is one patient who -- and this is really to address an issue that we thought is important as CGI just as surrogate for chorea, and I think this shows that it's really not. We have several examples of this. The -- sorry. The red bar is the change in the global instrument in the CGI, and we see it starts at 4 and goes down to 1 in this patient.

And if you jump over to this plot, I apologize, this is the change in the patient's chorea score over that time. So they're going from a baseline of 10 down to around 67. The patient experiencing adverse event of restlessness at week 7 and we see that without a significant change in their chorea score from 7 to week 12, their CGI too shot up to about a 6.

So it really suggests that the investigators were not just looking at chorea, but were really looking at other measures than -- other things than chorea -- side effects and other measures as well.

Okay, those are the additional slides that we've been able to prepare.

MR. GOLDSTEIN: Thank you. Before we turn to the questions, I'd like to just invite the committee again if there are any other questions that they'd like to ask for clarification, any other information from the sponsor or from the FDA before we begin discussing the questions. I just wanted to give you the opportunity to do so. Dr. Couch.

MR. COUCH: One quick question. The question of -- the rate of titration, will there be a recommendation from the company as to what the rate of titration should be -- should it be once a month as was suggested by one of the speakers or once every two week, what?

MR. STAMLER: Well, I -- it certainly couldn't be any faster than once a week, I think perhaps once very two weeks could be a reasonable approach, I actually

might want to ask Dr. Jankovic to comment, because he's probably got more experience than anybody in terms of how he titrates his patients.

MR. JANKOVIC: So I'm just going to answer based on my long term experience over the last 25 years in -- well over a 1,000 patients. Generally, I start a patient on 12.5 milligrams, and then once a week, I increase it by 12.5 milligrams with careful instructions to the patients to let us know as soon as they experience any adverse effects, and then usually I hold at about 50 milligrams, and then ask the patients to come back reevaluate them and then see if there's any need for further increment in the dosage.

MR. COUCH: That was another question. That is with many other chronic illnesses we find that over a period of time it may be necessary to readjust the dose after 6 weeks or 24 weeks or 48 weeks, we see that in headache preventative medications all

the time, occasionally with seizures, do you find that with tetrabenazine?

MR. JANKOVIC: Absolutely, and part of our protocol, actually, is to periodically, actually lower the dosage to see if there's any need to continue tetrabenazine, because in some cases, because of the increasing rigidity, the chorea actually improved spontaneously, so there's less need for tetrabenazine. So it's really, really important to individualize the dosage, and to adjust the dosage, you know, as needed periodically, but I think it should not be increased anymore frequently than once a week.

MR. GOLDSTEIN: Dr. Koski.

MS. KOSKI: Yes, would there also be a protocol for reduction for a perceived side effect or adverse effect?

MR. STAMLER: That's a good question as to whether or not that should be specified as to how to reduce it or to rely

on clinical judgment, I mean, I think from a labeling standpoint, the recommendation would probably be for the clinician to make that decision based on their -- based on the individual patient number, on the severity of the adverse event.

But I do think that with any adverse event that that is of any concern to the investigator that suspension or dose reduction is appropriate. I don't know that we would want to be so specific about saying that you would reduce it by x percent, because I -- again, I -- and I don't know -- maybe Dr. Jankovic can comment, if someone has an adverse event, how he would approach that.

MS. KOSKI: You know, my way of looking at this is that you're going to go from a few centers that have a great deal of experience, and have seen a number of patients to centers that may have only seen a very limited number of patients, and I think

particularly in the beginning, you know, if you are going to set up a RiskMAP, it would be wise to set up a number of parameters, some ideas about what are examples of what you consider are more severe versus less severe. I know it sounds a bit cookie cutter, but I think that, you know, that type of thing, you know, at least makes other treating physicians aware of what's expected of them.

MR. STAMLER: Right. No, I -- we're certainly amenable to any, you know, any logical thing, so we can put in the label that will safeguard the patients. I just -- I can't tell you what those are right now.

MR. GOLDSTEIN: Yeah. And I believe, the way the questions are laid out, we'll have fuller discussion about these types of issues later depending upon the votes that we take earlier on. Any other clarifying questions -- data questions, Dr. Hurtig.

MR. HURTIG: On the matter of long term observation and supervision of these patients, there are a couple of small matters that came up including the prolonged QT interval, and a few patients had abnormal liver function tests, is there any plan to advise for periodic monitoring of -- on those matters?

MR. STAMLER: I'll -- maybe comment on the liver enzyme issue and then I'll ask Dr. Kowey to comment on -- whether or not he thinks, you know, what sort of cardiac monitoring. Right now the proposed labeling has -- well, let me go back to the clinical trial. The one patient who had a -- what I think is a clinically significant increase in liver enzymes, had abnormal liver enzymes at baseline, and was involved with binge drinking around the time that his liver enzyme abnormalities decreased.

That subject actually stopped therapy and then ultimately reenrolled in the

trial, in the long term extension and did okay. Our proposed labeling, not for this patient, but for metabolism reasons has a contraindication to patients with significant hepatic impairments. So it's not our belief based on what we've seen in the clinical trials, that liver test monitoring is something that's required. Dr. Kowey, would you comment on the cardiac monitoring issue?

MR. KOWEY: My name is Peter Kowey, I'm an electrophysiologist for Philadelphia. It's a great deal of pleasure that I have an opportunity to address this issue, because it has been a point of concern with regard to the FDA reviews. If I could -- if you could get slide S62 ready for me and S57, okay -- not -- yeah. First of all, the comment that Dr. Bhattaram made regarding the exposure, and the information we have about the QT interval was absolutely correct.

We do not have data that tell us what would happen to the QT interval under

conditions where patients were receiving a 100 milligrams of this drug in the presence of full metabolic inhibition with a 2D6 inhibitor. However, having said that I believe the company has really done due diligence in trying to completely understand the issue of the Qt interval within the constraints of what they've been able to do in clinical trials, if I -- and pre-clinical information -- if I could have the slide up please.

This is a slide of the hERG assay. HERG is an assay specifically to examine the effect of the drug on the most commonly influenced current and -- by drugs that prolong the -- the non-cardiac drugs that prolong QT interval and cause torsades, that's IKR. What you're seeing here is the IC50 for the hERG effect for the parent compound, the alpha and the beta metabolite. What you're seeing on the right of the -- concentrations that one might achieve with a

100 milligram dose under conditions of 2D6 inhibition modeled, because obviously, these data are not available clinically. What you see on the very right-hand side is the ratio of the IC50 to the Cmax that might be achieved, the assumption being that it is the Cmax, which is the concentration of interests and concern, and you can see that for both of the metabolites, the alpha and the beta, there is a more than 30 percent --

Times or 30-fold difference between the IC50 and the Cmax that might be achieved. We, under usual circumstances, consider a 30-fold difference to be somewhat reassuring. If I could have the next slide please.

I apologize, this violates every principle of slides, and the kind of information you should put on slides, but I use this slide, because it is the composite of all the information that we have, clinically, with regard to the QT interval. There are actually three studies, and David

showed you data from 015 and 018, I also included the 017 study. 015 was the Thorough QT study, the 017 study was the study with the metabolic inhibitor, 25 milligrams with the Moxi comparator with -- in a placebo, and then the final study, the 018 was the second DDI study using 50 milligrams plus paroxetine, compared to 50 milligrams alone without a placebo and without a Moxi comparator.

What I would point out to you is that across the board for all of these studies, which were studies that reflect what we think will happen when this drug is used at its proposed labeled indication, that in fact there really isn't a whole lot there. The upper bounds of the confidence intervals for the most part as you can see here, scrape along around 10 in the Thorough QT study and are approaching 10 in the second DDI study.

I'd also point out to you -- and the reason I'm showing this slide is because

there's very important outlier information here. There are no patients in any of the studies who had values that exceeded 500 milliseconds, and there are no patients across all of these studies who had values that changed the delta greater than 60 milliseconds, which are the areas of major concern in the guidances that we use to that judged the importance of a QT effect.

So the other reason why this is important is because in order to do what the FDA has suggested that we -- that might be done, that is to study a 100 milligrams in the presence of maximum metabolic inhibition, could not be done with single dose, because a 100 milligram single dose is not tolerated. Consequently, use -- we'd need to use multiple doses. The problem with multiple doses is that your baseline values are far removed from your observed values and it introduces a level of variability that we simply don't like to see in Thorough QT

designs.

So it would be very difficult to do a high dose of thoroughly inhibited study in a Thorough QT design that we will be able to interpret. Thus, I would conclude for myself that I'm very comfortable that we have adequate information that in the presence of maximum doses of this drug -- and you heard David earlier tell you that there are plans to warn physicians not to use 2D6 inhibitors in the presence of maximum concentrations.

With that labeling stipulation, I think we have adequate information to be reassured that the likelihood of a long QT causing torsades, especially with the information from all of the clinical trials in which there's never been a case of torsades, and from all of the spontaneous adverse event reports in which there's never been a case of torsades, that this drug can be safely used at its -- at the concentrations that are being recommended.

Dr. Katz.

MR. KATZ: Yeah, maybe you can educate me. It's true that nobody went above 500 and nobody had an increase greater than 60, but for the other sort of intermediate outlier criteria or less severe outlier criteria, you see the same thing on tetrabenazine as you do on moxifloxacin, so --

MR. KOWEY: Yeah.

MR. KATZ: Does that mean anything?

MR. KOWEY: No.

MR. KATZ: Okay.

MR. KOWEY: It's --

(Laughter)

MR. KOWEY: That's the short answer.

(Laughter)

MR. GOLDSTEIN: Short is good.

MR. KOWEY: No, well, just to be clear, the thing you really want to be concerned about moxifloxacin is what kind of

an effect it generated on its central tendency. And you can see that it's right in the middle of where you expect Moxi to be with an upper bounds of about 15 milliseconds. So I have no -- I have great confidence that Moxi did what it's supposed to do. In any individual experiment, Moxi may push you over 500, and it may push you greater than 60, but not every time.

MR. KATZ: Okay.

MR. GOLDSTEIN: I just have two quick questions for clarification, and then I think we can move on to the FDA's questions. One, at the -- when this -- the primary study was done, were the assessments done by an investigator who was blind to the treatment phase of the trial, or was it done by the investigator who was also treating the patient?

MR. STAMLER: Excuse me. The CGI rater was not blinded to the treatment. I don't know if we captured the data

specifically about whether it could be the investigator, but I --

SPEAKER: I'm sorry -- didn't hear the question.

SPEAKER: -- sorry --

MR. STAMLER: Well -- I'm sorry. Was it blinded to treatment or blinded to the patient's --

MR. GOLDSTEIN: Blind -- in other words, was the person who was doing the treating, doing the dose escalation in treatment phase. Was that also the person who did the outcome assessment?

MR. STAMLER: Yes.

MR. GOLDSTEIN: Okay, thanks. The second question is, you know, we -- I think the thing that we're really struggling with, is we understand how important chorea is, and how -- what a big impact it is on quality of life, and on activities of daily living, yet looking at the data, the data doesn't seem to follow that way. And that's the thing that I

think we're really sitting here struggling with, and I think that's one of the things that the FDA is struggling with.

Could it be that what we've done is as we're treating the chorea, we're increasing other extrapyramidal symptoms, and other side effects so that the net sum gain ends up being zero in terms of function. In other words, we may be clearly greatly impacting on the chorea, and I -- the data is what the data are. But could these other things that are going on at the same time either singly, or in combination, be attenuating that effect so that we end up having no net functional improvement?

MR. STAMLER: Yeah, if I could get the slide on the TFC components, yeah, I think that's a -- that's an excellent question. We --

(Laughter)

MR. STAMLER: We realize that the functional measures in the study -- yeah, the

-- slide up -- aren't necessarily sensitive to the improvements of chorea. And this is the change in the total functional capacity by item as Dr. Como mentioned. There's a component regarding occupation finances et cetera, and this is one item that focuses on ADLs that is administered by the investigator to the patient and/or caregiver if they're available.

And perhaps one of the issues with the analysis of the functional assessment items, which Dr. Davis conducted, is that although it looks at those individual items, they can only be binary, they're yes, no, whereas the ADL scale ranges from 0 to, I believe, it's 4, 3 to 4. So I think there may be more sensitivity in this scale that has more divisions. The other thing is -- could I have the next slide as well.

This is the functional impact scale, which is the scale that was piloted by the Huntington Study Group in this trial, and

what this showed, and I think the FDA had some -- you know, this is not a validated instrument and they had some legitimate comments about the fact that it wasn't normally distributed, and there might be a ceiling effect, accordingly for the -- I'm sorry, a floor effect for the placebo patients.

But for tetrabenazine, it did really appear to improve dressing, feeding and social isolation, and I think social isolation is an issue that is not really captured in any of the other functional instruments, but I would encourage, you know, Dr. Marshall or anybody else to comment if they can have something to add on this issue.

MR. GOLDSTEIN: Dr. Temple.

MR. TEMPLE: Well, I asked this before, but I wondered, if you'd look -- suppose you look at the 50 percent of people that had a -- an effect on chorea for movements of 6 to 10, 12, whatever, and

looked at their scores on these things?

MR. STAMLER: You know, I know you asked -- we were answering to -- answered all these other questions, I -- we didn't get to that, but, I -- I'm sure we did that in part of our complete response, and while you're discussing this --

MR. TEMPLE: Okay.

MR. STAMLER: -- other questions, I'll go -- I'll look through that, and see if we can locate that answer.

MR. TEMPLE: Right and I'm not alleging that that's statistically legitimate, I'm just sort of curious.

MR. STAMLER: No, I understand, I --

MR. TEMPLE: Right.

MR. STAMLER: -- my hunch is that we looked at it, and may not have found something, because we looked hard.

MR. MARSHALL: Did you want me to address that?

MR. TEMPLE: Sure.

MR. MARSHALL: My recollection is that -- just with our own biostatistician at the University of Rochester, we did look at it by tertiles and we didn't find what we were looking for. But having said that, I think I'd like to address the functional assessment, the checklist, which is a 25-item binary checklist as you've heard, and I want to do that by acknowledging the FDA's concern that on the sub items that they selected, there was an adverse impact actually of drug against placebo; they identify in your briefing books, you know, 10 items that they thought would be associated with adverse ADLs. And if we could have X101.

It's 101. Slide up please. So these are the 10 items and this is -- these are the FDA's numbers, these are based on their briefing document, and as you can see actually tetrabenazine doesn't look like it's doing very well here. In the FDA reviewers

slides, actually 9 of these 10 items were shown, it was interesting that the dressed self item, which favors tetrabenazine was omitted from the slides, but I'm sure that's -- again, I don't mean to -- I'm not trying to pick fights here. I just -- I want to try to understand how this could come to be and what its significance is.

And so I'd like to go to slide -- to the next slide, please this one up. So as shown on item 68 of the UHDRS, more placebo patients filled out the checklist by themselves, 47 percent versus 26 percent, which was statistically significant maldistribution for this rating, which is to say, we never actually had caregivers filling out these items independently, we have data on whether or not the items were filled out based on information from the patient, or information from the patient and the caregiver, and so you can see here that this maldistribution -- may be worth looking into

a little bit more.

My thought about it as a clinician is that often times it's the case that I'll see a patient with Huntington's disease in my office and sort of go through the behavioral checklist or the behavioral assessment scale and ask them how they're doing, and oftentimes the responses are relatively monotonic, that is to say, patients will say, yes, or no or -- they'll get stuck on one answer, and then continue on with that answer. So I often find it valuable to have the caregiver information.

And if I were designing the protocol, again, I'm certain that I would have requested that the caregiver be -- the -- you know, there to provide the data on every single assessment, that's something that I learned from this study, but nonetheless I want to just have the next slide up, and show you what happens now when you restrict these numbers that the FDA

themselves picked out to just those patients who had a caregiver providing information at the same time that that -- you know, both at baseline and week 12. And you can see on the prepared meals item, actually, now it favors with the caregiver supplemental information tetrabenazine -- let me just use the pointer here.

So it goes from -1 +2 in favor of placebo to +3 -2 in favor of tetrabenazine. And virtually down the line you can see the same kind of pattern happening here, it goes from -20 to +3 -4. I think at the end of the day I don't want to make too much of this data. I think it's a reflection of the fact that there's wiggle in this test, and that in the greater scheme of things, we're talking about 54 patients, you know, 2 who got worse, 0 who got better, 3 who got worse, 4 who got better, on these binary items.

The other thing to mention on the functional assessment is that the -- it --

the -- oh, next slide please. It's a lengthy assessment, and the FDA called attention to some that they thought might be associated with functionality, in more particularly, ADLs, but you could see actually, there's a lot of other things that might also be predictive of ADLs, and that -- anyway I could go on. But in the interests of time.

MR. GOLDSTEIN: Now, I guess, the other way to interpret it is that the ones where the patients were able to do it themselves, they were too impaired to do it, so the caregivers did it, and the caregivers underestimated their severity. And the problem is you can look at these data in any way you want to.

MR. MARSHALL: You could, but I think the really important take-home message that I'd like to leave with the committee is that in my opinion as a clinician, given that there was no single sub item of this list that was statistically significantly adverse

against the drug, it's very hard to know what to make of adding them all up, and then deciding that that's an adverse signal against the drug.

MR. GOLDSTEIN: And I guess, that gets back to the point I made in the morning session about the validity, and -- of the -- of these various assessments that we're having to make judgments on. If we can't trust the numbers, then we're still opposed.

MR. MARSHALL: Yeah, I would say that we're in -- as the -- as Huntington Study Group, investigators, we recognize this as an issue, and we're in the process of trying to improve our scales.

MR. GOLDSTEIN: All right.

MR. MARSHALL: We don't have a scale for how you -- whether you kick your neighbor at the theater.

MR. GOLDSTEIN: Got it. Okay. One more question, and then I think we need to get to the questions. Dr. Hurtig.

MR. HURTIG: Yes, I just want to get clarification on one more thing, and that is whether you plan any warning on the use of antidepressants in patients who're taking tetrabenazine?

MR. STAMLER: I think the issue of antidepressants in particular 2D6 inhibitors like fluoxetine and paroxetine is only probably important in patients who are on stable therapy, and it's added. If someone's on a 2D6 inhibitor, coming in, they're likely to start low and titrate slowly, and stop once they achieve higher levels. But yes, we do think that some level of precaution or warning is warranted for patients who are on a stable dose and have to add a 2D6 inhibitor like any antidepressant.

MR. GOLDSTEIN: Dr. Katz.

MR. KATZ: Yeah, as long as we're looking at data in many ways that we weren't planning to, I -- the case has been made that when looking at the scales as designed and as

intended to be analyzed that for the functional non-cognitive -- even for the ones that go numerically in favor of placebo, the differences are small and the contention is that maybe we don't know exactly why that's doing it, although you'll have some explanations, it doesn't really matter, clinically.

We saw for the effectiveness data the chorea -- we saw a presentation of the distributions, you know, the -- how many had more than 10 point improvements, 6 point, the -- you know, in bins. Did you do any of that for these other scales for the functional scale, the cognitive scales, the ADLs, did we look at distributions of changes? I mean, does it -- does that small mean change represent some people who did a lot worse than placebo or -- did we do anything about that?

MR. STAMLER: Yeah -- I mean, I -- we probably looked at that most closely for

the functional assessment where we did have some big declines. There was one patient in particular I recall at week 12 -- 7 or 12, that had a 13-point decline. So if you think in a -- in the tetrabenazine treated patients, there was overall about a 1/2 point decline in 50 patients, that one patient having a 13-point decline was a big driver. So yeah, I think there were some people that had significant adverse events that did drive that, but in terms of distribution, I'm not sure if that's -- I don't think we've created slides on that, if --

MR. GOLDSTEIN: Thank you. Well, I think what we will do now is turn to the questions before us, and the committee has obviously seen these, and I believe, they're in the record. The -- we have two questions to vote on -- with the vote on the second question really being contingent on the vote to the first question. Let me also just reiterate for the -- for my committee members

who haven't been to one of these things before, is that the discussion is as important, if not more important than an actual vote -- we're here to give an independent view to the FDA about what our thoughts are given the data that we've had in the discussions that we've had so far.

So the first question is the one that we actually -- is asked -- we're asking for a vote on is, do the findings on the secondary efficacy outcomes, (the lack of beneficial effect of tetrabenazine on numerous measures of function and cognition), endure the numerical superiority of placebo on some measures, by themselves raise sufficient concern about the utility -- and let me underline utility -- of tetrabenazine's effect on chorea to just -- justifying not approving the application?

And I think a lot of the data that we've heard, and a lot of the discussions that we heard have really sort of floated

around this very critical, critical issue. So this first question is open for discussion and remember again, the discussion is as important as the vote, so committee. Let's go around the table and --

SPEAKER: Right --

MR. GOLDSTEIN: -- that sounds like a plan since nobody is volunteering, let's start off on the left, and go around, and please voice your opinions.

MR. TWYMAN: I think Dr. Temple raises a good point in the group that had a "super response," that is 6 point or a greater change, it's rather remarkable not to see a functional change, but I think the study size is actually quite small, and I'm not quite sure whether or not these scales have the resolution with that small sample size to see a clear difference, but with that -- without the data, I just don't know from that sample, but it is surprising not to see a large functional effect somewhere along the

line.

MR. GOLDSTEIN: Ms. Milek.

MR. TEMPLE: Before you leave that, it is surprising, we all know that, how does it make you feel about that? Sooner or later you got to get to that question. I'm talking to anybody --

MR. TWYMAN: Oh, I -- respond to that --

MR. TEMPLE: -- you're right it's puzzling, we're all puzzled by it as is the company, but --

MR. TWYMAN: Yeah.

MR. TEMPLE: What's the implication?

MR. TWYMAN: Again, in my mind it is rather surprising not to see some improvements that have been remarked upon at least anecdotally that with the treatment of tetrabenazine there is a remarkable ability to --

SPEAKER: Yeah.

MR. TWYMAN: -- function at least at home, and eat, or otherwise perform at home. And so it is remarkable, at least on some of these scales, that some measure of reasonable functional improvement was not detected even in the super responder group. So it does make at least me feel a little hesitant, but again the sample sizes might be too small here to actually resolve the difference.

MS. KOSKI: You know, I must admit, you know, I think the -- you know, we've heard some testimonies, we've seen certainly with the chorea scale that, you know, the changes can be actually quite striking. You know, the issue is, is that many of the other ones with the exception of the functional assessment scale were really sort of like trends, you know, if a drug came in here, you know, with that type of data, you know, you certainly weren't going to approve it. So I think the only way one can get around this is

to continue collecting data. And you -- and for that you have to have actually, you know, a placebo group.

MR. KATZ: But again, the question is we need to know how the committee feels about how strongly you feel about this. In other words, do you feel strongly enough that the data taken as a whole are more or less uninterpretable, or we don't understand the clinical meaningfulness of it to not approve it at this point? And acquire more data perhaps before we consider approving it. So it would be very useful for us for -- folks to sort of get -- get an actual conclusion about the question.

MR. TEMPLE: Yeah, just to be clear. You could conclude that -- since I don't understand it, I'm not prepared to believe that the chorea effect is valuable, or you could believe that the chorea -- the value of the chorea effect speaks for itself, and we don't understand why it didn't work.

But it's not a reason to take that position. We're not telling you what we believe, that's -- we're asking you.

SPEAKER: You know --

MR. TWYMAN: So let me further clarify that. My feeling is, I think the total chorea score is actually a very reliable measure, and as you pointed out, replicated. And so I do believe there's a dramatic effect on the chorea itself. I would tend to believe that score as a measure of improvement of the motor function than a functional measure that we're trying to do here in an obscure way. So I would believe that the total chorea score actually does reflect an improvement in overall functional capability even though we can't resolve that in the scales that we see here.

MR. GOLDSTEIN: Ms. Milek, did you want to make comments, sorry, we passed by you before?

MS. MILEK: Yes. Hi, yes, I agree

to that -- what you see with the chorea is totally positive, and we are never going to figure out the whole thing, and anybody who's followed the Huntington's disease, it's not really a cut and dry kind of a disease, yes, you find the gene and all, but the symptoms differ a -- even when -- and within a family -- from family members, and it's going to take centuries for us to find something that we can follow, and it's going to be that cut and dry. But with this chorea, we're all overly amazed at how much we see up here how good it is, and I have had -- you know, I -- I don't know -- we all read the letters that we got, and we listened to these people talk, and they are well -- that's true, that's a fact, that's right here in front of us. And I -- I'm going to believe that what I see.

MR. GOLDSTEIN: Carolyn.

MS. KOSKI: Well, I guess, I sort of expressed myself earlier, I basically think that this is a valuable drug, at least,

to release to the community. I think it is readily available, you know, in Canada and Europe, and I assume that patients are going to continue to get it from those sources; those that can afford to do it. It's just that -- and I think that it would be reasonable to go ahead and say, "yes, let's release it," but you know, with very careful controls, very careful follow-up reporting back to the FDA, you know, so that we -- if we do continue to see these trends that, you know, that the drug perhaps would then be removed, but --

MR. GOLDSTEIN: Dr. Holmes.

MR. HOLMES: Yeah, I -- just not to repeat anything everyone else has said. I mean, as a short study, it's very few patients, the data is kind of soft, and you can interpret it in many different ways, but the bottom-line, I think it really works well for chorea, and I certainly don't think it -- there's anything I heard that would raise any

sufficient concerns on my part to not approve this application. I think the benefits of the drug far outweigh everything -- yes, I'm a little surprised, but not -- I'm not really concerned at all.

MR. GOLDSTEIN: Dr. Rudnicki.

MS. RUDNICKI: They -- the statistics are so strong supporting the chorea, and I find that the data looking at the functional outcomes are frequently not -- don't reach statistical significance, and so I feel like the -- many of the others do that the chorea benefits probably outweigh the trouble with looking at the functional outcomes.

MR. GOLDSTEIN: Okay. Dr. Couch.

MR. COUCH: The -- in addition to what's been said, the drug has been available for 30 years now in other parts of the world, and we haven't really had any bad -- I haven't seen any papers that say, you know, people are dying from heart attacks from

excessively aspiration pneumonia things like this. I think that, at least from other places where it's available, we would be seeing something -- if the things that they were pointing out were really that prominent, I don't want to downplay them.

I am surprised as everybody else is, about the fact that the chorea is dramatic, it is reproducible, and yet somehow or other it doesn't translate into a functional gain, and I'm wondering if we really know how to measure functional gain. If somehow or other, the instrument that's being used is not really measuring what needs to be measured, so perhaps that needs additional work.

Nevertheless, the combination of good results on the chorea scores from the small study, number two the fact that we -- that it's been used for a long time, and nothing really bad has been said, and then number three we heard -- we certainly heard

some very dramatic testimonials from the public. I think that it's a drug that needs to be out there in the marketplace and then we need to design the follow-up on it so that it's going to be watched carefully, and if we see things developing under this observation, we can then take additional steps.

MR. GOLDSTEIN: Dr. Anderson.

MR. ANDERSON: I -- I'm just struck by the disconnect between the fervor in which chorea reduction is associated with functional improvement from the patients that I had seen before, and the patients that we've heard today and the inability to really establish anything convincing for improvement, and that seems to me like a puzzle that should be really interesting to all of you who are doing this, and has been more defended than addressed.

I noticed that there were nominally statistical significant differences for cognitive components. In early Parkinson's

disease, Stroop effects will -- Stroop impairment will occur. That's been related to dopamine levels measured by, I don't know, I think it was SPECT, but maybe it was PET. And it seems to me that there is a plausible working hypothesis that you are exacerbating the cognitive impairment of Huntington's patients while at the same time it's improving their chorea, and you're getting a cancellation out in terms of functional measures.

There are, I think, better functional measures that were employed in this study, which in hindsight you would've used if you had known this was going to be the critical issue. I would regret if, sort of, approval lead to a loss of opportunity to understand better why tetrabenazine wasn't showing improvement, and so this ties into the second question -- I'm sort of running my mitigation issues into sort of the approval issue.

So personally, as a physician, do I think that this would be a drug that I would like to have available to treat patients given the information I have before me today and the answer is, yes, but I would hope that such an approval wouldn't lead to a situation where it no longer became possible for us to get the sort of data that we needed in a placebo controlled way to understand why we weren't able to see something better that might not only address how to use tetrabenazine, but whether some other medicine that came down the road, what it should be measured for, what it should be looked at, in addition to sort of chorea manifestation. So I'd -- that's the summary of my opinion, I'd like to understand better whether there were cognitive consequences of the drug that cancelled the functional benefits when weighed against the motor improvements, and how that could be provided in sort of subsequent monitoring or

mitigation.

MR. GOLDSTEIN: Thank you. Dr. Rizzo, the -- you've been sitting there, we think. Are you there?

MR. RIZZO: Can you hear me?

MR. GOLDSTEIN: Yes, we sure can.

MR. RIZZO: Well, I've been listening all day and I guess, suffered through a sort of intermittent connection having to call back 6 or 7 times, but I'm convinced that -- well, having heard the lectures this morning, heard the discussion by the committee, and having read through all the materials that -- and I -- substantial side effects that would mitigate the use of the drugs, not depression, not drowsiness, not parkinsonism.

MR. GOLDSTEIN: So he's in an airport.

MR. RIZZO: And oh, sorry. Just making noise here. And then -- so then the other thing is that -- I think because of the

potential benefits in the chorea, and the improvements in the chorea scores that I would favor -- considering the drug and approving it to the FDA. I guess, I'm generally in favor of the drug, I think that the benefits, as best I understand them, outweigh the risks.

MR. GOLDSTEIN: Thank you. Dr. Jung.

MS. JUNG: Well, I want to briefly, just outline, I think the -- some of the same comments, which is that the primary endpoints of the study have been met in showing that chorea has clearly been effectively treated with this drug. I've heard a lot that the functional scales that we're using are not clearly validated, are not clearly understood. And given the small size of the study and the short length of the study, to then -- with -- and having said that, had such significant primary endpoints met, suggests that the drug should be approved

from my standpoint.

I think that in addition to that, we've had 30 years of real life experience with this drug all over the developed world, and we have not heard of any significant adverse events that have come about as a result of that. And my fear, actually as a clinician, is that we're overly cautious, and that as I heard the description of the RiskMAP, offered this morning by the sponsor, even though, the FDA has not requested one, that we don't over -- that we don't overburden the process.

I can't imagine how you would be able to use this RiskMAP to monitor the treatment of patients. I would urge that I haven't heard anything about this drug that makes me think it's any more dangerous than any of these other drugs that have been released and we're using out there, and to put such a burdensome process -- in is not fair to the patients out there. So those are

my two cents.

MR. GOLDSTEIN: Dr. Green.

MR. GREEN: Well, just like when we treat Parkinson's disease, we're used to making an inventory of symptoms, and recognize that if we treat one target symptom, it's possible to worsen another, and I think this is probably very similar. And therefore, as long as we understand this very specific target symptom of chorea here and educate both doctors -- and frankly, more than usual, caretakers to these potential issues will probably be okay going forward. I was also very moved by what I learned about functional improvement by the public probably more than I did by the studies.

MR. GOLDSTEIN: Dr. Lu.

MR. LU: Yeah, I think I'm convinced that it -- that the drug control chorea, so in that aspect there's no question. For the secondary effects the -- efficacy endpoint there are some questions,

but the sample size is small and is a major issue about correlation, so the directional issue is kind of difficult to argue. But the behavior side, and the functional side was -- behavior was supposed to be relatively independent of the other -- measurement was not in favor of that -- the treatment.

So in that sense, I think there should be some more study to -- you know, I think -- just for symptom control, it was clear there should be no question, so you know, in the -- as a field like osteoporosis, they have this two-dimensional, like, control, the BMD as a prevention treatment, and then the control fracture treatment indication. So I don't know if there's any different levels of sort of overall benefits patients has one higher level as chorea as -- you know, chorea is one level of the control indication, but that's as a consideration.

MR. GOLDSTEIN: Dr. Hurtig.

MR. HURTIG: I agree with

everything everyone has said. But I'll elaborate. I feel that we have a -- sort of a bit of a clash here between evidence-based medicine and medicine-based evidence, meaning that what you see in practice is often dramatic compared to what you can try to prove with a difficult clinical trial, and I think that's one of the problems where you have something that's relatively easy to measure, which is the chorea, and it shows a very robust effect, and compared to the things that are more difficult to measure, and I'm also persuaded when I hear the additional evidence that with more caregiver input to the evaluation, that the results are more positive.

So I think some of it is how you tweak the information, obviously you don't want to over tweak it, but still there's a bit of -- more mining that needs to be done. So in summary, I think, I agree that this is a powerful drug, and I'll -- in full

disclosure, I can say I've used it quite a lot and I'm impressed. That's my medicine based evidence.

MR. GOLDSTEIN: Thank you. My view is that what I think we may be seeing to some degree is this problem where we're using unvalidated tools to measure things that we think are important. And again, taking the example of our stroke trials, which God knows have been challenging over the years, we could have very significant improvements in things that really matter to patients, things, for example, like aphasia or visual field defects, that aren't -- wouldn't be manifest in -- on some of the activities of daily living skills like, for example, the Barthel Index, you can have an aphasia, a global aphasia, and score a 100 on the Barthel Index, which is our functional outcome measure.

So we look at the panoply of measures together and -- to try to get a

picture of as to what the drug is doing. I think that's really the challenge for the Huntington's disease community, to really go through that process so that we can have a better understanding of whether therapies that we're developing and using are actually helping or not helping. Having said that, sometimes helping a symptom is very, very important, even though it may not be manifest in some of these admittedly not great global scales.

My own feeling is that I think the first trial, although small, clearly demonstrated that it did what it was supposed to do, that it decreased chorea. I think the second trial, I think, supports a biologic effect, it was -- it certainly was not an efficacy trial, and I think the -- in the spirit of the data -- of the FDA's rules for 10 years, that the second trial, I think, supports a biologic effect, I think it does that, although it sure doesn't support

efficacy. So that's my view, and again hearing the testimony from the public, and having taken care of patients with Huntington's disease and other conditions over the years, I know how important some of these symptoms are to daily functioning, and they may not just be manifest in this -- in the way the scales are being used.

So any other comments from the committee before we bring the first question to a vote, and does the FDA have anything else you'd like us to address relative to the first question? I think more will come out as we move on afterwards.

MR. KATZ: Yeah, I -- there was one other thing, which is -- some of the adverse events that also are part and parcel of the natural history of the disease, of course, can be -- we think caused by the drug and they're sort of easy to see if depression gets worse. I don't know how easy they're to see, but they're seeable if you're looking

very closely, I suppose. But if you really believe that some of the cognitive issues are trending in favor of placebo, but in 12 weeks, very minimally, is it possible or do -- or are you worried about the fact that that difference if it's real could increase over time, and that I would think would probably be undetectable, you know, from a clinical point of view, and so the patients could continue to get worse in those areas.

Again, there are just hints of it if you even believe it in the 12 weeks. I'm just wondering whether or not that difference could expand over time, and that I don't think people would pick up clinically. And so you would be treating people's chorea is benefited, but in fact they're getting worse in ways that are important, but will probably never be attributed to the drug. So I just wonder if that is something people are concerned about.

MR. ANDERSON: Well, I mean, that's

what gave me pause in sort of -- my reflection was that I felt -- I didn't hear any real discussion of the cognitive, we were all talking about the motor symptoms, which are the most obvious, and I was -- when I read some of the -- and heard some of the mitigation approach of, you know, monitoring the drug and you know, and issues related to depression and insomnia, those I feel come out.

I don't think you necessarily -- they may overlap with the spectrum of the disease, but they come to the attention of the clinician and the family much of the time, and I was much more concerned about how you would address sort of a baseline assessment of functional cognitive status that you could, as a clinician in a practical way, monitor over the course and time of therapy to actually be able to be aware of things, because that's even more likely to overlap with the course of the disease that

if you're given medicine that slightly afflicts executive functioning, and suddenly somebody needs a little more help doing the laundry than they did before, you know, are you really going to report -- you're never -- so unless you have some structured assessment of these things that form a baseline for the clinician, the clinician no matter how well intentioned is not going to be able to detect them.

And I think that is a challenge that I didn't hear addressed in the presentations today. I personally wouldn't use that at this point for my own vote to invalidate a recommendation of approval, but I would really like to see it, you know, wrestled with.

MR. GOLDSTEIN: And again, we can -- we'll -- after this first question is dealt with, then we can discuss these and many other issues that I think flow from this. I guess, Dr. Katz, I think, the point

you make is obviously a good one. We face this all the time, we have pharmaceuticals that are approved with relatively short term studies; a week -- you know, a month, two months, three months, six months, that patients are then on for the next 20, 30, 40 years. And we have -- clinicians face this all the time, we have no data on these long term effects, aside from what goes into these, you know, open reporting systems.

The comments, again, for the -- just to make sure the committee has this in an appropriate frame. Although the drug has been used extensively in Europe as we've heard, the reporting on this is spotty at best, and it's entirely possible that there's some significant effect that hasn't been reported, because it hasn't been recognized. So we can't -- I don't think we can rely very much on that, and I would just hold that on the side, I wouldn't weigh that very much. Dr. Temple.

MR. TEMPLE: Well, just to observe that you have some longer term data that included some cognitive function, but without a control group it's really --

MR. GOLDSTEIN: It's uninterpreted, it's --

MR. TEMPLE: -- hard to know, so your best shot's going to be something so dramatic, it is obvious even without a control group and that seems very unlikely, but it's very hard to get at those things.

MR. GOLDSTEIN: Yeah. Okay, if there are no other -- we have one other, sorry.

MS. MILEK: Well, I, as a person who has Huntington's disease, would like then to be able to make that choice, to decide to go on a medicine that could particularly have some other effects down the line, I may want to choose then not to stay on the drug, but having the choice to get on the tetrabenazine is going to be just -- there is no words for

it -- just something that can make my life much better. And we, hear today, can make that happen.

MR. GOLDSTEIN: Any other comments from the committee? Okay, seeing none, do I need to read the question in again, or is the --

SPEAKER: -- hands --

MR. GOLDSTEIN: Okay. So I've already officially -- I've to follow the rules, I've officially read the question into the record before. So I hope everybody knows what we're voting on. So the process is that, first, I will ask everybody who votes, yes, or, let's see -- make sure this is not a double negative. Do the findings by themselves -- actually -- so it's a -- yes, means that you think that there is a problem, no, that means that you think that there isn't a problem.

SPEAKER: -- say no --

MR. GOLDSTEIN: Okay. It's -- it's

written in a negative as opposed to a positive. So --

MR. KATZ: There was a reason for it at the time, it's rhetorical.

MR. GOLDSTEIN: Just reading, you can't write more than it is. I think you've been in government too much.

(Laughter)

MR. GOLDSTEIN: Okay. So -- just so that we keep it straight, the no votes mean that there -- that you do not think that there is something that would -- that you're concerned about, that should block approval, okay. So I'm going to knock all the rules, and do the no vote first. And the way we do this is everybody then voting no raises their hand, and then we'll go around, and then you read your name into the record saying that you voted no to the first question.

So first question to vote -- all saying, no, that there isn't a problem that you're concerned about. Okay. Let's go

around and -- just say your name and say, no. Yeah, everybody leave your hand up. So we know who to call on.

MS. MILEK: Karen Milek, no.

SPEAKER: Turn your mic on.

MR. GOLDSTEIN: Turn your mic on, please, so it goes into the record.

MS. MILEK: Karen Milek, no.

MS. KOSKI: Carol Koski, no.

MR. HOLMES: Greg Holmes, no.

MS. RUDNICKI: Stacy Rudnicki, no.

MR. COUCH: James Couch, no.

MR. ANDERSON: Britt Anderson, no.

MS. JUNG: Lily Jung, no.

MR. GREEN: Mark Green, no.

MR. GOLDSTEIN: Dr. Rizzo.

MR. RIZZO: I can't raise my hand, but I'll say no.

(Laughter)

MR. GOLDSTEIN: There you go. You can raise it.

MR. LU: Ying Lu, no.

MR. GOLDSTEIN: Okay. And the chair votes, no.

SPEAKER: (off mike)

MR. GOLDSTEIN: Oh, I'm sorry. I saw Dr. Hurtig --

MR. HURTIG: My hand wasn't up.

MR. GOLDSTEIN: Sorry.

MR. HURTIG: Howard Hurtig, no.

MR. GOLDSTEIN: Thank you. The chair votes no, and any vote -- anyone voting, yes. You've one choice left. Anyone abstaining? No, we've got everybody, very good. So I think the FDA has the unanimous, for a change, vote of the committee. Now, the second question for a vote then is not -- is now moot since it was asked if not -- is the panoply -- oh, I guess, let's see, I don't know which way you're --

MR. KATZ: It's not -- no, it said, "if not" and you said, "not," so --

MR. GOLDSTEIN: Okay.

MR. KATZ: We have to discuss,

sorry, we have to discuss it.

MR. GOLDSTEIN: Sorry about that, you're getting -- okay, if not --

(Laughter)

MR. GOLDSTEIN: You know, Supreme Court, might be your next job. If not, is the panoply of adverse events associated with tetrabenazine use sufficient to justify not approving the application, okay. When considering this question, are we particularly interested in hearing the committee's views about whether or not a dosing regimen can be identified that would provide a benefit on chorea without an unacceptable risk of adverse events, failing this we would be interested in hearing the committee's views about any maneuvers that might mitigate these risks sufficiently to justify approval such as reducing the dose, discontinuing the drug, instituting concomitant treatments, for example, antidepressant therapy.

Further, we are also interested in the committee's use of the aforementioned agency concerns that are -- might be difficult for the practitioner to discern if clinical worsening in various areas such as cognition and depression is drug related or not with the possibility that if drug related, the adverse events could become severe and/or irreversible. So that is the question, and I think we've discussed around the issue, but I think we -- I think now is the time to really try to cone in on this. So if we're saying that -- and I think we did -- that we think that the drug should be available. Now, is there anything that really needs us -- needs to -- that we need to really consider carefully in making further recommendations?

MR. TWYMAN: Yeah, I could start, Larry.

MR. GOLDSTEIN: Okay.

MR. TWYMAN: I think I got this

right, and so my view would be no, that I do think there is a avenue for a risk benefit proposal around the dosing regimen itself. And so as I pointed out before, I was very intrigued by the apparent 50 milligram threshold, in that it appears that at 50 milligrams, it has some prediction perhaps at least in the small sample size that those who are not responding by 50 milligrams do not really have a pretty good chance responding even with a -- with an increase in dose.

It also appears that the adverse events of interest -- and particularly, the depression, and some of the extrapyramidal symptoms, in particular, the dysphagia symptoms, might appear later -- during -- in the course of titration, particularly at the higher dosages that by 50 milligrams, one could appreciate the risk benefit by identifying those patients who are -- appear -- that appear to be responding, and therefore could potentially benefit by --

further by increasing the dose, and one can then weigh the risk benefit of the higher dose against that benefit, and the potential adverse events that might be developed after that point.

So -- I am very intrigued by that 50 milligram threshold and potentially as a target dose for initial therapy itself. As for the RiskMAP in detecting depression, I'm not quite satisfied that that -- that the approach there to detect depression is adequate. It is well-known that these dopamine depleting agents can indeed exacerbate depression, or even cause depression. And I do note that in -- at least in one label that was obtained from XUS approval that the -- a ongoing episode of depression, or a previous history of depression is actually contraindicated.

MR. GOLDSTEIN: Dr. Koski.

MS. KOSKI: I think if I remember correctly that in depression, some of those

were noted at about 25 milligrams, maybe I'm misremembering that, but you know, that's one of the reason that I liked Dr. Shoulson's approach to go a little bit slower, giving the caretakers, giving the patient and the family more time to sort of notice changes in what's going on with the patient. So that's my only issue with that.

MR. GOLDSTEIN: Thank you. Dr. Holmes.

MR. HURTIG: No, I agree, like many things we use, I think start low and go slow should be the rule here, and having people recognize it, you can start seeing symptoms at 25 milligrams, and you probably did not need to go above 50 milligrams in most cases I think would be very useful information for the clinicians.

MR. GOLDSTEIN: Thank you. Dr. Rudnicki.

MS. RUDNICKI: I agree that it makes sense to do it slower than the study.

Normally, we look to the studies for how to dose, and I think this might be the exception to that general rule that -- you know, you're treating a symptom that you don't need to get rid of tomorrow. So it makes sense to be conservative with dose escalation.

MR. GOLDSTEIN: Dr. Couch.

MR. COUCH: I think there is -- there's probably three things that we need to look at here, one, is long term follow-up. We should have 30 years worth of data, but we really don't, and I think that as this is built in, we ought to at least have some kind of a minimal follow-up instrument that the physicians -- I am assuming most of these are going to be neurologists, the physicians that are using this drug are going to need to follow-up. The -- perhaps Tysabri would be somewhat of a model, so that was built in to the Tysabri study.

But that -- that's really the -- one of the critical things, what happens over

a long period of time, does somebody have a 2 percent per week, per month, per year decline, extra decline in cognition, and when and if does that become significant, we don't know, and that -- this kind of data, this is very difficult to collect, but if we don't start trying to collect it, we're never going to get there.

The other aspect of it is there needs to be some kind of training, somehow or other -- some educational program for the physicians that are going to be using it. The -- this was mentioned earlier, but -- as -- this is not going to be something like using the next antihypertensive, okay, you do, you just start writing prescriptions for it and kind of learn on the fly. There needs to be some kind of a situation, where you said okay, if you're dealing with -- first you have to recognize Huntington's disease.

And if you're dealing with it then these are going to be the things that you're

going to need to look for, and especially if we -- are there -- be careful about using antidepressant, be careful about using other drugs that may cause accumulation and lead to side effects, perhaps cardiac side effects, I don't know, but since the average patient that -- I think we all see the thing used to be over age 60, everybody's on about 3 medication, now over age 60, everybody's on about 10 medications. And then all of these might be important, or at least some of these are going to be important in using tetrabenazine. So I think we need to start trying to collect data now and educating people that are going to be dealing with this drug as early as possible with some kind of a packet that say okay cook book, this is how it is, 1, 2, 3, 4, go from there.

MR. GOLDSTEIN: Dr. Anderson.

MR. ANDERSON: Well, now, I'm just thinking a little bit as I go, which I guess, was part of the request. So the low and slow

certainly sounds sensible to me. I was also thinking that perhaps sort of chorea abatement might not be the goal, but it would be more sensible to recommend sort of chorea reeducation since -- if the side effects that we're talking about are related to the actual mechanism of the biochemical action of the drug then it may be that the harder you push, in terms of trying to eliminate chorea, the more likely you are to invoke some of these other counterbalancing issues, and that sort of -- sort of the seat of the pants thing might be if families can actually identify the thing that is critical, oh the difficulty with reading or kicking the seat at the movie theater, that might provide the proxy to use for titration.

So that you could get away with 12.5 or 25, because there are still a lot of chorea, but it was -- you know, it addressed the one thing that was sort of most relevant for that family at that time, and how you

incorporate that in a educational program, I guess, somebody would have to think about. But it -- maybe just that issue that perhaps something in the instructions would reflect that sort of the goal of sort of chorea elimination wasn't necessarily the most sensible therapeutic goal. This idea of titrating to absence like you might with headaches or seizures might not be the model to use for chorea with tetrabenazine.

MR. GOLDSTEIN: Dr. Rizzo, you there? And they've lost him. I guess not. Well, if he shows up, we'll try him again. Dr. Jung.

MS. JUNG: I would favor a -- hi Matt.

MR. GOLDSTEIN: He's back.

MR. RIZZO: Did you call me?

MR. GOLDSTEIN: Yeah, sure did.

MR. RIZZO: I can't hear you very well.

SPEAKER: We're waiting for you to

talk.

MR. RIZZO: Is there a question?

MR. GOLDSTEIN: Yeah, we were asking whether you had any comments relative to question 2.

MR. RIZZO: No, I have no comments.

MR. GOLDSTEIN: Okay. Dr. Jung.

MS. JUNG: Well, I would favor a slower titration than what was used in the clinical trials. Recognizing that we're the head of a consumer representative, I would -- I think we all recognize that the system requires a overhaul in terms of how we monitor drugs post approval, and I'm not sure that this is the appropriate venue to be doing it. You know, we're looking at a specific drug, and we're recognizing that the system of drug approval across the board does not allow us to look at issues post marketing.

And I think that tying the two together just doesn't make a lot of sense,

particularly in this drug, where I don't get the sense that the risks associated with its approval are as great as those that those of us who are in the committee last year recall around Tysabri. So I'm a little anxious about getting overly -- again, designing a system that's overly burdensome for a particular drug just because we're nervous.

MR. GOLDSTEIN: Dr. Katz.

MR. KATZ: Yeah, just a point of clarification. We do -- and this is actually --

MR. GOLDSTEIN: Question 4.

MR. KATZ: -- question 4 --

MR. GOLDSTEIN: Yeah --

MR. KATZ: -- but we do have mechanisms for requiring sponsors to do studies post marketing if we think that's appropriate. You may not think it's appropriate, but that mechanism exists for sure, and again, we -- we'll just -- we'll ask you to discuss that more formally in

question 4.

MR. GOLDSTEIN: Thank you. Dr. Green.

MR. GREEN: Okay. Just as I said before, I think the importance -- safety concerns will be minimized by education of not just the doctor, but the caretakers, because we can't rely on self reported side effects and everyone going forward. Caring for people on this drug, really have to be very attuned to whether the curve of depression, for example, seems like an outlier. That takes a lot of education to families -- it's actually a big burden in responsibility for them.

MR. GOLDSTEIN: And Dr. Lu?

MR. LU: Yeah, I think I agree with the previous discussions, and one thing that I noticed for the chart that if you look for the visit 4 which is about 50 milligram, and there was not much different. I mean, the actual gain for -- through the visit 7 was

less than one point in the chorea scale. So the benefit, you know, and so it's sensible to look for those that are not very high. I mean, go to 50 or less, but because main efficacy was achieved by that visit 3 in the chart. Other than that, I think one thing we need to recognize that -- a lot of adverse events was dose related, but cognition is not, at least not proved to be dose related. So you should be very careful in terms of monitoring that.

MR. GOLDSTEIN: Dr. Hurtig.

MR. HURTIG: Yes. I'm -- everybody's said good things, and I agree that if the drug is approved that people should use it carefully, it's like any other drug that gets out there, it relies a lot, after approval, on the good clinical judgment of the clinician, and my sense of this drug is that the people who will be prescribing it will be sort of a restricted group of people with expertise in handling this disease, and

patients, and families who are already experts in living with their disease will certainly automatically become educated.

So I'm not too concerned about that. I agree with Dr. Jung there shouldn't be -- we shouldn't over overregulate this drug after it's approved, if it does get approved, because that's just -- is too hard to monitor and too difficult for the prescribing physician.

MR. GOLDSTEIN: So you know, my opinion about some of these things is one, it seems that what we're really doing here is treating symptoms, we're not reversing the course of the disease, and I think getting to the point about dose, I think the lowest dose that controls symptoms in a way that makes meaning for the patient in the family, that's the dose. And I don't think there needs to be a rapid dose escalation; it makes no clinical sense at all.

We heard about patients that may

have masked very significant clinical improvement with a very, very small dose. There's no reason to escalate the dose in that patient as long as their symptoms are controlled, and therefore hopefully we'll ameliorate some of the side effects that we think may be dose related, get the clinical effect that you want without hopefully the side effects.

The second point I think is a bit more difficult. When we have a disease and a drug that may have side effects that mimic the disease, how do you tell the difference? You know, when we went to medical school, the rule 1 that they taught us is, above all else don't hurt anybody. And that's the rule that physicians always live by. And we don't want to be inadvertently hurting people without even knowing it. Now, how do you get at that without having control data; there isn't a real good way to do that.

One thing I think is the way the

trials were done -- the trial was done, was with people who were really quite expert in dealing with Huntington's disease and movement disorders. You don't want to be overly restricted, but I understand from the risk minimization plan that there is a possibility of limiting who can prescribe the drug, and what I would suggest is that be limited to people who know what they're doing, to experts in Huntington's disease who -- if anyone would be more sensitive to picking up differences and -- unexpected from the course of the disease and be aware of these potential side effects, it would be them.

Now, whether that's movement disorder specialists per se or neurologists in general, I think that's a point of discussion, and that that could be held, but I don't think you would want people who don't have -- who have very limited experience with the disease dealing with the drug where we're

not sure about what's side effect and what's real drug. So any other comments or -- Dr. Temple, did you want us to expand on anything else?

MR. TEMPLE: Well, I was -- it's extremely -- I mean, we do like to say things like people should be knowledgeable about the disease, but we would be very troubled -- I'm just trying to think whether we've ever done it, to say you have to be an oncologist, you have to be a neurologist, or you have to be a movement disorder neurologist or anything like that. We may insist -- did we do that for say -- we -- I don't even think we did it for Tysabri.

MR. GOLDSTEIN: Yeah, we did, yeah. I was on that committee, we did.

MR. KATZ: Yeah, you can --

SPEAKER: Yeah.

MR. KATZ: -- we're allowed to do it. Again, we've certainly never done it in neurology even with Tysabri, where we

actually talked about that; we decided not to do that.

MR. TEMPLE: Well, you -- it certainly --

MR. KATZ: Well, no, I'm saying we talked about it, but it was not restricted.

MR. TEMPLE: It certainly refers to being knowledgeable about it, but to specific qualifications, I think that's very unusual --

MR. KATZ: It is unusual.

MR. TEMPLE: -- if ever.

MR. GOLDSTEIN: I don't -- I'm trying to find a way out of this conundrum that we're in. The conundrum, again, is that we have -- the data are what the data are, and we've talked over and over again about what all the deficiencies are. We're talking about a drug that we think has some potential side effects that may affect efficacy, that also can -- may mimic the disease itself and as a middle road, given that we don't have

the data that we need that we can put in there in a little PDR, little thing that physicians can look in and check off the chart, the only way I know around this that makes any sense is to have people who have a lot of experience with the disease be the ones that are using the drug. It may be new ground, but I -- if there's another way around it, that's what this is all about for you.

SPEAKER: Yeah.

SPEAKER: Yes.

MR. GOLDSTEIN: Dr. Green?

MR. GREEN: Just got a question. Does anyone remember the labeling, or the -- when Lotronex was reintroduced in terms of specialty? I think it's something similar and I think it --

MR. TEMPLE: See I don't think it, like, limits it to gastroenterologists, I could be wrong.

MS. KARWOSKI: Claudia Karwoski,

risk management team leader at FDA. Lotronex and Tysabri don't specifically require, excuse me, a certain specialty or qualifications of any type. But they do mention that the physician should have knowledge, again, of the disorder or what if -- you know, have a fair knowledge of treating the adverse event.

MR. TEMPLE: Okay.

MR. GOLDSTEIN: I think the wording could be done in a way so that physicians would feel uncomfortable about using a drug like this unless they had that level of expertise. So even if you don't have, say, your board certified neurologist or whatever, I think you could get there by doing -- by wording it correctly. I'm sorry, Dr. Jung.

MS. JUNG: It's hard to believe that Seattle is in the middle of the west, but you know, we serve four states and there are lots of areas in Alaska, Montana, eastern Washington, that does not have access to

movement disorders, neurologists; they're happy if they have access to internists or neurologists, and so I think it would be an unfair burden for patients and their families to have a drug, which seems -- again, I don't want to call it benign, but compared to something like some of the other drugs that we use in medicine, to be restricted. I just don't see any value to that. I think any physician who is a responsible clinician would not want to use a drug that he or she is not comfortable with in a condition that he or she is not comfortable with, and for us to put that type of restriction just doesn't work, especially in the wild west where I live.

MS. KOSKI: You know, I basically agree with what you're saying Lily, but I think that this is not the type of thing that you would want to have a person that has a single patient, you know, using, because they don't have the experience or the comparison.

MS. JUNG: But then we're going to need to do that for a number of other drugs that are on the market, because I think that there are a lot of other drugs that I can name that are a lot more dangerous, have a lot more significant side effects than this drug from what I've seen, and I know that, you know, we don't have the post marketing data from Europe, but we have 30 years of data on this drug, I see people using Tysabri on people that they -- that are -- that we're not (off mike) so I think that we're -- we need to back off and not -- you know, I think that there are other ways to manage how the appropriate authorities use drugs that they should be comfortable with, and this is not the place for it.

MR. GOLDSTEIN: Again, I think you're hearing different views on this. Dr. Katz.

MR. KATZ: Well, I just want to question one of your presumptions. It --

we're -- I think what we're talking about here is identifying an adverse event that might look like the disease, which for all -- in some cases may be so slowly emerging that it's imperceptible until -- you know, it's like the hands of a clock, you don't see it move, but all of a sudden it's 2 hours later. So you know, the effect may be so imperceptible that you're not going to pick it up for a long time, but the presumption is, and we have the world's experts in the room -- the presumption is that experts or folks with experience in the -- treating the condition will also be expert in detecting -- discerning the difference between an adverse event, and an event that occurs as part of the natural history.

Now, maybe that's true, but I don't know if it is, because I think that's the actual critical question, not is the disease progressing, or something about the disease, it's can we tell the difference between an

event that looks exactly the same whether it's drug induced, or part of the natural history of the disease. I -- again, we have the world's experts here, and maybe that's something that an expert can do, but there are things that not even experts can do.

MR. TEMPLE: But it could be that anybody, experts too, need careful reminder of this fact and that labeling needs to make that very clear. K: Well, that's for sure, that's clear. Certainly, people need to know that this is a possibility and need to look for it. I'm just wondering whether or not expertise in a particular condition automatically generalizes to expertise into discerning the difference between a drug induced event and a natural event that are clinically identical, not to offend anyone.

MR. GOLDSTEIN: You know, I -- the one thing that I think we do have is data that people who are -- who are -- have greater volumes are used to seeing a disease

process do better, the -- there are study after study after study that shows this, and part of that is knowing how to use individual drugs and drugs in combination for -- and -- or other interventions for disease conditions. So that's part and parcel of what that expertise is, it's a hard thing to put your finger on, what exactly is it, but when you look at it in total, study after study after study has found exactly the same thing.

I -- you know, I'm from the center of North Carolina, but we have lots of places in North Carolina where there are no physicians and no neurologists, and I fully empathize with the point that was being made. However, at the same time, you don't -- I wouldn't want somebody to be using a drug that they have little experience with -- with the disease that they have little experience with and inadvertently hurting people, that also is not a good option.

MR. HURTIG: You can say that about any drug, and I think in this case, with a fairly low concern about seriousness of side effects. So I think we ultimately will have to trust the judgment of the doctor, and I think that will sort itself out. You can say the same thing about any -- in our field of movement disorders, we'd like to think that we can treat Parkinson's disease better than anyone else, but we are not restricting the use of the drugs for -- we're not -- there's no restriction on the use of levodopa, and in fact, probably the majority of Parkinson patients are being treated very well by the general practitioner.

MR. GOLDSTEIN: Point taken.

MR. HURTIG: And they consult us when they get into trouble.

MR. GOLDSTEIN: So -- again, let me ask the FDA, if something were released first in a more restricted way, and then when the experience has been obtained, then widen it,

is that an option here, just because we've done like this before, we know what troubles we've gotten into by doing business as usual, just because we did it that way before doesn't mean that's the way we should do it in the future.

MR. HURTIG: I agree with that general principle for sure. Well, again, we'll even have to check whether we have the authority to restrict it to specific practitioners. I thought we did, but I don't know, we'll go back and look at that. There are many ways that you can -- or there are many sorts of regiments -- post -- immediate post approval scenarios that you could think of as restricted, not -- but not include restricting it to specific practitioners. You could have a registry, you could have a requirement for a Phase 4 controlled trial, so that you can actually learn about these things. You can have many other sorts of ways to follow patients in the immediate post

marketing period to get more experience and then convince yourself one way or the other about what the next step is, but that don't include restricting the prescribing privileges to specific practitioners.

MR. GOLDSTEIN: Yeah. And I don't think that that's necessary. I think the wording that we've used for many other things, expert or experience in the -- in treating the condition, I've -- you know, given these issues, I think is perfectly reasonable. Dr. Temple.

MR. TEMPLE: We can, under our accelerated approval rule, impose a variety of restrictions necessary for safe use of a drug, one of which for example, may not be -- I'm not sure we would say you have to be a neurologist, but it would say you have to read these things before you prescribe it, and we can do things like that. We're -- I think, Dr. Jung is saying some of this. We do this carefully and for good reasons,

because it's moderately disruptive to do things like that although the company seems to be proposing it.

There are a few that -- that's how thalidomide goes out, you know, it's not at your corner drug store. So those are possibilities. If you thought there was some guidance you could give somebody at the time of prescription, tell him what to do, the other possibility is that people could be trained in some other way that the company might develop, and would then -- that's one of the things they have to think about.

We are -- we certainly are conscious of having, you know, every drug with its own distribution system. And we have at least one experience of a drug for maintaining normal sinus rhythm in patients with atrial fibrillation, where the system designed to protect people against torsade de pointes arrhythmias has driven people to take quinidine instead, which also causes

torsade de pointes arrhythmias. And so that's been studied by Duke and it was not the desired outcome. So we do worry about the balance of these things. But there are things that we can do, under the accelerator approval rule, if they were considered really necessary.

MR. ANDERSON: Can I --

MR. GOLDSTEIN: Dr. Anderson.

MR. ANDERSON: I wanted just to add sort of the counterpoint that I would support the idea, and think it'd be more practical to require a level of awareness of potential side effects rather than restrict to a class of experts, because I think I disagree with the notion that somebody who is expert in a particular condition can detect these subtle differences. I think they're going to have a narrower window in which they get confused from somebody with less experience with the illness, but you can take an Alzheimer's expert and ask him with an individual

patient, is this person getting demented a little faster than they should've, and they're not going to know; they're going to be better, but they're not going to know. And so knowing what to look for is the key, and I would try to counterweight what I think has been suggested that this drug isn't that bad or that unsafe.

SPEAKER: We don't know --

MR. ANDERSON: It's not that it's caused heart attacks and people die that we're aware of. But I think it is a situation of the dog that's not barking; the fact that such dramatic, robust reductions in chorea was not associated by obvious improvement in other scales, is, to me, a yellow flag, but not a red flag. And so I would like to support that.

MR. GOLDSTEIN: Very good. Well, I hope you've had a diverse set of opinions, which is the purpose of the exercise for you. We do though have to vote, right, on the

second question. The second question, just to remind people was that if not -- and remember we said, no, for the first question. Is the panoply of adverse effects associated with tetrabenazine use sufficient to justifying not approving the application? You guys got to do something with these double negatives in here. Okay. So is there anything in here that -- probably, that we've discussed that would make you not -- want to not approve the application? Okay.

SPEAKER: A no vote means you want to approve the application a yes vote means you don't want to approve the application?

MR. GOLDSTEIN: Is there anything --

SPEAKER: That's correct, right, yeah.

MR. GOLDSTEIN: A yes vote means that you would not want -- the -- yes, means that you're concerned -- just like the first one.

SPEAKER: Just like the first question?

MR. GOLDSTEIN: Yes, means, no. Yes, means that you're concerned. Okay. So no means you're okay with it, okay. And again, we each have to raise our hands first -- first for the no, which means that you're okay with it. Okay. And then you have to say your name, read it into the record.

MS. MILEK: Karen Milek, no.

MR. HOLMES: Greg Holmes, no.

MS. RUDNICKI: Stacy Rudnicki, no.

MR. COUCH: James Couch, no.

MR. ANDERSON: Britt Anderson, no.

MR. GOLDSTEIN: Chair votes no.

MS. JUNG: Lily Jung, no.

MR. GREEN: Mark Green, no.

SPEAKER: Matthew? Dr. Rizzo?

MR. GOLDSTEIN: Dr. Rizzo?

MR. RIZZO: Matt Rizzo, vote no.

MR. GOLDSTEIN: Yes.

MR. LU: Ying Lu, vote no.

MR. HURTIG: Howard Hurtig, no.

MR. GOLDSTEIN: Excuse me. No, she didn't, she only -- so for those present, it is again unanimous, no. Okay, the third question was that if the committee determines that for any reason the application should not be approved, so at this time we don't have to deal with it, it was said if it wasn't, and we've said the opposite. And then the last question, if the committee determines that the application should be approved, are there any studies the sponsor should perform post approval? And this gets to the question that was being raised before in some of the issues that we've been talking about. Open for discussion.

MR. HURTIG: So --

MR. GOLDSTEIN: Yes.

MR. HURTIG: A quick question about the question.

MR. GOLDSTEIN: Yes --

MR. HURTIG: It says, if the

committee determines the application should not be approved --

MR. GOLDSTEIN: No, it says should be approved; this one doesn't have the "not" in it.

SPEAKER: We skipped through it.

MR. HURTIG: Oh, we skipped number 3, I'm sorry.

MR. GOLDSTEIN: This is the only one with the "not".

MR. HURTIG: Sorry about that.

MR. GOLDSTEIN: Yeah, we skipped 3.

(Laughter)

MR. GOLDSTEIN: Actually, you know what, let me start this way. Dr. Hurtig, why don't you start first. I've gone around this way, my right sided -- handedness, but let's go left to right this time.

MR. HURTIG: I think we've all said that there are a number of interesting questions that need to be looked at further with more research. I'm not sure that I

would say that we need to require the sponsor to perform them, but I think they certainly should do it.

MR. GOLDSTEIN: And do you have any specific recommendations, because that's what the agency is asking us for?

MR. HURTIG: Well, I think it's important to try to get a better handle on the functional assessment than we now have and I'm sure that's in the works. Any -- I think further research on other side effects, including the ones that we've highlighted, particularly those that are more important than others such as depression, parkinsonism, et cetera, that might help to determine the difference between disease related symptoms and drug related symptoms.

MR. GOLDSTEIN: Dr. Lu.

MR. LU: Yeah, I think that this -- if -- you know, once it's approved it's not ethical to conduct any placebo, because this is only treatment that patient will have. So

maybe there should be some dose range study that look for dose related -- and I think the key endpoint should focus on the overall performance of patient, not just single index. I -- I'm not expert -- and we hope there are -- you know, there's a way that you can work out a composite endpoint.

MR. GOLDSTEIN: Dr. Green -- Dr. Rizzo, sorry. Dr. Rizzo?

SPEAKER: Dr. Rizzo.

MR. GOLDSTEIN: -- lost --

MR. RIZZO: Nothing to add. Hello?

SPEAKER: Yeah.

MR. GOLDSTEIN: Yeah.

MR. RIZZO: Yes, I'm here, I've nothing to add, thanks.

MR. GOLDSTEIN: Okay. Dr. Green.

MR. GREEN: I don't -- I'm not sure this is sensible, but the concern -- some concern would be, would there be any evidence of any rebound effect from stopping the drug, in other words, should we identify what we

think might be an adverse event and we stop it, is there any evidence that symptoms -- some symptoms like depression, could they be worsened by a rapid discontinuation? I'm not sure I've formulated that in my mind, but something in that order.

MR. GOLDSTEIN: Dr. Jung?

MS. JUNG: I think we've talked about the questions of long term separation of cognitive function from the chorea as well as validation of some of the functional scales. I think that having argued pretty loudly that we shouldn't put the burden on the company to do this, I would also urge that the patient advocacy groups who've stepped up to advocate for this drug being approved should work with the companies to do these post marketing studies.

MR. GOLDSTEIN: Dr. Anderson.

MR. ANDERSON: Yeah, I've nothing at the moment to add from my earlier comments.

MR. GOLDSTEIN: Dr. Couch.

MR. COUCH: I'd already mentioned my comments about long-term follow-up, and I think that that's really where it's going to be. I agree with Lily's comments about bringing the patient advocacy groups and -- in to help us out, but I think we'll -- the longer term follow- up over 5, 10, 15, 20 years, which was about the -- 20 years about the average survival, and that it is important to know how long the patient can take it, and if -- when the patient has taken a 10 years -- after 10 years, do you start seeing really adverse effects. We -- certainly, with L-dopa we began to see that after a time, the effect -- there was a longer term effect of L-dopa -- we may see the same thing here, and that will only be identified by having some kind of good long term follow- up.

MR. GOLDSTEIN: Dr. Rudnicki.

MS. RUDNICKI: One comment about

just having a better -- is somehow being able to develop something better to follow people in terms of function, because if we ever get to the point of looking at a disease modifying drug, we're going to run into the same question. So using this opportunity to develop a better functional scale for chorea patients would be a benefit long term.

MR. GOLDSTEIN: And that's certainly, I think, a common challenge that we've all talked about here, as we're facing this; it's a common challenge for the disease advocacy community also to advocate for it. Dr. Holmes.

MR. HOLMES: I don't think I would require them to do any follow-up, but I agree they should, and I think the -- what people have mentioned already, I'd be quite interested in the long term cognitive effects. How -- when people went on this drug, how long they stayed on, and why they came off, I think we should collect that

data, and also try to get a better handle of cognition. Although, I recognize it's very difficult if you don't have a placebo group at this point.

MR. GOLDSTEIN: Milek?

MS. MILEK: I have nothing to add, I agree with everyone.

MR. TWYMAN: I would expect that doses up to 100 milligrams might be used in practice and so a QTc study at this high dose is something I would be -- I would think would be important to obtain. The other aspect of the labeling is modified to have a slower titration rate. It would be great if that were backed up by data, but I think a head to head comparison between a slower titration and the current titration would have a sample size that will be excessively formidable and really not tell you very much objectively. So I don't think that's feasible. As to long term follow-up, I think the companies or the sponsors proposed a

registration program, and this should actually be adequate to provide data into an --

MR. GOLDSTEIN: Yeah, and I -- my only -- my recommendation would be some form of registry, especially looking for things like drug-drug interactions, the depression issue, to see whether that seems to be greater than would be expected, and some of the other side effects, given -- knowing that we don't have a placebo group that's going to be limited. But especially things like drug-drug interactions, looking for adverse events. Oh, yes, Dr. Temple.

MR. TEMPLE: I don't agree that placebo controlled trials can't be done with this drug, once it's approved, it's a symptomatic treatment, it doesn't delay anything permanent that we know about, so you could; whether anybody would enter them is another question. But I want to throw out a study design that might be informative, it

will not answer all of your questions about why we don't see benefits in some of the places we would expect to, but it might help and that's this.

Given that a fair number of people will be on the drug, it should be possible to identify patients who by history -- and we heard some people here today report on this -- have had major changes in their quality of life, ability to do things that they couldn't do before; it might be different from average person, but that's okay. You can then do what's called a randomized withdrawal study. The virtue of which is you don't have to wait around for people to come in, they're all identified, they exist and the second virtue of which is as soon as there's any deterioration, you stop the trial, because the person have had the endpoint of concern.

If you put into that study people who had had unequivocal, what appeared to be, quality of life benefits, you then get to see

whether those benefits go away rapidly, and you can get an answer on that question. It still won't explain why there isn't a more general improvement, but at least it would show -- and this would get in the label if it was successful, which seems to me is worthwhile, that at least some people have a substantial benefit in their quality of life. We've seen these kinds of studies in a number of areas, that are relatively easy to do, if people are willing to do them, and it would help enormously if the community it interest -- was interested in finding this out.

MR. ANDERSON: Don't you think you'd have a problem with actually blinding that withdrawal since the effect on chorea is so prominent and fast, that the minute you stop the drug within, I mean, 12-24 hours, there's marked increase in chorea, that patients themselves and their family members would be unblinded almost immediately.

MR. TEMPLE: Well, you have the

same problem when you do a randomized trial, giving the drug in the usual way.

MR. ANDERSON: Right. So that -- there's -- we never discussed the issue there probably was significant interference with the blind just because of the therapeutic affect on chorea.

MR. TEMPLE: You know, all I can say is when people have looked at unblinding and trials of beta blockers and organic nitrates, which have obvious effects, you'd think it turned out people didn't really know so well what drug they were on.

MR. GOLDSTEIN: Yeah.

MR. TEMPLE: But you're right, there probably would be some unblinding. I think the hope is that the dramatic difference that's described would be so large, it would be reasonably persuasive anyway, but a lot of drugs have side effects that unblind them, and what can you do.

MR. GOLDSTEIN: You know, that --

well, that's actually why I was asking way back when -- about whether the assessments in the study was done by somebody who wasn't doing the treatment, that's the way you get around that, is that the guy given the drug, who said, "Oh my God, it went away," he's not the one -- he or she is not the one doing the assessments, it's somebody who's never seen the patient before, they're coming in just doing the scales.

MR. TEMPLE: Right. And I didn't try to describe what assessment would be done, it could be done by a third party. The main point is you identify people who are absolutely positive their lives have been changed by this, and then you -- you know, you could use a visual analog scale, there's a lot of ways to do it, but we'll probably talk with the company about this. But if everybody -- if any -- if everybody thinks it's a really dumb idea, you should tell me.

MR. GOLDSTEIN: Really dumb now.

MR. TEMPLE: Okay.

MR. KATZ: Yeah. We didn't ask this specifically, but maybe now is the time, and a number of people have commented on already, which -- and this is the question of the RiskMAP, which of course -- it can mean a lot of things to a lot of people, the company has proposed a very specific, a very detailed plan. I don't think we need to go through or need to hear or have you go through -- going through every detail of that plan, but there were some sort of major elements of that plan that we would like to get some view from the committee on, like limited distribution.

I believe, they proposed some sort of a standard for limited distribution, frequent contacts, this sort of thing. So we'd just like to hear your thoughts, whether or not you think that that's necessary, do we need that, is there anything -- and again, there have been some comments already about this, is there anything that you think that

they should do, or we should ask them to do in the -- in Phase 4 as far as minimizing risk education, that kind of thing.

MR. GOLDSTEIN: Sure. Well, I don't want to talk to that. Dr. Jung?

MS. JUNG: The problem with using a limited distribution is that you penalize patients depending upon their payers, and we've encountered that with other drugs that we won't mention, because we've already talked about them enough here, but it's not -- you don't have a open fair playing field, and I don't think it's fair for the patients.

MR. GOLDSTEIN: Dr. Rudnicki. Rudnicki, I got to get your name right.

MS. RUDNICKI: Rudnicki, that's okay.

MR. GOLDSTEIN: I got it close.

MS. RUDNICKI: One of the things I think they had up there was no refills initially, and I think that's a reasonable thing, where you have to have contact with

the physician, I can't remember how long they've -- I think they said 4 weeks, and I don't remember what they said after that, but I don't think that would have to be ad infinitum, but perhaps, initially, for the first 3, you either had to have one on one contact, or at least phone contact with the physician to have an approval. Not unlike, you know, with scheduled narcotics.

MR. GOLDSTEIN: Yeah.

MR. HOLMES: Yeah, I would not be in favor of RiskMAP, I don't -- again, I haven't seen anything presented that makes me that concerned about this drug, and why -- it's just going to limit access to patients, and I don't think there's going to be any tangible gain to it. It was really a dangerous drug, I could see that, but I'm just not buying this argument that you have to have nurses call people and all this and that; that's a job of the physician, the physician prescribed in the drug should be

the one monitoring the patient, not the pharmaceutical company.

MR. ANDERSON: And --

MR. GOLDSTEIN: Dr. Anderson.

MR. ANDERSON: -- I was sort of, I guess, one of the people who've been sort of -- have -- addressing more concern for it, and even I wouldn't feel that the RiskMAP that I heard outlined was what I thought would really address the concerns that I had, and it does seem overly restricted for providers and for the patients.

MR. GOLDSTEIN: Other comments? You know, something reasonable might be an online education thing for the prescriber, that the prescriber would have to go through first, to assure that they understood what the drug was, how it worked, what the potential upsides and downsides were, what we know and what we don't know about it, that -- and that way, at least there'd be -- the issue of the level playing field is

addressed, anybody can do that, and at the same time we'd have some evidence that at least they've gone through that level of education. Other comments in response to Dr. Katz's question? Very good. If Dr. Katz, Dr. Temple have -- the committee addressed all of the questions adequately for you, is there anything else -- Dr. Hurtig, you just had another comment?

MR. HURTIG: I just have one question, and I want to know if it's appropriate to ask what this drug is going to cost if it gets approved and goes out into the marketplace.

MR. GOLDSTEIN: No.

MR. HURTIG: No?

MR. GOLDSTEIN: I don't know --

MR. KATZ: Well, certainly, we don't ask that question or get to ask that question, it's not part of our decision.

MR. HURTIG: So it's not appropriate, thank you.

(Laughter)

MR. KATZ: Not appropriate to ask me.

(Laughter)

MR. GOLDSTEIN: As cheap as possible, all right. Okay. If there are no -- if the FDA has no other questions for us or anything else you'd like us to expand on, I think we have done the job that you've asked us to do. So the meeting is adjourned, I thank again, all the members of the public that have come, that have come and spoken to us, the sponsor, the FDA and my follow members of the committee, thank you all.

(Whereupon, at 4:05 p.m., the PROCEEDINGS were adjourned.)

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