patients with a response usually that is measured by decreased by immunosuppression in approximately 60 percent of patients. It appears to be well tolerated. We have also done ACTH stim. tests. It does blunt the adrenal response, but it doesn't have the same systemic effects. I don't know if this is due to the first pass effect on the liver, but these patients do not become Cushingoid, do not develop the same hypertensive, et cetera, side-effects that patients who, for example, are on metrol or prednisone. It is the only drug that has been added up front that appears to be fairly safe. Studies using such drugs as ATG have shown actually inferior outcomes when they add the steroids up front. This drug doesn't seem to cause that. Again, we used it primarily for further- stage GVHD patients, but it appears to be fairly safe. We think it is useful therapy for both acute and chronic GVHD.

That's my talk. Thank you.

MS. CLIFFORD: Thank you.

CHAIRPERSON HUSSAIN: Thank you. That

concludes the public hearing portion.

MR. KANZER: Can I make a statement?

CHAIRPERSON HUSSAIN: Are you registered, sir, to speak?

MR. KANZER: Can I speak?

CHAIRPERSON HUSSAIN: Were you registered to speak, sir?

MR. KANZER: Yeah. I would just like to make a statement.

CHAIRPERSON HUSSAIN: I don't believe you have been registered. Unfortunately, we have --

MR. KANZER: I am, Dr. Hussain, from Ann Arbor. I do know James Ferrara.

CHAIRPERSON HUSSAIN: That doesn't matter, sir.

MR. KANZER: Do you know James Ferrara?

CHAIRPERSON HUSSAIN: I know Dr. Ferrara.

MR. KANZER: You know, Dr. Ferrara. When was the last time you spoke to James Ferrara?

CHAIRPERSON HUSSAIN: Sir, please sit down. We need to get going.

MR. KANZER: No. Actually, I would like to

say something. Okay?

CHAIRPERSON HUSSAIN: Can we turn off the microphone?

MS. CLIFFORD: Can we cut the mike, please?

CHAIRPERSON HUSSAIN: Can we turn off the microphone, please?

(Pause in the proceedings.)

MR. KANZER: I have a question --

(Simultaneous discussion.)

CHAIRPERSON HUSSAIN: Sir, sir, excuse me. Like everybody else, if you want to speak, at least identify yourself and you're going to have two minutes.

MR. KANZER: My name is Steve Kanzer, and I'm from Ann Arbor Michigan. I work with the University of Michigan, okay. I am familiar with your background, okay, and your association with James Ferrara, okay. Now, you have not disclosed that, have you, in your disclosure as responsible --

CHAIRPERSON HUSSAIN: Sir, if you have something useful to say, please just say it.

MR. KANZER: Yes. Have you disclosed your conflict of interest at the University of Michigan with

James Ferrara?

CHAIRPERSON HUSSAIN: What is the conflict?

MR. KANZER: What's the conflict?

CHAIRPERSON HUSSAIN: Yes. What is the conflict, sir?

MR. KANZER: What conflicts have you disclosed?

CHAIRPERSON HUSSAIN: Who are you, sir? What gives you the right to stand up here and question me?

MR. KANZER: Well, what's your problem? When was the last time you spoke to James Ferrara? When was the last time you spoke to James Ferrara?

CHAIRPERSON HUSSAIN: When was the last time you spoke to anybody?

MR. KANZER: Okay. Yes, I'm sure you've spoken with Dr. Ferrara.

(Pause in the proceedings.)

MR. KANZER: When was the last time you spoke to James Ferrara?

CHAIRPERSON HUSSAIN: Thank you very much. We're going to proceed with our discussions.

MR. KANZER: (Shouting) Can you answer the

question? Can you answer the question?

(No verbal response.)

MR. KANZER: I guess you don't have to feel like you have to answer the question. No, it doesn't matter. Can you answer the question? When was the last time you spoke to James Ferrara?

CHAIRPERSON HUSSAIN: Months ago, sir, and nothing to do with this. He is a colleague of mine and I do not --

MR. KANZER: No, you're a liar.

CHAIRPERSON HUSSAIN: Sir, I'm not a liar, and you have no right to speak to me that way. Okay?

MR. KANZER: Yes, I do.

CHAIRPERSON HUSSAIN: No, sir, you don't.

MR. KANZER: (Shouting) You're killing patients. You kill patients. You sit here and you kill patients.

(Pause in the proceedings.)

MR. KANZER: (Shouting) You're a scam. All you people are. You have blood on your hands.

MS. CLIFFORD: We have called security. They are on their way up.

MR. KANZER: Yes, right.

MS. CLIFFORD: Thank you. If you would, just leave

MR. KANZER: Yeah, yeah, right, right, sure.

MS. CLIFFORD: Thank you.

(Pause in the proceedings.)

CHAIRPERSON HUSSAIN: Okay. I want to apologize to the Committee on this disturbance.

MR. KANZER: (Shouting) Don't apologize.

CHAIRPERSON HUSSAIN: We are going to proceed with our agenda.

Can I have please the questions to the Committee up?

QUESTIONS TO THE ODAC AND ODAC DISCUSSION

CHAIRPERSON HUSSAIN: We normally don't get this kind of excitement up there. I've got to go back and -- no, no, does the audience need a break?

(No verbal response.)

CHAIRPERSON HUSSAIN: No. We're going to proceed.

The question is in relationship with the agent that is before us is specifically based on the data

submitted, has substantial evidence of efficacy been demonstrated for OrBec in the proposed patient population?

Before we discuss the question, I'm going to get back with the FDA requesting, again, clarification for the record because we have new members on the Committee with regard to this magical word of "substantial evidence."

DR. JUSTICE: Okay. I will just repeat what was said this morning, that in general substantial evidence requires at least two adequate and well-controlled studies, each convincing on its own to establish effectiveness. The requirement for more than one trial reflects the need for independent substantiation of the experimental results.

Substantial evidence also may be provided by the results of a single, adequate and well-controlled study when a single, multicenter study of excellent design provides highly reliable and statistically persuasive evidence of an important clinical benefit such as an effect on survival such that a confirmatory study is not ethical.

In all cases, it is presumed that the single study has been appropriately designed that the possibility of bias due to baseline imbalance, unblinding, post-hoc changes in the analysis or other factors as judged to be minimal and that the results reflect a clear prior hypothesis documented in the protocol.

CHAIRPERSON HUSSAIN: Okay. Thank you.

Any discussion within the Committee with regard to the first question?

(No verbal response.)

CHAIRPERSON HUSSAIN: Any comments that anybody wants to make? Yes?

DR. FLATAU: I guess I'm troubled. I mean, I think it's relatively clear that the scientific evidence is not where we would like it to be.

I think if you look at it from what is going to benefit patients, which it seems to me is the important criteria, and it looks like there is probably some efficacy with this drug.

There aren't really any major safety concerns. I think to do another trial to have scientific evidence

is going to postpone this drug for three, four, five years at least. I think that from a patient point of view that is not the right thing for patients.

It is better to get this drug that probably has some efficacy, we think it has some efficacy, we don't have a high degree of confidence, but it probably has some efficacy, and use it.

I think the other thing is that some patients will take this drug if it's approved and they won't be helped or they will fail treatment. I think they won't be that much worse off, and they will go on to whatever other drugs are available to try and treat GVHD, except that they won't be getting BP compounded in corn oil.

I think on balance, from a patient point of view, that approving this drug makes more sense than not approving it at this time.

CHAIRPERSON HUSSAIN: Thank you.

Dr. Perry.

DR. PERRY: I know your story, a little of your story, and I know our position and I think I understand that. I think there is this, the issue before us, but there is also a bigger issue. If we

lower the bar for this drug, then we lower the bar for every other drug.

We, "we," meaning the scientific community as a whole, will never get the answers that we need. I think the only way to get the answer for this drug is to do a proper and appropriately designed trial.

There are thousands of transplant patients every year. I think to do the appropriate trial is a whole lot simpler than it would be in some of the other circumstances we talked about in the last several years I've been on the Committee. I don't think the manufacturers have proved the point. While it may be helpful in some, it hasn't proved its efficacy overall. I think we simply need a better trial, and so I'm not going to vote to approve it.

DR. PAZDUR: I would just like to reiterate that there are alternative mechanisms to get drugs out to people while they are further being studied. One of them would be a treatment IND.

It actually allows the Sponsor even to recoup their costs for manufacturing the drug and for some developmental costs of the drug. That can be a very

large treatment, single-arm trial.

Here again, one of the questions that I have, if that would be ongoing, would people even consider doing another trial? Would another trial be feasible to do? That's another issue.

CHAIRPERSON HUSSAIN: Is this an issue you want us to discuss now, or this is an issue that we want to discuss after the vote?

DR. PAZDUR: Probably after the vote or it can be discussed during the vote.

(General laughter.)

DR. PAZDUR: It's really going to be part and parcel of a decision here.

CHAIRPERSON HUSSAIN: Yes. Just a point of clarification. If someone gets an IND for a specific treatment, who pays for the cost of the drug?

DR. PAZDUR: Usually, the Sponsor would assume the cost of that. Under the treatment IND mechanism, however, which is a special type of expanded access program, there can be some cost recovery on the part of the Sponsor. We would entertain in a situation such as this that type of program.

CHAIRPERSON HUSSAIN: Is the Sponsor planning, or has any studies in progress?

MR. RODELL: There are no studies currently in progress. The possibility of other studies has been discussed, but I would like to ask Dr. McDonald to talk about the relative likelihood of being able to repeat any of the studies that have been done so far.

DR. McDONALD: I think there are two, perhaps three issues. One is the ethical issue. I'm not sure my IRB faced with published literature of efficacy in treating GVH and the survival benefit would approve a placebo-controlled trial entering these same kind of patients.

The practical issue is I would have to write a consent form that explains this to patients. I'm not sure accrual is practical when I have to put into my consent form what's in the literature. We have three publications in the literature, the Phase I, the randomized Phase II, and this week in blood the randomized pivotal trial.

I think this is perhaps open to discussion, but I don't think a placebo-controlled trial can be done

in this group of patients for ethical and practical reasons.

CHAIRPERSON HUSSAIN: Could you not consider doing a trial, not placebo-controlled but with equivalent doses of steroids to make the point that your agent has a superior profile with regard to infections, complications of steroids, and things of that sort? It doesn't have to be necessarily a survival-driven trial but an efficacy trial?

DR. McDONALD: I think that is a consideration, but actually there are some data that bears on the question. If you look at the placebo arm of 875, you will discover that 41 percent of people required only 10 days of prednisone. If you look at the placebo arm of the pivotal trial, 55 percent required only 10 days of prednisone.

I think it is very difficult to argue that a high-dose prednisone regiment would benefit any of those patients who required only 10 days of prednisone. I think the same ethical issues exist in doing a very high-dose prednisone versus this approach.

We have already proved, I think, that the

minimum prednisone approach protected by BDP has far superior results to our 25-year standard of care. Again, it is not the GVH that is killing people; it is the treatment for GVH that's doing the job.

I think we have adequately proved that BDP has a steroid-sparing effect. I'm not sure I can go back 25 years in time and grab our old regimens. I am quite convinced. I think it might well be unethical to do that kind of a comparison.

DR. RODELL: Excuse me. Dr. Sullivan from Duke was actually not involved in the trial.

CHAIRPERSON HUSSAIN: I just have another question, though, please. If you say you don't want to go back to the past and grab old regimens, and if your drug is currently not available on the market, and we have heard that people use the oil-mixed product with something, is that what people are currently using? Is that what the alternative out there is?

DR. McDONALD: The alternative is what I call the ad-hoc way of formulating something that is similar to what we are using in these trials, that is, to use the corn oil combined with budesonide.

At our center, this is written into our standard practice manual, this is how we treat GVH that presents with nausea, vomiting, diarrhea, and anorexia.

We do this kind of make-it-up-ourselves approach that approximates what has been done in these two randomized trials. It is our standard of care because my transplant oncologist are firmly convinced by the data having seen patients on this approach.

CHAIRPERSON HUSSAIN: Thank you.

DR. SULLIVAN: Thank you for the deliberations and the comments. No, we can't use the corn oil, and it just can't be tolerated. What I would like to do is kind of give this in a 30-year context.

You certainly are right in saying you don't want to lower the bar. The difficulty is that shifting time line from day 50 to day 80 where you do have a positive efficacy, and so that's a conundrum for you.

The other is, why does it work in non-myeloablative better than the other? We don't know, but I think what I would like to do is put it in context as a transplanter. I just updated the Thomas textbook on graft-versus-host disease, and so these are fairly

current.

In the last 25 years, there have only been 30 worldwide trials with GVHD as a readout. Eighteen of them were for prevention of GVHD where the readout is GVH, yes or no, and twelve have been for GVHD treatment.

Of those 30 trials, only five trials had a survival advantage proven. Of those five trials, only one was in treatment of GVHD, and that was the 875 BDP Study.

I would urge the group to kind of look at the totality. You said it. Look at the totality of evidence, see how that fits within the framework of keeping rigorous studies.

To show a day 200 reduction in mortality of 71 percent, a one-year reduction in mortality of 46 percent in the context of prior GVHD treatment trials has just not been seen. That's why this is a really important deliberation for you, and I appreciate your deliberation.

CHAIRPERSON HUSSAIN: Thank you.

Yes, Dr. Richardson?

DR. RICHARDSON: This trial included the 00-

02 trial, included a number of patients with renal cell carcinoma, all of whom I assume would have gotten the non-myeloablative regimen. If you take out that group, what do these numbers look like? Presumably, these folks have a different immunologic makeup.

MR. RODELL: Mr. Cruickshank.

MR. CRUICKSHANK: Yes, let me just briefly respond. There was one patient that had renal cell carcinoma in the study.

DR. RICHARDSON: Okay.

CHAIRPERSON HUSSAIN: Dr. Mortimer.

DR. MORTIMER: I think we keep perseverating (sic) on this distinction in the non-myeloablative regimen. I wonder what the complications were in a non-myeloablative group versus the marrow-ablative group?

I mean, I truly want to embrace the notion that this drug is superior and it does preserve the complications of long-term steroid use.

But as I look at the briefing documents, there was more hypertension in the BDP arm. There was more bacteremia in the BDP arm. There was more hypercalcemia.

I'm having a hard time buying that even though I thoroughly agree that there were fewer fungal infections in the group that got BDP.

Was that because there was a non-marrow-ablative group, and therefore they had a better immuno-constitution and were less likely to get fungal infections? I'm having a hard time buying that argument.

MR. RODELL: Let me comment briefly on that. I think, first of all, the adverse events rates are low enough that it is a little bit difficult to look at them from a subgroup perspective, but let me address some of the specific ones that you have raised.

With respect to hypertension, hypertension was reported as an adverse event more frequently in the BDP arm, although the numbers are very small and the differences are small.

But when we actually went back and looked at the individual blood pressures in all of the patients, and we checked blood pressure at every single clinic visit and looked at change over time, looked at the individual ranges all of those, there is no difference

between the groups.

With respect to the laboratory values also that were reported more frequently as adverse events, and those included hypophosphatemia and hypocalcemia. The medians and the ranges and the frequency of treatment-emergent abnormal values, almost no difference between the group. We think that that actual represents reporting bias rather than anything meaningful.

I think the two areas that are a little bit difficult, more difficult, to address are we can't really say very much about fatigue because there is no laboratory test that we can do for that. There may be a couple of other ones.

CHAIRPERSON HUSSAIN: Any other comments or discussion points?

Yes, sir.

DR. FLATAU: I just wanted to address Dr. Perry's point about efficacy and lowering the bar. You know, I'm an AML survival, that means I participate in here. It's a rare admission. I have been on three panels now and at several teleconferences, and I think this is the first time I've heard about a randomized

trial.

Yes, I am worried about lowering the bar. I'm waiting for some drug company to come up and say, "Well, we have one patient we treated and we want to prove this drug." That seems to be where it's going.

I think that this is certainly far from the bottom in terms of what has been presented and what's been done. I guess I want to reemphasize the point that for patients I think they have to realize that even if we do another trial and it's positive, it's still kind of a crap shoot. The best guess we can make now is that it probably is going to benefit some patients, and we should approve the drug.

CHAIRPERSON HUSSAIN: Just a clarification point again. We are not voting to approve. That is not our role. We are an advisory to the FDA. Our role is to vote on the question of substantial benefit, and I think that is what we are stuck with.

You have to take it into the context of the question and not so much into the big picture, recognizing in the last two and a half years that I've been on the Committee there have been votes when

overwhelmingly we were against something and the FDA approved it anyway.

(General laughter.)

CHAIRPERSON HUSSAIN: They don't necessarily always listen to us. Thank you.

If there are no other burning questions or comments, I'm going to try to ask that we go ahead to the vote.

Put the question up again, please.

(Staff complies.)

CHAIRPERSON HUSSAIN: We will begin around the table. No description of why one is voting yes or no, just the vote yes or no. Identify please yourself and speak clearly into the microphone.

Dr. Link, can we begin with you, please?

DR. LINK: Michael Link. I vote no that it has not shown substantial evidence.

MS. HAYLOCK: Haylock, no.

DR. HARRINGTON: No.

DR. MORTIMER: Mortimer, no.

CHAIRPERSON HUSSAIN: Hussain, no.

DR. RICHARDSON: Richardson, no.

DR. PERRY: Perry, no.

DR. SPORTES: Sportes, yes.

DR. FLATAU: Flatau, yes.

CHAIRPERSON HUSSAIN: Two yes, seven no.

Dr. Pazdur, do you want us to go into the second issue of design, of study design?

DR. PAZDUR: We've already started the discussion.

CHAIRPERSON HUSSAIN: Yes, but I thought it was for discussion, not for a vote.

DR. PAZDUR: We've already started the discussion.

CHAIRPERSON HUSSAIN: In terms of what ideal study design is?

DR. PAZDUR: Yes.

CHAIRPERSON HUSSAIN: Maybe I can begin and ask the sponsor first, when you look at your data and you look at what you started with and then what you got, what do you think, like in your gut with yourself looking at this, where do you think your strongest point was? Because that seems to me where you should then go back to look at that area because that may be where

you're going to get your real clear answer.

DR. RODELL: Well, I think the two strongest points are the time-to-treatment failure through study day 80 and the mortality. I'm going to ask Dr. Gooley to address the issue. We think that attempting to power a study for mortality is probably not something that can actually practically be done.

DR. GOOLEY: Yes. Ted Gooley, Fred Hutchinson Cancer Research Center. Thanks, Dr. Rodell.

As Dr. Rodell indicated and as you probably know, power for time-to-event endpoints is driven by the number of failures. If we tried to power the study for mortality, the power would be driven by the number of deaths, and a number of assumptions would go into estimating power for time-to-event endpoints.

We don't know exactly the population that we would do a potential future study in, so we don't know for certain what those assumptions would be. But if we make some very simple assumptions, for example, if we assume that the true hazard ratio is 0.7, that would require, roughly, 330 deaths, not patients but deaths.

If we assume that the true hazard ratio is 0.6

between treatment arms, it would require, roughly, 160 deaths and a true hazard ratio of 0.55 would require, roughly, 120 deaths. The accrual would be quite substantial.

CHAIRPERSON HUSSAIN: Any words of wisdom from committee members as far as study designs or suggestions to the Sponsor or to the FDA with regard to what they should advise them to do?

Sir?

DR. FLATAU: Yes. I would like to think at least a secondary endpoint of overall survival at least at one year, if not longer, would be interesting.

CHAIRPERSON HUSSAIN: I guess the only concern I have about survival is unless you make the population entering very uniform with the same diseases, the same regimen, the same everything, you are never going to be able to interpret the results, it would seem to me, unless you stratify very clear where you include several groups of people clearly stratified equal in each arm. I can't see how you would do it if you argue that we don't have a huge population.

DR. SPORTES: Actually, I was wondering and I

should have asked earlier why the secondary endpoint was not the primary endpoint.

It seems to me from a transplant perspective that a followup at 80 days is probably the strongest endpoint, which is why I voted yes is because I think to me conceptually this is much more a reflection of the entire intervention. Why was that not chosen? I just seek some explanation.

DR. RODELL: May I respond to that?

CHAIRPERSON HUSSAIN: Yes.

DR. RODELL: I think it's important to recognize the history of how this drug was developed. The initial study, the initial efficacy study was Study 875 that was done essentially on a completely open field, that is, this type of study had never been done before and so the 30-day endpoint was selected in that study, essentially, arbitrarily.

Once the results of that study were know, Dr. McDonald spoke with and talked to the FDA, shared with them the results of that study and began to design the 02 Study.

The two components with respect to efficacy

that were requested essentially by the Agency at that time were to extend those to see if the percentage of responders could be increased, whether the signal could be amplified, and then to look for durability of response, that is, to make sure that the patients the moment they came off the drug didn't immediately fail treatment.

The 50-day endpoint was an arbitrary endpoint at the time. No previous trials had been done that looked at like this. The day-80 endpoint was simply done to add 30 days to demonstrate durability.

I think that, as we discussed before, very clearly the failure to reach the 50-day endpoint was based on what happened in the first 10 days, what is essentially an imbalance and loss of power, as Mr. Cruickshank said, in the first 10 days.

If you will indulge me for a minute, I think one of the things that is important for us to point out is that this is a patient population of 7,000 patients a year. This study took three years to enroll and half of the patients had to come from the Fred Hutchinson because it is such a busy center.

The practicality, even without getting into the economics of doing another study, is going to be a significant issue in terms of the future development of the drug.

CHAIRPERSON HUSSAIN: Thank you.

Any other comments?

(No verbal response.)

CHAIRPERSON HUSSAIN: Well, we will begin with Dr. Link, then, and we will go around the table.

DR. LINK: I have two. The first is a question of what if you actually -- the mistake maybe was that you started the clock too soon in terms of you started on the day of randomization. Either if you if you had randomized after the 10 days and only randomized responders -- Dave, you're not going to shoot me here, are you?

The second things is to actually do an analysis, start the clock when they achieve remission and throw out people who didn't achieve remission, which is often done in transplant studies. That would be one suggestion.

What does it look like? Does it look better?

Does it look like you had achieved your goal, just out of curiosity?

DR. RODELL: Yes, let me ask Mr. Cruickshank to address that.

(PowerPoint presentation is in progress.)

MR. CRUICKSHANK: Going back to that question about, what is the effect of those early failures, we did do an analysis to look at the effect whereby patients who failed during the 10-day high-dose induction period of prednisone.

If you sensor the patients at the time of treatment failure, you can see here that we lose the effect of the crossing Kaplan-Meier curves. We have a fairly clear, sustained difference between the arms at day 50 as well as day 80.

DR. LINK: You should have presented that. Second of all, I was impressed with the ability of the bone marrow transplant community to do study with soft-tissue endpoints, a lot of patients, a "New England Journal of Medicine" article, very prompt approval.

I'm just wondering why you're so discouraged about doing a trial like this? Admittedly, not

everybody gets bowel GVH. But if you're transplanting 60-year-olds, you probably will get a lot of it. I'm just wondering why you're so pessimistic about getting it done? We're going to do it in pediatrics, and we don't have that many patients.

DR. McDONALD: I'm pessimistic about doing a placebo-controlled trial because I don't think we can get our IRB to approve one based on these data. I think there are other options.

I mean, we have thought about a prophylaxis trial, for example, but that's a different indication, though. This indication is for treatment of acute graft-versus-host disease. A prophylaxis trial is for prophylaxis of acute graft-versus-host disease.

From the FDA's comments, you don't like merging of different kinds of trials to come to a conclusion. That would take, what, two placebo-controlled prophylaxis trials for that --

DR. PAZDUR: We are always open for negotiations.

(General laughter.)

DR. McDONALD: All right. That's one thought,

that is, if this drug is as highly effective as a topical therapy for treatment, it should be equally effective and relatively nontoxic as prophylaxis. I think that is one potential option.

CHAIRPERSON HUSSAIN: Gee, prophylaxis sounds like very attractive. Why wait until an event happens? I mean, that would be a clinically meaningful endpoint.

DR. McDONALD: I agree. Plus, it's easier to enroll patients who aren't sick.

CHAIRPERSON HUSSAIN: Correct, correct.

DR. McDONALD: You can get a larger accrual. Seven thousand patients should provide enough to enroll. The hope there is that one would with effective prophylaxis take what would ultimately be Stage IV and turn them into Stage III, take Stage III and turn them into Stage II, take Stage II and make them end up being Stage I. I think that is a feasible thing. I can't speak for the company.

I think there are some financial issues. This is a relatively small company, and I think that is a consideration. In addition to the ethical and practical issues, I think there are financial issues.

DR. SCHABER: Dr. McDonald -- Chris Schaber, president of Dor Bio Pharma -- that is in fact the issue. For a company our size, we've put a lot of time, effort, money, and resource into this study to support Dr. McDonald and the rest of the investigators to go after an indication that, quite honestly, big pharma didn't want to touch because it is a very small patient population.

Although, as was outlined here and the experts have spoken, we did not achieve the primary endpoint without maybe the right sensoring or guarantee period.

With regard to the direct correlation of 80-day as well as survival, which as Dr. Sullivan has clearly stated in all of the trials that have been done has never been seen, this is really an important trial for us. To move forward from here and start over is really economically not feasible for us with this product.

CHAIRPERSON HUSSAIN: Dr. Mortimer.

DR. MORTIMER: Yes. My suggestion was going to be a prophylactic study, but also it seems to me that the biggest selling point of this drug is that it

minimizes toxicity of steroids.

However the study is designed, a comparison of this agent against steroids, if you demonstrate an improved toxicity profile, I can't but imagine that it would move farther up in line for the indication indicated here today.

CHAIRPERSON HUSSAIN: Okay. If there are no other questions, I think that the FDA -- I'm sorry, Ms. Haylock.

MS. HAYLOCK: I just wanted to suggest that since some of the side-effects that were of concern to people, for example, fatigue and then also some of the other psychosocial issues, that some of our public presenters brought up, there are quite a few psychosocial tools or instrumentation available that could be pretty easily incorporated into any trial. I would suggest doing that. I think that would help as well.

MR. SCHABER: May I say one more thing, please?

CHAIRPERSON HUSSAIN: (Chairperson moving head up and down.)

DR. SCHABER: Dr. Pazdur had pointed out a treatment IND and I wanted to maybe put out another possibility of an accelerated approval type of mechanism where we could follow along with Phase IV follow-on studies, but be able to have the drug available to the patients and out there and marketed for the current indication while we do follow-on studies.

CHAIRPERSON HUSSAIN: He did say he negotiates.

I think we will conclude now as there are no additional comments or questions. I assume the FDA got all their questions answered. I am going to raise a question with the FDA, and this is not stimulated by the excitement that just happened a minute ago, but it began actually at lunch. We were chatting about it.

Considering the two votes that went here to considering the two cases that were brought in front of ODAC and understanding the advantage of transparency, public education discussions and such, what I get from the last two and a half years on this Committee is that not meeting your primary endpoint is a fatal flaw.

Barring some surprising, phenomenal benefits

in survival, and we've seen some survival advantages but nothing spectacular, barring something like that, what would be the point in bringing these discussions forward?

DR. PAZDUR: I think to get public input on and for discussion of points that may be missed by the FDA reviewers. I am very thankful for the discussion that we had today.

Personally, this drug because of this discussion, irrespective of the vote, has a much different impact in my mind. We will have discussions internally on this drug and discuss the points that were presented here.

CHAIRPERSON HUSSAIN: Thank you.

Dr. Perry, a final comment.

DR. PERRY: Yes.

Dr. Pazdur, could I ask that we have security next time?

DR. PAZDUR: I had asked for that previously, and I will ask the executive secretary here to contact her supervisors to ensure that. Please resend my email that I sent to your boss.

CHAIRPERSON HUSSAIN: Dr. Pazdur, can they come with me until I get to Ann Arbor to my home?

(General laughter.)

DR. PERRY: The members of this Committee, if we get paid anything, it's lost in the expense accounts.

DR. PAZDUR: I actually apologize for that.

DR. PERRY: Yes. We perform this as a public service. We take a lot of grief from the public, the people who speak, many of whom speak off topic and look at this as a bully pulpit to criticize the members. I think at the very least we should be secure. We should have some degree of security so that our Chairman is not threatened.

DR. PAZDUR: I couldn't agree with you more.

DR. PERRY: I didn't think we would differ on this issue.

DR. PAZDUR: I could not agree with you more, and I have brought this up to the FDA management staff. I am directing Ms. Clifford to tonight to please contact her boss. I think it is imperative that even before the next meeting, tomorrow, our next session, that something be in place.

CHAIRPERSON HUSSAIN: Is that the Department of Defense I hope?

(General laughter.)

CHAIRPERSON HUSSAIN: Okay. Thank you very much. We will adjourn.

(WHEREUPON, at 4:28 p.m., the meeting was adjourned.)

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