barely function.

I am not permanently immune-compromised because of my splenectomy, which failed to raise my platelet counts for more than three weeks.

A reasonable side effect profile is an essential component to an effective treatment regimen, and from the data I have seen, the TPO mimetics seem to be fairly well tolerated.

I am very much in favor of approval for this class of treatments because they offer a different approach to treatment, one that may work where others fail, and one that does not further compromise the immune systems of patients with ITP.

Thank you.

DR. ECKHARDT: Thank you. Our last speaker in the session is James Bussel.

DR. BUSSEL: Can I get the first slide, please.

My disclosure, my family owns more than $10,000 and less than $100,000 worth of stock in Amgen and in GlaxoSmithKline in trusts that are not under my control and in my wife's IRA. I receive support as a clinical investigator from Amgen, from GlaxoSmithKline, from MGI

Pharma, and from Ligand, which are the companies most involved in thrombopoietic agents.

I have been doing clinical investigation in ITP since October 2nd, 1981, and have a very vested interest in trying to help this field move forward, and I am here on my own because I believe that these agents are very important to use.

One thing that has not been touched on is the effects of ITP on quality of life. This is from a recent publication that Dr. George is on, and it's Dr. McMillan's publication and Janet Nicholson's of people people that are here.

The dark line--I don't know if this is reaching--the dark line on the top and on the bottom represents ITP patients on a different scale of something called the SF-36, which measures a number of parameters of wellness and health care and vitality, and you can see on the top that ITP is less or as bad as people with arthritis, hypertension, and so on, and on the bottom scale it is almost as bad as people even with diabetes.

So I think an unrecognized part of this disease is its impact on quality of life, and these effects are

multiple and some of these we studied in conjunction with Joan Young through a survey in PDSA. There is clearly an organic part that is related to fatigue that we at least so far and I don't think anybody else have understood.

We have thought it might be related to serotonin, but that is part of the ITP itself. Then, there is the anxiety and fear of things happening with thrombocytopenia and, for example, you heard those from Ms. Moriarty about how she felt about it, and then of course as you have heard from a number of the speakers, there are the side effects of treatment.

So I believe strongly that we need new alternatives. I think that these agents are easily the best thing to come to ITP since IVIG in the 1980s, and I am hoping that they will all move forward and be accessible to patients.

I should say that I have entered more patients than I think any other investigator on AMG-531, and I would just like to make one other comment related to the bone marrow issues, and that is that I believe--and I have mentioned this to people at Amgen and people at GlaxoSmithKline--that if we wanted to be able to do more

marrows in adults, we should do them the way we do them in children, as Dr. Kulkarni and Dr. Link are aware of, which is to give short-acting anesthesia, because the biggest drawback in my view is the pain and, in general, there is no reason that a little Versed and a little Propofol wouldn't allow this to be a 5-minute procedure that the patients wouldn't mind at all.

So, to me, that is where we wouldn't have to pay a million dollars for a marrow, we might not even have to pay anything, but there would be a little extra cost of the anesthesia.

Thank you very much.

DR. ECKHARDT: Thank you.

I would like to thank all of the speakers in the Open Public Hearing portion and now we will close that portion and no longer take comments from the audience, so that the panel can actually move forward with the questions, as well as discussion.

Questions to the ODAC and ODAC Discussion

DR. ECKHARDT: Really, the first discussion that we need to have is the panel and I think we talked about it a bit in the morning, but probably not quite as directed, is

to really think about what was the endpoint with regards to durable platelet response rates.

I think the question here is when you looked at the overall bleeding rates, certainly, they weren't as different as the durable platelet responses and whether or not this, in fact, is something that we need to think about is the clinical benefit parameter.

If you look at the severe bleeding episodes, clearly, that was higher in the placebo group. But, overall, if you just asked with regards to bleeding rates, there was much less of a difference than there was in the durable platelet response.

I think the question is, can the durable platelet response be thought of as a surrogate for clinical benefit for this compound. I have actually been thinking about this because I was also a little bit surprised. But, really, when you think about it, in my view, I think that there are so many different reasons that can cause bleeding in a patient.

I think this can be related to concomitant medications, it can be related to underlying illnesses, and I think my concern would be that it would be virtually

impossible unless you did it a priori to really stratify for those types of underlying tendencies.

My view is that I think the durable platelet response rate is a good surrogate for clinical benefit. I would also like to go on and say, having also followed these patients, that the quality of life of a platelet count of less than 10,000, which requires constant monitoring, and you can see how this is affecting the ability to lead an active life, that I think there also is another quality benefit, as well.

I will be happy to take other comments. Discussion on that point?

DR. PERRY: It seems to me that half the people who take this drug have a benefit which is better than we do with a lot of chemotherapeutic agents for other things, and if they have to continue the drug, and we convert what is sort of a chronic disease into a chronic chronic disease, at least one that can by managed by therapy rather than enduring repeated episodes of bleeding, that that is a useful benefit.

So I think this is a worthwhile benefit from the drug, and I think the difficulty of administering the drug

subcutaneously once a week sort of pales against the alternatives. For first-line therapy, I am not this excited about this drug. But, in second- or third-line therapy, I think that this could have an important role.

DR. ECKHARDT: Dr. Link.

DR. LINK: I just would echo the parent of children, since I am a pediatric hematologist, so the impact on life for those people that have taken care of young children, I mean you don't have to worry about slipping on the ice, you can't restrain them, I mean we have to put kids in helmets with ITP and things like that, so I think this would be an enormous benefit in terms of quality of life, and the platelet count really is a very meaningful surrogate.

DR. KULKARNI: I think I echo that wholeheartedly and I hope that studies would be done in children because I think--I mean these are heavily pretreated, some of them are splenectomized and all that.

I think and I hear the mom talking about her child, and I have taken care of such children where nothing really has worked, and besides the parents, the physicians also are very, very concerned about the children, so I agree

that should be taken into account.

DR. ECKHARDT: Dr. Mortimer.

DR. MORTIMER: I think we all agree with you, when you answer the first question, you can't control people's activities, so platelets have to be the only surrogate marker of efficacy.

DR. ECKHARDT: I think we can move on then. I think we agree with that.

Really, the next question is related to what we have spent a lot of time talking about this morning, and that is with regards to the risk-benefit profile. I think we sort of talked about the idea that we would like to envision that there would be some kind of risk minimization program.

Obviously, the down side of that is that you limit access. But, on the other hand, it is something that we feel may be important since there is relative limited safety data. So I think probably, rather than just rehashing the whole discussion, there are some more crystallized bullet points that we should address here.

I think probably the first one would be whether or not the panel generally agrees that this should be limited

to patients with a diagnosis of chronic ITP, and I will take comments.

DR. PERRY: Yes, of course.

DR. ECKHARDT: Looking at the data that we have seen today, I think it is pretty clear that we feel comfortable with that limitation.

The question of documentation of "qualifying" platelet count values, I would assume, Dr. Pazdur, that you are talking about the entry or the entry criteria. I think this goes back to the issue of this often, well, essentially is a clinical diagnosis often made of exclusion.

I think the question here is whether or not you would have the documentation relate to the diagnosis or whether or not you would actually want it linked to a specific level of refractoriness, so to speak.

Comments?

DR. LINK: Again, I will echo myself from earlier this morning. I think that if we feel that this drug should move forward, I think we should be careful that we make the access readily available in such a way that it is practical, again in a way that people can have the drug on hand for use when needed.

I would also again recommend a method of physician education and the physician being the one that has to be approved as opposed to the patient because I think that creates a potentially dangerous and unnecessary delay.

DR. ECKHARDT: Dr. Perry.

DR. PERRY: Yes, I would like to speak against a qualifying platelet count of whatever number. In an individual patient, a platelet count of 50,000 may be sufficient. But, if that same patient has a bleeding tendency, if he has a peptic ulcer, for instance, has some other ongoing problem, then, a platelet count of 50,000 may not be sufficient, and I would hate to deny the drug to somebody whose platelet count maybe, one day, 50,000, and the next 49,000, and have to play a game with numbers and repeating platelet counts until you found one that qualified.

I think we have to allow some room for judgment in medicine, and I think this is a place where specifying a specific platelet count is likely to be more troublesome than helpful.

DR. RICHARDSON: But you are not going to allow people with a platelet count of 70,000 in or 100,000.

DR. PERRY: If they had 70,000 and needed to have brain surgery, yeah, so that is the kind of exception I mean. On a routine basis I wouldn't treat somebody with 70,000, and they wouldn't require therapy. But that is because you and I share the same good judgment.

DR. ECKHARDT: This actually does raise a question, and that is the fact that there will be certain situations where a patient will need surgery or something that requires a higher platelet count, and that relates to the range at which you allow patients to increase their platelet count.

I think maybe that is why you wouldn't necessarily want to pick a specific upper level. But my concern is if you don't have some restriction, about the upper level with so little safety data at the higher doses, whether that would be a concern.

So what I am asking is whether or not you would think for patients in which you do need to achieve a higher platelet count for an invasive procedure, would that be sort of labeled as such, that the platelet count could reach a higher target, or would you just not put an endpoint.

We have been hearing that the threshold would be

50,000. But what is the top end of that threshold? Would you put one?

DR. PERRY: I would prefer not to put one. If I had to pick a number, I would pick 100,000. But again that claims that whoever draws the guidelines understands the entire universe of patients with ITP and all their concomitant illnesses and concomitant medications. I am not that smart.

DR. ECKHARDT: Dr. Kulkarni.

DR. KULKARNI: As a hematologist, another condition which is associated with thrombocytopenia, albeit rare, is type 2B1 Willebrand's disease, and I am just wondering whether either when you have a platelet count or documentation of bleeding, do we have anything to say that should be excluded or at least should be thought about in some of these patients.

DR. ECKHARDT: Comments? Dr. Link.

DR. LINK: I thought we agreed on ITP and we should stick to it. I can think of other disorders where this should work, but I think we ought to prove that it is safe and in the order where it has been tried, and then you can expand.

I mean I think that there are other immune thrombocytopenias that if this works, it should work. I would not open a Pandora's box.

DR. ECKHARDT: So I think what we are saying with regards to the population, that this would not be related or tied to a fixed entry criteria with regards to platelet count.

I think most of us would agree that it looks like the next bullet is really related to monitoring or a registry type of program, and I think we would all agree with that.

I think we did have some discussion about bone marrow biopsies earlier and so I would like comments with regards to whether this would be something, you know, what would be the particular scenario that would trigger further assessment.

DR. PERRY: Well, I think it is important to recognize that most patients with ITP, one, may not have a bone marrow aspirate and biopsy done at any time during their course. If they do, they usually have one done, they don't have another one subsequently, so the reticulin fibrosis issue can't, in my mind, be separated from maybe

the natural course of ITP itself. I mean there is a considerable question there.

So I think that we ought not to mandate routine bone marrows on that basis. Having said that, I think that the issue of a safety effect needs to be evaluated perhaps in a subset of patients who are carefully followed as Dr. Richardson pointed out earlier, at intervals that include a time frame that would make it clinically useful - 6 months, a year, 18 months, et cetera.

DR. ECKHARDT: I agree that the idea, you know, I think the trial that was proposed with sort of prospective monitoring of bone marrow biopsies is a good one. I would just make the case that perhaps the time and frequency of those interventions needs to be more carefully examined, and it may need to be earlier.

Other than that, I would assume that one of the ideas is treating physicians would obviously, when they see a nucleated red blood cell in the peripheral blood or had concerns, would go ahead and assess the patient, knowing the safety data.

Any other comments? Dr. Link.

DR. LINK: Do we know that that 200-patient study

is going to be done with the close monitoring, and I guess I would want statistical colleagues to ask, you know, will it be powered to detect this incidence of reticulin in the marrow.

DR. PAZDUR: We will ensure that it will be done. Probably, we will exercise our new authorities under FDAAA to ensure that this will be done.

DR. HARRINGTON: We have talked about the style of monitoring for the risk management plan, and there are lots of constraints here which will make it very difficult.

I guess what I would urge is to the extent possible, that every patient who enrolls in this is monitored in as close to the same way as possible because it is going to be a small data set, it is going to be relatively sparse, the safety signals are going to be probably weak.

If there is too much heterogeneity in this patient pool, followed on the risk management pool, it may be very, very hard to interpret the data and act on it. So, understanding the need for clinical flexibility here, at least in the first part of this plan, I would urge that it be very carefully thought through and as best as you can do

in an observational study to make it uniform.

DR. PAZDUR: We have had some discussion on that. Obviously, we are going to go ahead with a clinical trial that looks at this. But, specifically, would people recommend as far as this risk management program or restricted distribution program that bone marrow biopsies be part of that as far as an entry criteria or subsequent.

I didn't get that feel from the discussion. That is why this is going to be interjected presently here.

DR. ECKHARDT: I think we were recommending that the study be done, but we felt it was sort of outside the general clinical scope of practice for these patients to have routine--

DR. MORTIMER: Since the reticulin was associated with higher doses and I presume longer duration, is it unreasonable not to get one for people who are on it for protracted periods of time, six months, one year, whatever, to pick a point to look. I mean go where the money is at, the people who are on it longer and high doses.

DR. PAZDUR: One would kind of need a baseline obviously to know where you are at.

DR. ECKHARDT: Which really becomes a clinical

protocol in some respects.

DR. PAZDUR: Yes, exactly, how much does this risk management program or the restricted distribution take on the flavor of a clinical trial? Obviously, that is not the purpose of a risk management program to be a clinical trial. It's two different issues here.

DR. ECKHARDT: My concern would be that would get back to the whole question of restricting access. I think there would be physicians and patients that would have concerns. But, on the other hand, I think going on with the clinical trial where you had prospective, you knew that you were going to get the data, and I think it is clear that that needs to be a well run study that is adequately powered to look at this.

Otherwise, I think the question is what actually triggers you to perform the bone marrow biopsy.

DR. PAZDUR: I would imagine that this type of study--I would like Amgen perhaps just to chime in here--could be an international study. Obviously, there are going to be questions from the EMEA that probably will mirror some of these on the committee here. But here again it gives us quicker access to larger numbers of patients.

Do you perceive a problem with that?

DR. BERGER: Actually, our current plans for this study exactly foresee that because a study of this size in this population, this orphan indication, is not feasible if it is not an international study, so we are planning for that.

DR. PAZDUR: My concern in particular, if the drug is approved, generally, then, it is harder to accrue to a study that is looking, for example, at bone marrows. It adds another complexity of getting on the trial, why should I go on the trial if I could get the drug commercially.

Here again we want to make sure that any type of approval would not interfere with the access to the information that we ultimately need, and it seems if there would be an international trial with a large accrual, both in the U.S. and in Europe, that the number issue would not be the mitigating factor here in getting the information.

DR. ECKHARDT: Dr. Katzen.

DR. KATZEN: I just want to point out that as we think further about the nucleated red cells and the indicators for a marrow, that patients that are post-splenectomy are going to have nucleated red cells, and in

this world of electronic CBCs with more and more of the trainees and maybe in busy offices, not looking at peripheral smears, I think that that is something that has to be a major part prospectively, not retrospectively, because I don't think that the one time you are worried about the blood count and you look at the smear and see nucleated red cells in somebody who has had a splenectomy, you may be reacting improperly.

So I think that prospectively, we have to be certain that we are aware that these patients have nucleated red cells, not because of the drug, but because of splenectomy.

DR. ECKHARDT: Dr. Perry.

DR. PERRY: This is a question for Amgen. Is Amgen planning a pediatric study as well with sequential bone marrows because it seems to me if we are worried about anybody, we will worry about the 5-year-old kid who might be on this drug for years and years, and has a 50-year period of time in which to--hopefully, he will have a 70-year period of time in which to experience side effects.

DR. BERGER: We are finalizing our Phase 1/2 study in the setting, a dose escalation study. We have not

finalized our plans beyond that but we are definitely going to take that recommendation into consideration.

DR. ECKHARDT: I just have a question. People are using Rituxan for ITP, and other drugs. Do we have a sense of how often they cause reticulin deposition? So we don't know, okay.

Other comments?

MS. MASON: I would just like to make a comment from the consumer point of view since all these other things I really don't feel like I can address very well. But I would like to make a comment regarding the risk management program.

For me as a consumer, I am representing consumers, I am really excited to see us looking at things from that perspective, that include the patient in making a decision about what kinds of risks and benefits they are willing to look at.

Many of us will take risks beyond what the general public might think we would when we are sick. Also, I am very pleased and would like to applaud that the sponsor says no direct consumer advertising. Thank you.

DR. ECKHARDT: Thanks.

Other comments? Yes.

MR. PETOSA: As far as levels, when to take it, we are talking about, you know, someone needs surgery, and take it you need a bone marrow to start with. Well, if you going to go start a treatment that you think you are going to be on for a year, you know, the would have, could have, should have, you need to take the conservative approach, get the bone marrow stuff done, so you have a baseline instead of looking back a year later and say we should have done that.

You have got to take the conservative approach to start with especially on an orphan drug right here, and you just can't look back and second guess yourself. Take the extra time and money to set it up.

DR. ECKHARDT: Other comments?

It looks like we do have a vote question here, and that would be, looking at the body of data here, do you really think that there is a favorable risk-benefit profile with this drug in patients with chronic ITP.

Now, the voting procedure is this. If anybody has further discussion that they would like to provide, then, I am happy to call upon them. If not, then, we essentially will raise our hands up for Yes, and then we will need to go

around the room, one by one, with people identifying themselves with their vote. I hope I have that right.

Dr. Link.

DR. LINK: I just have one comment. Why is the "certain" in the question?

DR. RIEVES: It ties into the Question No. 4. It's a lead-in to that, identifying the specific patients is the next discussion topic.

DR. LINK: Okay. Nothing works for everybody.

DR. ECKHARDT: If everybody is ready, we will go ahead and take our vote, so we will start out with a vote of Yes raising your hands, please.

[Show of hands.]

DR. ECKHARDT: Okay. We need to go around the room and identify. You have to keep your hands up.

DR. KULKARNI: Roshni Kulkarni. Yes.

DR. KATZEN: Harvey Katzen. Yes.

MR. PETOSA: Joe Petosa. Yes.

DR. LINK: Michael Link. Yes.

DR. ECKHARDT: Gail Eckhardt. Yes.

DR. RICHARDSON: Ron Richardson. Yes.

DR. MORTIMER: Joanne Mortimer. Yes.

DR. PERRY: Michael Perry. Yes.

DR. HARRINGTON: David Harrington. Yes.

MS. MASON: Virginia Mason. Yes.

DR. ECKHARDT: Thank you. All Yes, 10 Yes.

The next part of the discussion revolves around really what are the clinical characteristics that we feel comfortable with in identifying the patient population with ITP. I would like for us to consider that.

I think we all run into this in various parts of hem/onc and that is, what are we identifying as the intolerant population or refractory population with regards to prior therapy for their ITP.

I would like to hear some discussion, so that we can get a sense of specifically who this is targeted to.

DR. PERRY: Do we have to get into intolerance or insufficient response? There are people in whom, for instance, right off the bat you might want to avoid steroids in somebody who is a brittle diabetic. So they would neither be intolerant nor having failed steroids, but you would sort of want to skip that step.

Could we simply say that if the FDA in all its wisdom approves this drug, that it's approved for second- or

third-line therapy, and not specify had to have failed or be intolerant because then we have to specify what failed and intolerant mean under multiple circumstances?

DR. ECKHARDT: I think that would be reasonable. I think it will be very difficult to identify, to really codify, intolerance and I think refractory could also be very difficult to describe.

Does the panel agree with that kind of approach where it really relates to not front-line, but second- or third-line treatment?

I see a lot of nodding.

DR. MORTIMER: Yes.

DR. ECKHARDT: Any opposed to that?

The next bullet really relates to what we just said, but I guess we do need to consider the splenectomy question. I think we all know that there are patients who will make a choice as to whether or not they will or will not have a splenectomy.

We have seen the data really in the two populations, and so I think we have to consider whether or not this is something that is a requirement, is this just considered part of, you know, one of the front lines of

therapy, that the patient has to have failed, or is this something that should be optional.

DR. LINK: I think the results were better in patients who hadn't had a splenectomy, if I remember them correctly.

DR. ECKHARDT: I think that is true. I think the issue is they are generally less refractory, right?

DR. LINK: Right.

DR. ECKHARDT: But would you not allow patients who now are really stuck, who have had the splenectomy, not have access?

DR. LINK: Oh, no, I didn't mean it that way. I meant that as an all the more so, not the other way around.

DR. ECKHARDT: Dr. Curt.

DR. CURT: I think if we had seen only data in the splenectomized patients that would be appropriate. But it clearly works in both populations, and the operation is not without its down side, so I think it should be in both.

DR. ECKHARDT: I agree.

Any dissenters?

DR. RIEVES: Dr. Eckhardt, to be sure we all have a clear understanding with respect to this last question,

given the situation for a patient with chronic ITP, who is prescribed prednisone, has initial good response but then that wanes after a few months of prednisone, can you characterize the consensus of the committee, would romiplostim then be an option, or should it be an option for that patient who has essentially failed prednisone, if you will?

That is one patient. What about the patient who has sleeplessness, irritability with the prednisone, given those two patients, is the consensus of the committee that romiplostim should be a reasonable consideration at that point?

DR. ECKHARDT: Well, my view is yes, I think of intolerability being something that essentially the patient is failing or not responding, you know, it's a choice. I think we have heard a lot about the side effects, and I think it is difficult to say that the risk-benefit ratio between the prednisone is necessarily worse than what we have seen today.

But I would like some other comments from the committee whether or not they agree with that.

DR. KATZEN: I think that if you take that type of

recommendation too far, you are essentially mandating therapy and not leaving enough room for physician judgment.

I think the comments that we have heard all day really indicate that most of us have an understanding, for example, a patient that--I mean some of the patients that spoke, who had experienced steroids and had severe side effects, whether or not you could even convince them to have it again, I mean I think you have to leave room for physician judgment particularly in somebody that previously has been treated.

If you take our judgment out of it, I think you are going to limit the options way too dramatically.

DR. ECKHARDT: Dr. Link.

DR. LINK: Yes, I agree. I think that part of the reason that steroids don't work is because people stop complying with them because of the side effects, and I think that you have that thing, that individual decisions are to be made between the patient and their physician, so I think that that certainly echoes what I think should be done.

DR. ECKHARDT: I think here we are talking about chronic use and it is associated with many long-term side effects

Dr. Perry.

DR. PERRY: I would also like to mention that intravenous gamma globulin is not without its side effects. And it is also very expensive, which limits its use, and it is also in short supply. So it is not an easy fallback position to say, well, I will just go from steroids automatically to intravenous gamma globulin and, if that fails, on to the next drug.

So I think there has got to be some physician judgment in this.

DR. ECKHARDT: Other comments? Questions?

DR. PAZDUR: I just wanted to address the one issue that was brought up at the open public hearing, which I find quite disturbing, and that is, the boy that could not get the drug.

I find that very bothersome. We have several programs of expanded access and including single patient INDs that we really would like people to utilize. We will be coming out with more guidance on this.

Frequently, however, we hear through the grapevine, so to speak, that the commercial industry, the pharmaceutical industry is somewhat reticent about doing

either single patient INDs or expanded access programs because they fear some type of retaliation from the FDA if some type of side effect is discovered during a period while the drug is undergoing investigation.

As you can see with all oncology drugs or in drugs that we are treating with life-threatening diseases, we take a high degree of acceptance of very severe toxicity, putting drugs out there really that their side effect profile may not be 100 percent characterized.

I really would like industry to come to some understanding that the FDA is really not here to penalize anyone if a rare side effect occurs or some other understanding of the drug. It will be taken in the context of a risk-benefit association.

But we really want to emphasize that there is a need for expanded access programs as well as single patient INDs. And it really disturbs me when I hear that people aren't getting the advantage of our programs because of some ill-conceived or misperception of some action that may occur or may not occur by the Agency.

DR. ECKHARDT: Yes, I was disturbed by that, as well, and didn't know whether or not there were any

regulatory barriers to enrolling a younger patient on these treatment INDs.

DR. PAZDUR: Here again, I don't want to go into the specifics of a case, but I am just making that for a general comment.

DR. ECKHARDT: But that would be a question, when these come out, is there adult versus --

DR. PAZDUR: Not necessarily.

DR. ECKHARDT: Dr. Link.

DR. LINK: Are we finished with the questions? I had that question about--I am still sort of confused about the platelets drop when you stop the drug part.

Is the recommendation going to be that you dose for 12 weeks and then stop, or maybe if it's working you should sort of like keep going?

DR. RIEVES: Well, that is actually an interesting discussion topic because we have had it among ourselves and there were a small number of patients who maintained their platelets after termination at 24 weeks there, so it may enter into the label development there.

I am curious, does anyone else--we don't have a systematic organized database, that the study wasn't really

designed that way specifically. It was just an observation in the follow-up period.

But does anyone have any thoughts? To me, you know, as a clinician, it does somewhat make sense occasionally to try to terminate the drug. Anyone have any thoughts about a taper, if you will, rather than chump with that, or can you share some thought?

DR. LINK: I guess I was enlightened here, because, you know, in pediatrics, this is even the chronic ITPs often remit at some point. I was very surprised to hear that basically, if an adult presents with ITP, it is chronic ITP forever. But if that is the experience, that would tend to make you not want to quit.

We often try to stop doing something and see if somebody will have a spontaneous remission in many pediatric things because we don't want to commit a lifetime of something but I guess we need--I would be more interested to find out how they want to label the drug.

DR. PAZDUR: I really think that this probably represents a lack of information and really probably a need for further study to answer the question because I think, yes, you could venture opinions here. But what is really

the data at the end of the day, so maybe this is something that we really need to look at as far as future studies.

DR. JAMALI: I needed to comment regarding the Study 105 and ask the sponsor about how to match their data with my data that I had in my review regarding the endogenous thrombopoietin levels in Study 105.

Patients on romiplostim really did drop their endogenous TPO level at the end of the study. Median TPO level was lower than the baseline TPO level compared to the placebo patients.

DR. BERGER: Slide up, please.

[Slide.]

This slide does compare--remember I showed you only the pre-splenectomy study before. This slide we need to spend a minute to discuss that.

Here, you see the change of the TPO concentration from baseline to the end of the study, to week 25, and you have the two individual studies, you have Study 105 here, which is the splenectomized study, and you have got Study 212, which is the non-splenectomized patient study.

You have the placebo and the romiplostim-treated patients, and here for both studies. This is a level of

zero. So, zero indicates that there is no change between the pre-treatment levels and the post-treatment level in the studies and we see that, for both placebo and romiplostim, in the splenectomized patient study, the level is actually at zero, whereas, in the non-splenectomized patient study, there is a small, but nonsignificant, difference.

So, this is the data that we have here currently, and we can definitely work with you to reconcile those data with you.

If the Chairman would allow, I think the question of a drug holiday, I think Dr. George wanted to comment on that, if you would allow him as an independent expert to comment on that question.

DR. ECKHARDT: Sure, that's fine.

DR. GEORGE: First, I didn't mean to imply to Dr. Link that we sentence all adults with a new diagnosis of ITP to a permanent thrombocytopenia. But I think it is the typical course in adults and that drives our initial treatment.

Regarding the issue of drug holiday or a fixed administration, the way this has gone in our continuation studies where we have gotten the most experience, where I

have had the personal experience, is that over the course of years, in our experience as long as 3 1/2 years with one patient, the dose adjustment rules basically mandate changes in the administration of romiplostim, so that if a patient has a high platelet count or a higher than the threshold platelet count, there is a decrease.

So some of our patients, one I can think of specifically now, has incrementally decreased his dose of romiplostim during the course of therapy.

I think that is an implication that is consistent with your question and I think does serve the purpose of looking to see whether the spontaneous remission may occur.

I think the way the dose adjustment rules have been adjusted for the clinical trial approaches this problem, addresses this problem, and I think takes into consideration the potential natural history of the disease.

Does that answer your question?

DR. ECKHARDT: Yes. Thank you.

Dr. Perry.

DR. PERRY: On behalf of the people who are going to be prescribing this drug, I would like to ask Amgen and the FDA to try to come to some workable arrangement that

gets the maximum information with the least burden on the physician and the physician's office.

If you want the patient population to receive the drug, it has got to be minimally burdensome. And I would use the examples of the other drugs. Linalidomide is an example as something that is maybe scientifically indicated, but certainly leads people to think about is there an alternative to going through an hour of my time and my nurse's time to get this drug.

I think if you can come up with a workable solution that involves somebody else's time rather than my time or my nurse's time, that would be the best of all. We would like the drug available, but we would like not to have to jump over 10-foot hurdles to get there.

DR. ECKHARDT: Thank you.

MR. PETOSA: As far as what I believe I heard on the discussion on first-line, second-line, third-line, as far as options, I don't feel like we need to force people to take these other options first before trying this.

In my case, small sample, one child, the WinRho put her in the hospital. If someone was going to ask me, I would say you need to stay away from that especially if it's

a child, since I have some experience there.

I personally know two other 11-year-olds that are in the six-month window where they may go in and come back out of it. There needs to be flexibility. They shouldn't be saying they need to do WinRho or IVIG, steroid, do this, especially if we get more data collection along the way. And we have said this, and we stick to it for a year or two before we change it.

So I think there needs to be some flexibility in there.

DR. ECKHARDT: Thanks.

Dr. Kulkarni.

DR. KULKARNI: I just want to make a comment that I think, as I addressed this before, we sorely need surveillance including postmarketing surveillance, plus quality of life issues as Jim has presented. I think it is very, very important in this disease.

I mean just treating a disease, just a platelet count rise itself alone is not important. I think it is the quality of life that really plays a big role.

Life span issues, you know, if you eventually start treating children with this, you know, what happens to

them across their life span with this disease. I think we are, with this disease, where we were with hemophilia 10, 15 years ago. And this is again a population which receives a lot of blood products, so you require surveillance for, you know, IVIG, whatever comes out of that in terms of, you know, blood product safety.

That is just my comment.

DR. ECKHARDT: Great. Thanks.

Other comments, questions?

[No response.]

DR. ECKHARDT: If not, we will close the committee for the day and thanks so much for everyone's participation.

[Advisory Committee adjourned at 2:05 p.m.]