to raise their hand and then begin from Dr. Perry until the end, all voting members would say their name and say their vote being yes, so that it can be captured. The hand raise I understand is so that people in the audience will count the votes and see who raised their hands. Correct? Yes. Okay.

So, the question that we're voting on is do the current clinical data demonstrate a favorable risk benefit profile for the use of eltrombopag -- I have to practice this -- eltrombopag -- in the short-term treatment of patients with ITP?

Since we've discussed a lot, I'm not so sure that we have to discuss this one again. So I'm going to request that we go with the vote. And we'll begin again. All of us simultaneously, those who are saying yes, to raise their hand. And Dr. Perry begins with if he raises his hand in yes,

then he says his name and begins the vote.

DR. PERRY: Perry, yes.

DR. HARRINGTON: Harrington, yes.

DR. ECKHARDT: Eckhardt, yes.

DR. BUKOWSKI: Bukowski, yes.

DR. LYMAN: Lyman, yes.

DR. HUSSAIN: Hussain, yes.

DR. MORTIMER: Mortimer, yes.

DR. LINK: Link, yes.

MS. MASON: Mason, yes.

DR. GULL: Gull, yes.

DR. VOSE: Vose, yes.

DR. ALVING: Alving, yes.

DR. SANDLER: Sandler, yes.

DR. SZYMANSKI: Szymanski, yes.

DR. D'AGOSTINO: D'Agostino, yes.

DR. LESAR: Lesar, yes.

DR. HUSSAIN: We have 16 yes. And I believe all voting members voted. Are there any nos that I missed? Okay, so it's 16 to 0.

Any other comments or issues?

DR. PAZDUR: I think we've heard the discussion here as far as, you know, this dilemma of chronic use. I don't necessarily think we have to go back to the first question, unless somebody wants to give additional comments regarding that.

DR. HUSSAIN: I think there were plenty of comments, and I think the concerns were unanimous as far as somehow crafting something there to protect the patients and give some guidance to the physicians.

DR. PAZDUR: And here again, without the specifics of this I think a vote is kind of meaningless.

DR. HUSSAIN: Okay. Dr. Perry.

DR. PERRY: Going back to Dr. Vose's comments, I agree wholeheartedly that all practicing physicians who treat these patients want to have this drug available and will want the monitoring to be done. At the same time, the company is going to make a boatload from this, and I think they ought to

be the ones to pay for the pharmavigilance rather than the physicians' offices. Does the sponsor hear -- could you hear that? I don't think it's fair to say we're going to make the money but you do the work. I think that it ought to be a shared proposition. If you hire people to come around and look at how we do patients on clinical trials as monitors, you can sure hire people to come around and monitor the people who are on this drug.

DR. HUSSAIN: Thank you. Dr. Harrington.

DR. HARRINGTON: I just have a suggestion of how the FDA might spend its boatload of money, as well.

DR. PAZDUR: Small boat.

DR. HARRINGTON: It's a small boat. So we had a couple of instances over the last few meetings where risk management programs are being designed or put in place. And I don't know whether ODAC is the right setting

or someplace else, but I certainly would love to hear more six months or a year down the road about how well those are working and how rapidly FDA staff can turn around to treating physicians adverse event profiles that are building up from the data that are coming in in the risk management profiles.

DR. PAZDUR: Thank you very much. We have been thinking about this, and we're thinking of doing some type of workshop, specifically in oncology. There obviously is a great deal of concern about drug safety in the Agency. Oncology has unique perspectives. Given all of the comments here, we cannot have all the drugs on risk management programs or restricted distribution, or whatever you want. We have to be prudent on what we use. And if we're not prudent, the practice of oncology would be almost impossible to do.

So, we're aware of that, and I think we would like to have perhaps several

workshops, perhaps outside of ODAC and then bringing them to an ODAC meeting. But I think this is an interesting time. We've kind of had, you know, in the past risk management programs dealing with pregnancy issues, with thalidomide and other similar drugs -- Accutane, and then these ITP drugs, which would be kind of interesting to look at and view different types of programs. Also, examples outside of oncology.

DR. HUSSAIN: Thank you. So, if there are no other comments, I guess, on behalf of the graduating class -- the four of us leaving -- it's been a privilege, excitement, although I'm not sure that I want to live it again. And thank you very much. We will adjourn.

(Applause)

(Whereupon, at 12:30 p.m., the PROCEEDINGS were adjourned.)

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