cognitive measures by looking at the dose closest to when the adverse event happened, the previous dose, and then the previous non-zero dose, if the dose was withheld for some sort of an adverse event. But we really couldn't find any trend with respect to dose for all these measures what you are mentioning.

MR. COUCH: Well, this wasn't so much adverse events, but this was every time they did the rating scale, they should have basically had their Stroop and their Stroop interference, and those would have been numbers just like the chorea score. And I was wondering if you looked at those numbers versus the dose in the same way you looked at chorea score versus the dose.

MR. BHATTARAM: Yes, we did look at that, and we couldn't find any strong trends in those directions.

MR. GOLDSTEIN: Dr. Jung.

MS. JUNG: Dr. Villalba mentioned

in slide 37, safety issues and postmarketing reports. And since this drug has been used in other countries for over 30 years, I guess I have a question. Are there any other postmarketing reports of side effects such as akathisia and depression and dysphagia?

MS. VILLALBA: I think that the sponsor could probably answer better. That question overall, in my analysis, they were not something that is outstanding or different from what it is expected, because of the pharmacology of the drug.

MR. STAMLER: Would the Chair like me to comment on that? Yeah, in the postmarketing database, there were additional reports of akathisia, parkinsonism, depression, suicides, so things that we saw on our clinical trial database.

MS. JUNG: And how does that compare with what you have reported in your studies?

MR. STAMLER: In terms of, like

event rates, the problem with the postmarketing data is it is very old. It dates back to 1960, most of it, when the drug was originally developed by Roche. So we don't really have good denominator information to give you that. So qualitatively, we know it's the same.

If I might add just one small point of clarification that came up in the presentation, tetrabenazine does not block dopamine receptors. It inhibits VMAT2 and depletes dopamine presynaptically, but at clinically relevant concentrations, it doesn't interact with the dopamine receptor. It's got an IC50 over 2000 nanograms per ml.

MR. GOLDSTEIN: Dr. Temple.

MR. TEMPLE: This is for Dr. Davis, I think. One of the sponsor slides number 50, showed a responder analysis, and showed that about, well, I don't know -- about half the population had, what you might call, quite a nice response, and about half,

didn't. I wonder whether some of the -- whether it would be worthwhile looking at some of the functional assessments that didn't show what you might have expected due to the decrease in chorea. If you looked at those by subgroups of people who responded, a lot, that is, the left two ones on 50 where everybody had at least a six-point response; whereas on the right side of slide 50, all of them had less. Would it be worth looking -- I mean, I know, it's not randomized and everything, but would it be worth looking at some of the functional things that didn't work out in those two subgroups? And whether have we or the sponsor tried to do that?

SPEAKER: I think we did.

MS. DAVIS: I think we did. I think we did look at that in the initial evaluation for the non-responders on the -- particularly the functional scales. And I don't think that we saw any clear pattern that emerged as a result of the analysis.

MR. TEMPLE: So even the really good chorea responders didn't seem to -- that didn't seem to carry over to the functional measures. Okay. And my other question was related to dose response. One approach to analyzing titration data is a NONMEM analysis pioneered by Lewis Sheiner and his colleagues. In hypertension, it seems equally suitable to this setting. I wondered if the dose response had been -- I mean, I know we have concentration response data, and Dr. Bhattaram has that. But I wondered if we had also looked at the dose response that way. It's informative in a titration setting, or it can be.

MR. BHATTARAM: The analysis actually focused on the dose response analysis, because we didn't have concentrations in all these patients. So it's exactly the methodology what was reported by Lewis Sheiner in one of those publications.

MR. KATZ: Yeah, I have a question, probably for the sponsor. The trial 004 didn't detect in effect, dysphagia. Just one or two cases; and we couldn't tell it, there was no difference. But there was a lot of talk about dysphagia. And most of the data, I gather, at least the long term, comes from Dr. Jankovic's data. We are under the impression as, I think, Lourdes said, a number of those cases, we think, weren't reported, or they were recorded by Dr. Jankovic, and not reported as AEs, because they thought they were background events.

So I wonder if we could get some clarification about exactly what happened there. Were there recorded? Did Dr. Jankovic record them in all cases or make a judgment before deciding to record them as to whether or not they were drug or not drug-related? If he recorded, then were they all recorded by you as AEs? And then I have a follow-up question. Well, let me just ask

that. So I think we need some clarification about exactly what -- the methodology that was used to look at dysphagia.

And then the other question is, because it's all open-label, and it's going to be very difficult, if not impossible, to tell if it's related to the drug. Is there anything that you did or could be done to try and get at the question of causality of dysphagia from the open-label data? And I don't know necessarily what that would be, a temporal relationship, you know, what always occurred two weeks after the drug was started, or what attempts if any have been made to look at that part of it?

MR. STAMLER: Yeah. Well, you know, the one thing that we looked at -- I guess I want to comment on the data from Dr. Jankovic's site that we looked at, and then maybe ask Dr. Jankovic to comment on his reporting approach -- but if I could have the slide on. This is -- we are aware of the

concern about reporting of adverse events. And I know that -- slide on please -- that dysphagia was reported at Dr. Jankovic's site.

So in the chorea patients that had Huntington's disease, there were 19 reports of dysphagia. Some of those were new onset. So people that didn't have preexisting dysphagia, and some of those were worsening dysphagias, where it was preexisting and was recorded as worsening in severity or frequency. So you know, and obviously it was less common in the non-HD chorea patients. Regarding Dr. Jankovic's approach in terms of how he identified an adverse event, I would actually like to ask him to come up and clarify that.

Jo.

MR. JANKOVIC: Well thank you for the opportunity to respond to your question. Just to respond to your first part of the question, dysphagia is a normal consequence

of Huntington disease. And so just like in patients with Parkinson disease, when they come in and have tremor, we don't record tremor as an AE of whatever drug they may be on. And this is true for patients with Huntington's disease who have dysphagia. Since it has been present for some time, we don't usually record it as a AE.

On the other hand, if a patient with Huntington's disease reports recent onset of dysphagia, then obviously it is a signal for us that this may be an AE, and then we recorded it as such in those cases that are reported here on this slide, indicate those cases that developed dysphagia recently or there was a recent exacerbation of dysphagia.

So I think, to respond to your question, I think a clinician probably would not have any difficulty recognizing dysphagia as a side effect of tetrabenazine versus dysphagia as part of Huntington disease. Now

--

MR. KATZ: Can I just ask one follow-up, not to be too picky. But when you say "recent onset," it's hard to know exactly what that means in the context of how often the patients were seen. So how often were patients seen, and how did you decide whether it was recent, in other words, if it occurred between two visits? Was it automatically suspected as an AE or -- what's the relationship between when it happened and when patients were actually queried about it?

MR. JANKOVIC: Well, in our compassionate prospective protocol, we have standard procedures that we followed with every patient. And perhaps I can have BG 39. Okay. This is fine. So we systematically recorded all the side effects of patients when they were first started on tetrabenazine. They were given information about the drug, of course, and then there was a titration sheet that also included the

potential side effects that the patient and the family should look for.

The patients were instructed to call us if any new symptoms developed. And we obviously documented all these reports on our source document. So I believe that we accurately and systematically addressed the issue of AEs, and this was also reflected in the Prestwick and the FDA audit of our records. But -- again, to highlight the point that you are all making about recording AEs related to tetrabenazine, if there was any change, you know, especially in the last week or two after initiation of tetrabenazine or when a dosage was increased, the patients were instructed to call us. And, of course, at their follow-up visit, we again reevaluated this retrospectively from the time they were last seen.

MR. GOLDSTEIN: Dr. Couch.

MR. COUCH: Following up on that, since aspiration pneumonia is correspondingly

one of the acute problems that you ran into with dysphagia, do you have any data from this longer-term database on aspiration pneumonia? Secondly, with regard to either of these databases, do you have any data on the amount of weight loss that, you know, was there -- an acute change in weight -- or a subacute change in weight as opposed to a longer-term weight loss that the patients may experience, whether the pneumonia and weight loss from malnutrition, of course, are your two major problems that can result with dysphagia.

MR. JANKOVIC: If I could have the slide S23, because I think that addresses your point, Dr. Couch. So this is based on our assessment of adverse effects in patients followed in our center. So pneumonia was clearly the most common cause of serious adverse effect. End- stage disease, of course, was important, dehydration, infection, and so on.

So I don't think this is unexpected. In fact, it's consistent with what has been reported with other studies including the Prestwick, you know, studies. And keep in mind that there may have been up to a million people already exposed to tetrabenazine since 1979. And I think if there was a unique signal in terms of some unusual AE related to tetrabenazine, I think we would be aware of that at this point.

So I think the kind of AEs that we have encountered in our population are similar to what has been encountered in the Prestwick studies as well as in all the reported series. I hope that answers your question.

SPEAKER: Jo, I don't know if you want to comment on weight loss -- on that subject.

MR. JANKOVIC: Yes -- yeah, you asked about weight loss. Slide 95, please. So this was the frequency of weight loss --

14 percent of our patients reported weight loss that we attributed as a potential AE related to tetrabenazine. I hope that answers your question.

MR. COUCH: Yeah, thanks.

MR. GOLDSTEIN: Thank you. We drifted a little towards questioning the sponsor again, which is fine. But I just want to first make sure that we have addressed the questions that we need to, during this session, to the FDA. Dr. Rudnicki, first.

MS. RUDNICKI: Mine was actually a question to Dr. Jankovic.

MR. GOLDSTEIN: Let's hold off first, and then we'll come back to it. Promise. Dr. Twyman.

MR. TWYMAN: Yes. This is for Dr. Villalba. Your slide number 34 is actually quite interesting where you suggest that perhaps at week 3 at a dose of 50 milligrams, you might predict whether or not you have a

response in the long duration. I was just curious whether or not those who, the non-responders versus responders, past that point, have a difference in the AE rates, post week 3?

MS. VILLALBA: Yes. Actually we think it was appropriate even to make this kind of analysis, because the non-responders include those who didn't reach a drop in chorea score of three or more at week 3, and also include the patients that drop because of adverse events. So that includes patients who are in lower doses. And as well as the patients, for example, the patient who committed suicide, we had a very good response -- a good three. So this is -- there is a post hoc analysis.

I wouldn't put too much emphasis there, but more on the second analysis that probably by that time of week 3, you realize the ones who are going to respond already responded at some point in some extent. And

basically, if they did not respond by week 7, probably you don't need to continue to treat the patient much more. If once they've reached the 100 milligram dose, I wouldn't continue treating one more than a week after that, I think.

MR. GOLDSTEIN: Dr. Yung -- Dr. Lu, sorry.

MR. LU: Yeah, I have a question to FDA in terms of what's the policy and guidelines. And so this is like a single study that, you know, not duplicate in the second withdrawal study failed to get the P value. So what are the criteria for a drug that you will base a single trial, the very strong evidence, consistent, internally consistent in terms of primary end point, the question of you know, the correlation of primary and secondary. And so -- and also for this particular Huntington's disease, I know it's a new -- first drug. But is there any guidelines in terms of not only look for

one component of in the x, but you need to prove across both or just one component will be sufficient?

MR. KATZ: Well, let me answer the second part first. There are no guidelines. There's no precedent obviously for what should constitute, you know, positive, sort of, what should constitute sufficient evidence to -- to constitute substantial evidence of effectiveness. The primary outcome in this trial was chorea. We thought that was a reasonable primary outcome. Certainly, as I said in my opening remarks, there is no requirement that everything be effectively treated.

The question we are asking you is, in the face of what appears to us to be evidence that a functionality -- you know, what is the clinical meaningfulness of the effect you've seen in chorea that we need to have some independent measure of functionality or activities of daily living

to be also positive to say, well, this is worth having out there. So I mean, that's a large part of the question we are asking you.

So -- but there is no precedent, and certainly you could recommend that the effect that you've seen on chorea, if you believe it's a real drug effect, is sufficiently large that we don't need to have any evidence, that it does translate into something identifiably meaningful in terms of functionality or anything. But that's a big part of what we are asking you.

The first question had to do with, what are the standards for proving a drug on the basis of an effect -- of a single trial, normally we require replication. If you actually look at the approvable letter, it states as the standard, that we applied in this case, the standard of one adequate and well-controlled clinical investigation plus confirmatory evidence, the standard that we in the division, I don't believe, have ever

applied before. That's a standard that's been in law for 10 years.

And of course, it's not -- the law doesn't say anything about what should constitute confirmatory evidence. And -- but we do have a guidance actually that talks about the elements of a single trial that would certainly support a finding of substantial evidence or effect in this just on the basis of that. And it has -- that document talks about very low P values, internal consistencies so that multiple centers might be independently statistically significant, multiple subgroups, severe, mild-to-moderate patients all moving in the same direction, so there are lots of things.

In this case, I think what we considered primarily to be the confirmatory evidence that the law requires, was study 005, which was a negative clinical trial. And typically, I don't think the law anticipates that you would use as

confirmatory evidence, a failed trial. But in this case, we thought it was pretty compelling, because first of all, the P value on the analysis that we chose to do was 0.11, which of course doesn't meet the usual standard, but it's an extraordinarily small study -- extraordinarily small. And the treatment effect size was identical to the -- in fact a little bit bigger, I think, than the estimate of the effect in study 004. And you put the withdrawal data in study 004 with that, where, you know, it was clearly within a couple of days everything went right back to where it was.

So we considered that data package sufficient under the standard of one study plus confirmatory evidence. I think that's how we reasoned it.

MR. TEMPLE: The withdrawal phase in study 004, a very dramatic return to exactly where you were before, could be considered a --

MR. KATZ: I said that.

MR. TEMPLE: -- a piece of confirmation. Did you say that?

MR. KATZ: Yeah.

MR. TEMPLE: Oops, sorry. I didn't hear you. I must have been thinking about what I was going to say.

MR. KATZ: I was thinking the same.

MR. TEMPLE: And for what it's worth, and cardiorenal has been telling people that if you get the statistical equivalent of two studies, which is a P value of 0.000625, that's sort of a lot like two studies. At least in a multi-center environment we are not so worried about one person cooking all the data. And this comes close to that as well. But it's very much a judgment call, even when we interpreted the law as requiring two studies. If repeating a study seemed unethical like a post-infarction beta-blocker trial, we relied on a single study. So there's always been some judgment

in it.

MR. GOLDSTEIN: I have a question for the FDA folks. The drug apparently has been approved now in Europe, as we said, in some places for decades. But in a few cases, it's been within the last year or so, and for -- at occasions not dissimilar from what's being looked at here. Is there any information in those regulatory packages that we are not privy to hear that you might be able to get at that might provided some more evidence. Because again we are dealing with very small numbers, basically, a single trial?

MR. KATZ: I'm not aware of what's in those packages -- and as far as we know we have all the control trial data. So the company might know better what -- what data the other regulatory agencies rely on.

MR. STAMLER: Yeah. There were no additional trials conducted. And in some of the recent European approvals, I believe, the

Netherlands and France, the study 004 data was submitted either in part, in summary form or as, you know, complete data for their review.

MR. GOLDSTEIN: Thank you. Another question, again from the FDA standpoint. We are basing a lot, obviously everything, on the scale and on sub-portions of the scale. Is there a regulatory requirement for formal validation or reliability studies of a scale such as this? Some of these, you know, we faced this in my own area, in stroke, for years, where investigators would make-up scales, they hadn't been tested, hadn't been validated, and were trying to make conclusions based upon "not great data." Here we are dealing with discrepancies, and we are trying to understand them.

How is -- what's your view of the validity of the scale overall, the sub-portions of the scale, and then picking out individual questions within sub-portions

of a scale like this?

MR. KATZ: Well, I think there are questions about what a lot of these things are measuring, a lot of the sub-scales. But I think we thought that for the primary outcome, chorea, it seemed that the scale was sort of face valid. It was -- you could, I suppose, argue about, you know, the scoring and that sort of thing. But I think it was -- it seemed to be a fairly straightforward, self-evident, reasonably reliable way to assess chorea, abnormal movements. And so the other things I think are more complicated, definitely more complicated. I think we thought that the chorea scale was pretty self-evident.

And to answer your generic question, which is, do we require detailed psychometric validation of every scale we use? I think we are probably doing that more and more. But traditionally, I don't think we necessarily have. I think it's really

been a judgment. And I'm -- I think we have certainly relied on scales that seem to be face valid, seem to be measuring the symptom of interest, and seem to be reliable.

MR. TEMPLE: It comes up a lot in patient- reported outcome scales, where the conclusions are somewhat less direct than, say, measuring some, you know, pushing on someone's ankle and seeing how much edema they have. And we are asking for validation in a lot of those settings. But as Russ says, this one sort of looks like it's probably measuring what you wanted. And of course, everything is blind.

MR. GOLDSTEIN: Dr. Jung.

MS. JUNG: I have two quick questions along the same lines of what Dr. Lou asked. It isn't clear to me. Is the discussion of a RiskMAP generated by the agency or was that brought up by the sponsor? And --

MR. KATZ: That was brought up by

the sponsor. I think in response to the fact that we had numerous questions about the safety. And I think that was their response.

MS. JUNG: Okay, and then the second question is, have any of the other countries in which this drug has been approved, required a RiskMAP because of the adverse events?

SPEAKER: Let the company answer.

MR. STAMLER: Yeah. I'm not aware of that. I -- you know, we've always reviewed and had access to their labeling, but we are not aware of any country that's instituted a RiskMAP.

MR. GOLDSTEIN: Dr. Couch.

MR. COUCH: This is a question for the FDA. Given that the Huntington's disease rating scale is a very subjective type of scale, and we deal a lot with subjective scales and all kinds of things, the fact that this finding on chorea was so robust, how -- for a scale that requires a lot of intuitive

or not strong numbers type of thing, how impressive is the finding that the -- on this intuitive scale that the finding was so robust?

MR. KATZ: I think, we think it's quite impressive. It seemed to be reproducible almost to the tenth, you know, the decimal point in terms of the effect, the estimated effect across several studies. And again, everybody is -- we believe the studies were adequately blinded. We had experts evaluating this, which -- and again, I'm not sure there's a much better way to do it for something like this. So I think we think it's pretty impressive.

MR. TEMPLE: Are you asking -- I mean, you are -- usually if a scale is terrible, it introduces a bias toward not finding anything, sloppier it is. So it's sort of impressive that in a setting where you think it's highly subjective, it still came out. I mean, that's sort of impressive.

MR. GOLDSTEIN: Dr. Hurtig.

MR. HURTIG: It might be worth knowing from the sponsor and others what kind of validation studies have been done on the Huntington disease rating scale.

MR. STAMLER: I'd like to ask, either Dr. Shoulson or Dr. Como to comment on it because they were involved in the development of the UHDRS.

MR. COMO: Well, Peter Como, University of Rochester. Thank you, Dr. Hurtig for your comment -- your question. It's always difficult to understand what one means by validation because you have psychometric validation, and then you also have validation of a scale as it responds to a treatment. I think in this case, the total chorea score, you really have -- really the first signal of validation of the total chorea score. And as you recall, it almost reached statistical significance on the total motor score all together. So to that degree,

one would have to say, yes.

Regarding the other aspects of the UHDRS, certainly with function, and cognition, and behavior, that's something that we are continuing to do as we kind of proceed with ongoing clinical trials in Huntington's disease, to take a closer look at these scales and see if there are treatment effects, or are these scales just really not measuring, as Dr. Katz suggested, not measuring what we really think they are, and refine them accordingly. I don't know if Dr. Shoulson wants to add.

MR. SHOULSON: The only thing I'll add is, the scale was designed to look at the long-term natural history of Huntington's disease, not in terms of short- term experimental therapeutic studies. We've adapted it since, because there is an interest in doing that. Obviously, the ultimate validation is to find a change in the setting of a "Positive Clinical Trial."

And we haven't had too many. But this is actually one example where at least the chorea component of the scale seems to be valid in a consistent fashion in terms of indicating that type of validity. I mean, that's the ultimate validity in the study.

There have been factor analysis of the studies published in terms of what could be most sensitive to the change. Happy to give you those references. I don't think they are that germane to the study. There are inter-rater reliability studies that have been done and published too, particularly on the motor component. And as I said, these studies are -- the scale is principally in use in terms of long-term studies, looking at what happens to Huntington's disease over the long term, obviously in an effort to see if we can change the course of that natural history.

MR. HURTIG: Inter-rater reliability is good for the scale?

MR. SHOULSON: The inter-rater reliability is good for the scale. It's particularly good with -- it's particularly good in terms of picking up where investigators say this is definitely an extrapyramidal movement disorder, unexplained by anything else, and therefore what we call a "for a big change," at least in terms of the motor part. And they have people look at chorea too.

There's also a lot of training that goes on around this with the investigators not just at -- not just at meetings, orientation meetings, so to speak, or investigator's meetings, but just in general as we go on as a group to try to refine this. We also do it in terms of cognitive testing, training, and behavioral one, which is more challenging.

MR. GOLDSTEIN: And before we go on -- any other questions for the FDA, and then --

(Laughter)

MR. GOLDSTEIN: And of course, again, drifting off -- drifting off task here. Yeah. Dr. Lu.

MR. LU: Yeah, I have a question for FDA in their package about the motor score substrata called the chorea score. And -- because that's one of important indication in the Huntington study group that predict the prognosis of patients for disability. So I didn't see you mention that here. But I'd like to hear is there any change, because now you changed the analysis plan for twelve month data now -- twelve weeks, I'm sorry. So used to be the -- in the report, you had 9 to 12-week average, right?

MS. VILLALBA: I don't think there was a -- there wasn't a significant change.

MR. LU: So there still wasn't a significant change when you changed to 12 week. Okay. Thanks.

MS. VILLALBA: -- down here, but

no, there wasn't a big change.

MR. GOLDSTEIN: Other questions for the FDA? Okay -- we have a few minutes. I think that there were other questions earlier that wanted to be directed to the sponsor that I said we would deal with later and we still remember have time after the open hearing, but we have about 10 minutes now, so why don't we try to deal with some of those, if we could, and Dr. Rudnicki was first.

MS. RUDNICKI: So this is for Dr. Jankovic, because one of the issues is dysphagia and recognizing dysphagia and when it's expected or not expected. So our scores on the chorea score for, say, buccoorolingual, or truncal, if -- you know, if they have a lot of chorea in those areas, do you kind of expect to see dysphagia or aspiration, because that would be useful in knowing whether or not it's expected or unexpected.

MR. JANKOVIC: Certainly, one would

expect that a patient with Huntington's disease who has predominantly orolingual chorea, would also be the same patient who might have trouble with dysphagia, but I don't think that there is necessarily a direct correlation, you know, the mechanism of dysphagia in Huntington disease is really not well understood, but as you point out, it could correlate with orolingual chorea.

MR. GOLDSTEIN: Dr. Couch.

DR. COUCH: Yeah, one of the things that came out in the data analysis was that although the chorea was diminished, and I think we've seen this very robust effect, the number of falls were -- was greater in the tetrabenazine-treated group than in the placebo group, and I'd like to ask if any of the investigators of the company or -- would have any comment on that because that's really counterintuitive that your chorea would be diminished and yet your number of falls would be increased?

MR. STAMLER: Yeah, actually, we are trying to find the slide of the overall events in 004, but the rate of falls was comparable. It was, I think, 15 percent in tetrabenazine and 5 -- and 13 percent slide on in the placebo group. So it's true that there was no apparent reduction in the fall rate, but one thing to mention is the inclusion criteria required that the patients were -- had to be independently ambulatory, so it's possible that there was a ceiling effect and that they were not the most impaired-gait patients that could clearly benefit in terms of reduction in falls. I don't know if Dr. Shoulson wants to comment something else on that.

MR. SHOULSON: When you point to a challenge to Dr. Couch, because once patients see a reduction in their chorea, they are a little bolder in terms of risks to take in anticipation, so it doesn't work as one would like it, certainly as a clinician to see

that, and in fact often have to warn the patient that, yes, there is this improvement going on. There is a lot of cautions and warning going on, but one thing is, don't just translate this in terms of going out and trying to do things that you should be cautious about.

MR. GOLDSTEIN: Dr. Koski.

DR. KOSKI: Dr. Shoulson, since you're up there, I'd like to actually ask you a little bit more. You made the comment that you thought that if one used a less aggressive titration that you could avoid or identify side effects and drop back in dosage. Can -- could you be a little bit more explicit about that.

MR. SHOULSON: Sure. Yeah, I like -- thanks for asking. I'd like to elaborate on that. So this was -- this titration schedule, weekly, was done in the context of a clinical research study, where by the way, there was some pressure to try to compact

within a period of time and adjustment of the medication, and then a maintenance phase. In real life, a clinician would not be making a change that frequently.

And I think also the fact that in this double- blind type of study, since none of the investigators really had experience with this drug, that they were just trying to find out, you know, what it was at that point in time and I think we did encounter a lot of adverse effects because of that. I think it's actually very helpful, because I think it gives us the upper level.

We didn't really define the maximally tolerated dose, but I think we came close to defining a maximal titration schedule, and I think something less than that certainly in terms of my open label experience with the drug would certainly be much more suitable. I'm not talking about the dosage whether it's 50 or 100 milligrams; I'm talking about the rapidity of dose

adjustment.

MR. KOSKI: And what would be your experience then in terms of the rapidity?

MR. SHOULSON: Well, what I usually do in a situation like this is adjust monthly. There is often a call to the patient or to the caregiver on a weekly basis to ensure that some of these side effects are not emerging during that period of time. But you're almost chasing yourself every time you adjustment on a weekly basis, given -- I know that the half-life is relatively short of the metabolites, but still in terms of seeing the clinical effect I think a weekly type of adjustment I think was very aggressive, given what should happen I think in clinical practice.

MR. GOLDSTEIN: Dr. Green.

MR. GREEN: I have a question about weight. You report weight losses in SAE, but there is really no more discussion about weight, since the response is so robust in

regard to chorea, you'd expect that you would offset the calorie expenditure that a lot of these people have from constant chorea and they would gain weight, so what do we know -- do we know more about weight changes, not just weight as SAE?

MR. STAMLER: Yes. Well, in terms of weight loss, we did -- I don't believe we had any adverse events or serious -- certainly no serious adverse events pertaining to weight loss, but there was no between group difference in terms of the weight change in this trial, but that may be based on the fact there was only a 12-week trial, but there was no difference between the two groups in terms of change in weight.

MR. GREEN: I thought there was, but okay.

MR. STAMLER: I can check and confirm that.

MR. GOLDSTEIN: One last question before we break. Dr. Holmes, you've had a

question.

MR. HOLMES: If you could review a little more the MedRisk program that you're planning to do, you're going to restrict use of the drug to patients that have, you're going to restrict the dosing -- you want to see the dosing regimen, and the people who wanted to prescribe the drug, is that what you're going to be following?

MR. STAMLER: Right, I mean the proposed labeling would be explicit about, you know, not titrating any faster than once per week or you know, if based on discussion or perhaps a slower titration scheme. So that titration scheme would need to be indicated in the prescription from the physician, and if it is faster than the proposed scheme in the labeling, then the pharmacy wouldn't fill that. They would have to go back to the physician and say, we're not going to fill that at a faster titration rate based on the clinical experience.

MR. HOLMES: Are you going to require that the diagnosis be established or how are you going to handle that?

MR. STAMLER: Right, now, the plan is that the labeling that's assured in the -- normally, prescriptions don't have an indication, so right now the plan is not to have an indication-specific label or indication-specific prescription. But obviously, we have no intention of having this drug used for other than Huntington's disease.

MR. HOLMES: Okay. Do you have any information on pediatric dosing?

MR. STAMLER: I -- we have not done the trials -- I don't know, Dr. Jankovic may have some experience in treating pediatric patients.

MR. JANKOVIC: Just to remind you, I received my ID in 1979. Since that time, I've treated well over 1,000 patients with a variety of hyper-kinetic movement disorders,

including for example, Tourette's syndrome, which frequently occurs in children and in those individuals we had used tetrabenazine, of course, starting at a much lower dose and increasing it very, very slowly and so far we have not seen any unique adverse effects in children as compared to adults.

MR. GOLDSTEIN: Thank you. I want to thank the sponsor, the FDA, and the members of committee for -- oh, I'm sorry, Dr. Katz, did you have a question -- I'm sorry.

MR. KATZ: No, I just -- just with regard to the questions about the RiskMAP and what the company is proposing is -- I'd say, that was something that the company had proposed spontaneously. We have made no decision about whether or not we think it warrants assuming that you recommend the approval, whether it warrants a risk map. If it does, what the elements would be. So that's really open for a discussion. I just

don't want folks to have the impression that that's a done deal and you know, we can tweak it a little bit, but we are going to leave it. We want to talk about that in its entirety at some point.

MR. GOLDSTEIN: Thank you and again, I'd would like to thank the sponsor, the FDA who -- members who presented in the committee for an interesting discussion. We are going to adjourn until 1:15, when we will resume with the open public hearing, followed by which we will have more discussion, which I'm sure will be interesting and lively.

For the committee members, let me just reiterate that there can be no discussion about anything that we've heard or anything that we are thinking about, you know, talk about dude basketball, that's okay. Our lunch is out to the door to the --

(Whereupon, at 12:15 p.m., a luncheon recess was taken.)

A F T E R N O O N S E S S I O N

(1:15 p.m.)

MR. GOLDSTEIN: Okay, if we could come back to order. We're going to begin the afternoon sessions. And we begin with the open public hearing. Both the Food and Drug Administration and the public believe in transparent processes for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee, the FDA believes it is important to understand the context of an individual's presentation.

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

other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you've had any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, we will not preclude you from speaking.

The FDA and this committee plays great importance in the open public hearing process. The insights and comments can -- provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions.

One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully, and treated with

dignity, courtesy, and respect. Therefore please speak only when recognized by the chair. Thank you for your cooperation.

I just want to also reiterate the instructions that were given to each one of the open public hearing speakers. Presentations from individuals will be strictly limited to four minutes confirmed -- as confirmed in your e-mail, using a timer.

The timer light will be green for the first three minutes, then yellow for the remaining 60 seconds. This will be your warning to conclude your talk. The light will turn to red at the end of your time. The microphone will then cease to work. So four minutes is four minutes.

(Laughter)

MR. GOLDSTEIN: I'm ruthless.

(Laughter)

MR. GOLDSTEIN: Okay, having said all of that. And we all understand the ground rules. The first speaker on our list,

and we have, I believe, 14 speakers that have -- excuse me -- oh, sorry, 14 speakers on our list. The first speaker is LaVonne Goodman.

MS. GOODMAN: Are we ready?

MR. GOLDSTEIN: Set, go.

MS. GOODMAN: Yes, okay. I'm LaVonne Veatch Goodman from Seattle and I come as a family member and as a physician to HD patients. I'm coming to urge you to approve tetrabenazine because chorea hurts and this drug helps a lot.

Chorea hurts in so many ways that aren't measured in functional capacity scores. It isolates people, and that's a very important one that isn't measured. As an example, my -- when my husband and I were out to a movie, the woman in front of us became very irritated, because his foot kept hitting the back of the chair. Sounds minor, but he didn't ever go to another movie.

We know this sort of thing happens at all grades to HD people all the time.

Like it or not, the public is uncomfortable with chorea. Even in my waiting room, people sit away from my Huntington's patients. They're kind in this protected environment. Strangers move away from us in grocery stores, they move to the side on sidewalks. And even worse, they think we're drunk, have us removed, or even worse, jailed.

The consequences of isolation is that like my husband, social activities are limited, increasingly so, with the stage of the disease. Isolation is pervasive, and it's disabling and it needs to be treated by treating chorea.

And why tetrabenazine -- because it works better than any other drug that we have. I'll tell some stories about my patients because their descriptions are a lot more important than mine. It made a difference in their lives.

For one, it controls their head movements so she can read again, that's

important. For several others, it has improved their balance so they can return to activities they couldn't do before, like, gardening, using a weed whacker on his hilly ground, another, a previous cyclist has returned to riding his bicycle. These aren't things measured on functional capacity scales, but they are real important to people. This drug makes a difference.

For another patient, what's most important for her is that she can eat a piece of pizza again. And she can sleep with her husband. For another, it's kept his job longer. He works in sales, and using tetrabenazine, he has been able to have his customers not be distracted. And he has worked a couple of years past what he would have estimated.

These stories tell it, these and others. These things mean a lot to HD people. And treating chorea is important, it makes a difference. For me one of the most

convincing things is -- happened recently when my patients had trouble getting timely refills of their drug from Canada, they could not wait to get back on it.

Chorea matters and tetrabenazine works. I urge you to approve it even if it isn't perfect. No first drugs for dread diseases have been very perfect. This one isn't either. Do we worry about depression and suicide and other side effects? Of course we do. But I still urge its approval with appropriate warnings and education to physicians.

I worry enough about these problems that I require pretreatment with antidepressants. But I, even though there are side effects, I prescribe this drug because it makes a difference to patients. Chorea matters and HD people deserve the chance to use this drug.

MR. GOLDSTEIN: Thank you. I think the person who is scheduled to be our first

speaker is now here. Dr. Wexler.

MS. WEXLER: Thank you. My name is Nancy Wexler, president of the Hereditary Disease Foundation, Higgins Professor of Neuropsychology, Columbia University Medical School and no ties to Prestwick. My mother was diagnosed with Huntington's in 1967, following in the fatal footsteps of my grandfather, three uncles, giving my sister Alice and I, a 50-50 genetic risk.

For HD patients, chorea is the single, most devastating cause of morbidity and mortality. Chorea grasped each of my mother's limbs and gave them a mind of their own. Her arms flailed out in different directions, each leg kicked out, toes kicked out, fingers danced a different tune because they moved independently. Her trunk rocked back and forth and her stomach looked like a belly dancer.

Chorea attacked her face, contorting it into grimaces. Eye brows

raising spontaneously, her eyes opened and closed, her mouth twisted, her tongue thrust in and out, her neck swung from side to side. She had no control over any of these movements which possessed her body like a mad puppeteer. The movements were overwhelming and ceaseless from the moment she opened her eyes to the time she slept.

Mom's choreic jerking movements yanked her legs out from under her causing frequent falls and fractures. Fractures especially of the hip and neck and head injuries all lead to severe morbidity and mortality for HD patients.

People with Huntington's have a huge caloric requirement; they need 5,000-6,000 calories daily just to maintain their weight. But feeding mom was an absolute nightmare, chorea made her ravenous. But alarmingly, eating was one of the most perilous things she could do. She couldn't hold a knife or fork or cup, her fingers

opened and closed, she couldn't guide her arms and hands towards her mouth. They were opening and closing and tongue thrusting out, food ended up on the floor, on her body, but never inside.

Several people were needed just to feed her, to hold down her limbs, to hold her head, and spoon-feed into her mouth. So it took hours just to give her a little bit of food. At the end she was exhausted. She burned more calories eating than we ever managed to feed her.

Like all people with Huntington's she lost weight. At 5 feet tall, at the end of her illness, she weighed 60 pounds, looked like a Dachau victim, and was still moving constantly. Malnutrition contributed to her death like so many with Huntington's.

The constant choreic flailing of her limbs against every surface inevitably produced raw wounds on all parts of her body. Bed sores, despite the best care, developed,

got infected, brought her to the hospital with septicemia. We padded mom's bed with lamb's wool, but it was chafed away by her chorea.

Nursing homes and hospitals tied her up and tied her in bed, by putting restraints on her wrists, and ankles, and trunk. We thought she was being treated like a criminal and untied her. Chorea caused mom to choke continually, a source of terror to us, and to herself, and those trying to help her.

Finally, she died, under her many bouts of aspiration pneumonia caused by constant choking. Mom endured ten years of the most grueling, agonizing, unremitting slide towards death, only then was she still. In 1968, a year after mom's diagnosis, we learned that tetrabenazine was the first line drug of choice for treating chorea.

Mom died without its benefit as did many over these -- in the last decades. They

never were able to take advantage of what standard of care treatment for Huntington's throughout Europe, Canada, and parts of Asia. In 1968 father --

(Laughter)

MR. GOLDSTEIN: Thank you.

(Laughter)

MR. GOLDSTEIN: Thank you. Next is Ms. Boyle.

MS. BOYLE: Good afternoon, I'm Barbara Boyle, the national executive director of the Huntington's Disease Society of America. And I'm here today on behalf of our 30,000 Americans who have HD and our nearly 200,000 who are at risk for inheriting this disease.

There are those who believe that chorea is not a serious problem. There are those that chorea -- say bother the family members more than the persons affected. But that is simply not true.

Chorea is a serious debilitating

condition that steadily reduces a person's quality of life. Chorea affects their ability to walk, eat, swallow, read, write, use a computer, button their clothes, zip their zippers, sleep with their partners, and even enjoy the privacy in using a toilet. Chorea affects every aspect of their life, big and small. And no one can state that it is the patient themselves that is not suffering.

From a 42-year-old patient, I read you this. "Imagine, at the age of 42, being told that you have Huntington's disease. Imagine walking and your knees just buckle and routinely your arms move during a conversation and others move away from you or completely avoid you. Now, think of how these movements will progress over time without treatment."

And this person says "I know that they will become exaggerated and become more physically and emotionally debilitating. At

the age of 59 now, I find myself in a nursing home strapped to a wheelchair in a jumpsuit with Velcro in the back and a helmet on my head to protect myself from chorea. Five years ago, had the treatment been available, I might have been able to live a little while longer without that helmet or jumpsuit strapped to a wheelchair."

"Please," he said, "during the meeting with the FDA, mention my plight, and ask them to envision a condition of uncontrolled movements and my wish for the right medication to treat the movements called chorea. But I also would like other symptoms for this disease controlled as well. And to this end, I think of my son who now has a 50 percent chance of inheriting this disease, this incurable gut-wrenching disease."

"And we now have an opportunity to do something about a form of it called chorea. Imagine a life trying to cope with

the crippling effects of chorea, constant moving, making you incredibly hungry. You can't eat enough to assuage the hunger pangs."

From another HD family member who says, "My grandmother died in 1987, and we didn't know what it was. Well, I would love to know that there is a cure for this awful disease. I would have such comfort and solace in knowing that my beloved ones would not have to experience the effect of chorea and not have to watch them shake to death."

These uncontrolled movements have caused people to not be able to be with their partners, people who can't read a book, people who are affected, all across the board. Tetrabenazine might not be for every person with HD, who suffers from these chorea effects. But we believe our family members have the right to learn about this drug and have the right to make the decision.

So I leave you with these words.

There are currently no effective treatments and cure for HD. And our families are looking to you for the leadership and the fair and equitable decision. Do not disappoint them. Approve tetrabenazine today and give up --

MR. GOLDSTEIN: Thank you. We'll next hear from Maria Hardin.

MS. HARDIN: I'm Maria Hardin, vice-president of Patient Services for the National Organization for Rare Disorders. NORD is the nonprofit consumer organization responsible for the passage of The Orphan Drug Act. And we continue to monitor the accomplishments of government and industry in response to the law.

Our president Abbey Meyers wanted to be here today, but is unable to travel due to illness. So she asked me to speak on behalf of NORD. As we all know Huntington's disease is an orphan disease affecting only approximately 30,000 people in the U.S. It's

a very serious genetic degenerative neurological movement disorder that is untreatable and fatal.

We have known about the use of tetrabenazine in Europe for chorea, associated with Huntington's disease for many years. We are delighted that an American company is willing to develop tetrabenazine for the U.S. market.

Tetrabenazine can help a person's chorea to enable them to feed themselves or dress themselves. It would be a blessing for them and their families. There are decades of experience in Europe with tetrabenazine and the drug is known to be an important therapy for chorea associated with Huntington's.

Huntington's disease is completely debilitating and there are no other treatment options available in the U.S. Since Huntington's disease patients have been importing the drug from abroad, physicians

and families do not currently have the benefit of FDA approved labeling that could warn of contraindications and side effects.

We would like to see tetrabenazine quickly approved for marketing in the U.S. with patient education and materials and other risk mitigation strategies that you suggest. If the drug is not approved for use in the U.S.A., the desperation of Huntington's disease families is such that importation is their only option. This is not right, this is not safe.

The question of whether a specific effect is a side effect or a symptom of the disease itself is academic. It would be inhumane to further delay availability of tetrabenazine until you can decipher the answer.

It is FDA's responsibility to allow the drug in the U.S. market with any safeguards and educational materials that will ensure safe prescribing and management

strategies for side effects. American Huntington's disease patients have been waiting for decades for tetrabenazine.

We know that you, the committee, will do the right thing today and can be -- and this can be prescribed for the patients in need. Thank you.

MR. GOLDSTEIN: Thank you. Katharine Moser.

MS. MOSER: Good afternoon, I'm Katie Moser. I'm 26 and two years ago I was tested and I have a expanded Huntington gene, my repeats are 44. I enjoy knitting, baking, and decorating cakes, reading, skiing, and, juggling.

When I'm in my 40s, I'm going to start developing symptoms of Huntington's disease, the movements, the chorea, the impaired balance, as well as psychiatric and cognitive symptoms. I'm going to slowly have more and more difficulty participating in these activities I enjoy.

It's not cosmetic, it's quality of life. What will give my life meaning? I'll have increased difficulty with dressing myself, bathing, eating and all activities of daily living. I understand what's going to happen, I grew up watching it happen in my family, and I continue to witness it every day.

I'm an occupational therapist, I work at Terrence Cardinal Cooke Health Care Center in Manhattan, and we have a 50-bed Huntington's Unit. My grandfather had lived there for 10 years. As an OT, it's my job to help people regain or remain independent. Mostly with Huntington's disease, I have to provide compensatory strategies.

The thought that I am going to lose my independence and be dependant on someone has to be the most depressing fact that I could imagine. And once I have nothing left, what's the point?

A person with Huntington's disease

loses their ability to control their body, maintain their basic support, and coordinate their movements. If we were able to help people maintain visual tracking or reading, or a solid grasp on their pen or paintbrush, or finger tapping, or send an e-mail to their grandchildren, or stability in their gait while walking their dog, that's quality of life. If I have one extra year or even one extra day, it's worth it.

And I just -- I have a friend who -- she is in the late stages of Huntington's, and it takes a lot of effort for her to control her movements. And she -- with every effort she had, she's able to put her hand in the shape of an "L" to her forehead and call me a loser.

She's 11, in late stage Huntington's. And we understand that there might not be hope for her, but maybe for her 15-year-old and 17-year-old sisters who are both -- have juvenile onset, maybe there's

hope for them. Thank you.

MR. GOLDSTEIN: Thank you, next is Anne Pae.

MS. PAE: Oh my, I'm too short to do this.

(Laughter)

MS. PAE: Hi, I have brought slides, which is going to be too emotional for me to speak in front of. But I wanted to show some of the people that are affected in the -- I also work in the Terence Cardinal Cooke in New York City where we have 52 patients currently, and I don't want to go past that. But I wanted to show you some of the people.

The majority of my patients were admitted in their 20s, 30s, and 40s. Three quarters of my patients were admitted in their 20s, 30s, and 40s. If you can see from some of these slides, every chair -- well, I don't want to do the staff -- every chair -- every patient has a different chair,

different supports, different choreas, different dystonias and different needs, I'm sorry I'm going past this.

And I wanted to -- no, I need the slides off, so I can actually speak. But if you can see these are young people who cannot communicate, all have different qualities of life. And these people are in their 30s and 40s currently, for the most part, the patients.

I feel -- I've admitted patients from around the country, because there are so few places that are equipped to handle somebody with Huntington's disease. And I field -- you know, that's gone, so I can concentrate. And I field questions from caregivers, nursing homes and family caregivers from around the country, the questions are always chorea related, the other symptoms there are managements for.

The questions are 100 percent how do I care for, safely, these patients,

including the nursing home who kept a woman on a mattress on a floor of a padded room and they called to ask how they could safely transport her, so they can improve her quality of life. I can only imagine the limited quality of her life in that nursing home.

My staff, my experienced staff, who care for these patients who come to us in their 20s, 30s, and 40s, they stay with us for decades, not years, my staff need benzodiazepines, need restraints. And then it still takes two to five staff members to care for some of my patients due to the chorea, to perform simple acts of daily living.

We are able to build -- rebuild, pad and repad their chairs, their toilets, their beds, their tables, as we create safety around them due to the chorea and dystonia and as their bodies change through the decades that we care for them, to try to give

them some quality of life, the best we can.

My residents will rub the hair and skin of their bodies, they'll rub through the padding, they'll rub through the mattress, and most nursing homes are not equipped to take care of these patients.

Many of my patients would have stayed home with families who could have cared for them, but the chorea became too intense. And people with excellent intentions and support were unable to care for patients who will take out a toilet and rip a hole in your wall. My staff also suffered the abrasions and bruises and fractures that my patients do as well and they still keep going.

The depression that we see is one of the treatable symptoms and the depression comes from the disease. I think that, as clinicians, we'd be able to monitor safely and treat the depression.

Most of my patients have considered

suicide at some point from the disease alone. To keep them from any quality of life, to keep them from being institutionalized longer could only benefit them, and their family, the people around them. They come to us so young, before the prime of life.

And so I'm begging you to please consider offering them some -- some possibility of staying out of my institution for as long as they can. Thank you for your time.

MR. GOLDSTEIN: Thank you. Next is Gabrielle Hamilton.

MS. HAMILTON: Hello, my name is Gabrielle Hamilton and I am at risk for Huntington's disease. My -- this is a very important day for me, I'm sorry. My mother, grandmother, and aunt have already died with the disease. And my uncle is presently suffering with it. I'm here today to tell you about the unspeakable sadness and shame of the most obvious symptom of HD, the

chorea.

My mother, aunt, and grandmother's chorea caused them to lose weight. They were skinny, skinny, skinny. And they never had a calm, wakeful moment, because their bodies did not stop moving, not for one minute. The chorea even affected the muscles of the esophagus, making it very difficult for them to eat.

One of the first signs of my mother's illness was that she kept choking as we ate. At that time my mother was about 40 and a vice-president at Barclays Bank International, so smart, and so much fun.

And I am haunted today, by the memories of dinner with her, especially dinner, because we always sat together watching MASH. And she'd choke every five minutes. And she thought it was due to post nasal drip, she had colds or whatever, but it wasn't.

And when she reached the later

stages of the disease, my mother got sick with pneumonia more than four times and died with pneumonia, because she got colds from the phlegm that got into her lungs. This was painful for her, pneumonia was very painful. And her subsequent ambulance rides and hospital care were very expensive.

One day, before my mother's illness became apparent, she and I tried to rest together on the couch. But we were unable to do it because her feet wouldn't stop moving. And when I asked her to stop, she got angry at the thought of being sick and so she pushed me away.

And a few months later she, you know, her symptoms were still small and unrecognized, and she fell on a step and she chip fractured her foot and she couldn't work for two months. Another time, you know, she stayed at home and received disability, but she was never the same again.

When she was at her first nursing

home, she was prescribed Haldol, and she insisted on staying on it on the rest -- for the rest of her life even though the doctors at Columbia-Presbyterian told her to change medication, she refused. And it's very difficult to describe the distinction between her HD movements and the tardive dyskinesia, but the HD looked like an unsteady dance, and the tardive dyskinesia was, in the middle of the dance she would just bang her head back and start blinking uncontrollably and it was just horrible.

And it also made her temperament explosive, on top of her already unsteady movements. When I was pregnant, my mother tried to kick me in the stomach and this was totally out of character for the woman who was my best friend, she was my best friend, and she cheered when my brothers' children were born.

As I approach my own age of onset, I have nightmares about watching mother eat,

which became more and more grotesque as the illness progressed. I'm so afraid that my beautiful son Teddy will be embarrassed by my bony body and sweaty hands very soon. My family's age of onset is 42 and I'm 39. Teddy loves me and I would really love --

MR. GOLDSTEIN: Thank you. We'll next hear from Barbara Parker.

MS. PARKER: Hello, I'm Barbara Parker and I am a registered nurse, and this is my husband Gary who is a medical physicist. Gary was diagnosed with Huntington's disease in January of 2007, just this year. He was experiencing many other typical symptoms that you know of, about Huntington's disease. But the one that was most distressing to us was the choking. Every meal, we went through these choking sensations.

He was seen by his regular family physician who had radiological swallowing studies done that were normal; we went to a

GI specialist who did an EGD that showed that he did have some erosive esophagitis and a Schatzki's ring. He had that taken care of and had some proton pump inhibitors administered and that took care of the problem.

He, six months later had another EGD that showed everything was resolved. However the swallowing problem still persisted. We were choking at every meal, at every snack and everything he drank there was choking episodes. In August of 2007, his physician, his neurologist, prescribed 12.5 milligram of the tetrabenazine and within five days all of the chocking sensations stopped.

Every single last one of them, he went from chocking 4 to 5 times at every meal to maybe chocking once or twice a week. That's all. So we are just most grateful for this opportunity to have tetrabenazine even if we do have to get it from Europe. And we

do see that it has made a profound improvement in our family life and especially in our family meals.

MR. PARKER: The only side effect from the tetrabenazine we have seen is that I have gained a few pounds, now that I have regained the joy of eating well. I can now walk confidently with less weaving, I'm walking without tripping over my own feet, I can hold my wife's hand without fidgeting, I can hold items in my hands with very few dropping episodes, and I can look forward to eating with friends and family. I have a new confidence in living with Huntington's, now that my movement disorder is dramatically improved, and both of us are experiencing a reward hope for the future. In our opinion tetrabenazine is a breakthrough treatment for the involuntary movements I have suffered with Huntington's. Thank you.

MR. GOLDSTEIN: Thank you, Mr. Wesley Johnston?

MR. JOHNSTON: I am here with some friends from Ohio, we are proud Buckeyes. Ten years ago, my wife Millison Johnston, now aged 67, was diagnosed with Huntington's. This debilitating fatal disease has ravished her family across many generations. My wife's grandfather was diagnosed with Huntington's and suffered from chorea so severe that he had to be committed to a mental hospital.

The chorea experienced by my wife's mother prevented her from feeding, dressing, or completing her bathroom needs independently for the final years of her life.

During this long slow period of deterioration, she was not given any medication that effectively reduced her chorea. You've heard from other people testifying; how you will tend to become isolated, not go anywhere. I have gone into restaurants, looked of the people knowing how

unsettled they were while looking at my wife, and we've left. When I learned that Ohio State University Center for Excellence had been chosen to administer a drug trial for tetrabenazine, I immediately applied fully aware that my wife might receive the placebo.

She was accepted at the trial, and endured countless 6-hour round trips from Akron to Columbus. In the final face of the trial, we were informed that she was taking tetrabenazine. Throughout this part of the trial, she had less spastic movement and her disposition was more stable. We viewed her response to tetrabenazine as a temporary victory against HD.

Unfortunately, the trial was -- trial ended. I believe that once tetrabenazine was not available from Prestwick my wife's condition and ability to remain at home was compromised.

She was admitted to a nursing facility in June of 2005. I was willing to

buy the drug offshore, but since she was in a nursing home they wouldn't administer it. It was not FDA approved, her chorea and behavior worsened to the point that she had to be removed, hospitalized for two weeks, and placed at another facility that could better handle HD patients.

I believe she was betrayed, I say betrayed by a process that denied her a potentially effective treatment and placed her at greater risk for herself and others. By the time the patients are placed in the nursing homes, you've heard this from other speakers, they have often reached an advanced stage of chorea, I don't believe that groups of patients was part of this study.

So no one will know whether tetrabenazine can really help those patients, tetrabenazine does not work miracles in everyone. Yet, some patients like my wife treated at Ohio state, did well on tetrabenazine and have done poorly on every

other chorea medication since the drug trials stopped. There is no effective remedy for HD, tetrabenazine or any other drug that lessens the horrible effects of HD and makes the life, makes the patient's life easier. It should be available in the United States. In the United States, to those suffering from the disease and to those who will be diagnosed in the future. HD conditions in this country should have this drug available, thank you very much.

MR. GOLDSTEIN: Thank you. Cindy Diogo?

MS. DIOGO: I am at risk for Huntington's disease, my father, an avid bowler who triumphed in 1968, with a perfect 300 game, and a carpenter by trade was diagnosed in 1982, with HD. My daughter as almost two at the time. In 1982, care for HD in central Pennsylvania was very primitive; the neurologist asked myself and my siblings to be present.

We sat in a conference room and were given the good news, the good news that he had no cancer, no tumors, he just had a neurological disorder, and counseling was available if we needed it. My father was told what the course of the disease would be like, deep down he already knew, because the stroke his mother had which rendered her unable to walk or sit still was truly HD, which no one had ever talked about.

During the next few years after many car accidents, accusations of being drunk in the middle of the day, because his gait was so off and gross errors on the job, my father ceased living as an independent individual. His depression became so deep he required hospitalizations off and on, over a 10-year period.

He also attempted suicide many times. He never took tetrabenazine because it wasn't there. Eventually, his depression was managed, but likewise we knew what was

gone, including my parents' marriage. My father had many other psychological symptoms as well as the choreic movements. My father passed away on my mother's birthday, January 11, 2004.

We spent 22 years dealing with just a neurological condition. When confronting our maid Nana as to why the HD diagnosis of my grandmother was never discussed, her response was with the miracles of modern medicine we don't have anything to worry about. Well, we're still waiting on the miracle; any step that we can take to make this disease more bearable is worth it.

This is the reason we're here today, but my sole purpose of being here today is for my sister, Michelle, who at age 39 retried from her job as an ophthalmic technician of over 20 years, because the movements, the choreic movements were so severe that she was unable to perform her duties safe and effectively on patients.

I can't take the disease away from her; if I could I would, I'm here today for my sister because she sometimes is too embarrassed to go outside among strangers and those that know her, because she can't walk straight. I'm here today for my sister, because I want her to be able to enjoy her sons' graduations in 2009 and in 2014, as I was able to do with my daughter.

I'm here today for my sister that she can once again go out and lunch with old co-workers and not be self-conscious about the way she walks into the room, eats or that she can't sit still for the whole meal. I'm here for my sister so that she can once again have the energy to cook and bake in her own kitchen. I'm here for my sister so that she can once again feel like she does have some control over her life, and that she doesn't have to rely on others to carry her wash basket up and down her stairs or that she can push her own vacuum cleaner.

I'm here today for my sister so she can feel like she's taking care of her family and they aren't doing all the caring for her.

I'm here today for my sister so that she doesn't have to be fearful of falling down her stairs and worry if she will break a bone. I'm here today for my sister so that she can enjoy her new found love with her husband of a just a little over 2 years, and that they can enjoy life as it should be, not as what they have been mandated by a disease whose tentacles reach so far that it never stops touching people. I'm here today for my sister.

MR. GOLDSTEIN: Thank you, next Ann Russo.

MS. RUSSO: My name is Ann Russo -- (off mike) Russo. I live in (off mike) Virginia. I used to try and do everything myself. Now, lately my husband and my grand daughter Norah help me, stay there with me and they take me everywhere, doctor,

whatever. I also -- I need a drug to help my chorea. My sister Pat, who was 44 when she died, my family I saw her, in fact, they -- her husband left her, divorced her, she has two kids. She just -- nobody knew what it was then, took care of my sister, her daughter, and everything -- Laurie and I took care of her. I'm just saying it so, and in that days nobody cared -- I mean, the family -- at least my family is here. I hope to use a walker and every day I pray -- people, they are willing to pray for me, so that (off mike) walker. I have hope that I will be better and the drug will help me, tetrabenazine will help me if I can get the drug. And I have hope of getting better. I have my sister Rose, died last year. Her family, when we were in town didn't know what it was. Her husband was there who is still alive, he hates losing my sister. My brother might have had Huntington's, but he had (off mike) that but nobody admitted, I am here as

to -- I hope that (off mike) and I hope I can get the drug, and I hope that will help me and my family.

I took the -- I did used to be a -- I still, you know, practically, I used to go in and do home nursing. I miss all that activity and friends and neighbors. Nobody is friends anymore, your friends all move away and you are lucky to have a friend. Thank God, I got my friend at church who prays for me every week, they pray a lot for me. The priest and everybody prays, I'll get better and I hope this drug will help everybody, amen.

MR. GOLDSTEIN: Thank you Ms. Russo. David Born.

MR. BORN: Daniel Born.

MR. GOLDSTEIN: I'm sorry. David on my thing.

MR. BORN: Good afternoon ladies and gentleman and thank you for listening. My name is Daniel Born, I'm here on my own

time. I'm a vice-president at the Great Books Foundation in Chicago and a board member of the Huntington Disease Society of America, Illinois chapter.

My wife Mary has Huntington's; she began to take tetrabenazine in 2004, after it was prescribed for her by Dr. Kathleen Shannon. The impact of this drug on our lives including our daughter Liz, who is now 18 years old, has been dramatic and positive. Mary showed initial symptoms of Huntington's in 1996, at the age of 40. After her diagnosis she retired from her job as a successful family therapist and psychiatric social worker.

I wish she were here with us today, but travel and speech are becoming more difficult. The onset of Huntington's for Mary followed the trajectory of her own mother Lydia who also showed symptoms around the age of 40. Mary's behavior included involuntary facial twitching, movement of the

tongue, uncontrollable arm and leg motion and deteriorating cognition. This was a hard time for our family as we attempted to live in denial of what we were seeing, but denial as you know works for only so long.

I explained to Liz, then seven years old, that Mary had an illness that made her sad and nervous. By the time Liz finished junior high, she fully comprehended the hereditary nature of the disease, and the nature of her own risk.

Dr. Shannon's prescription for Mary to take tetrabenazine followed an especially difficult couple of weeks' vacation in Europe. Certain kinds of public activity were becoming a problem. Mary showed indecision about how to cross streets and we had several close calls, and given Mary's erratic behavior in the crosswalks, I arrived at a new appreciation for European drivers.

Speaking about the movies as we heard earlier, I also learned that

theatergoers in London can get just as irate as theatergoers in New York, if you kick their chair. The positive impact of tetrabenazine was immediate and dramatic, Mary's involuntary movements did not merely diminish, they stopped, and her depression lessened, it didn't go away but it lessened.

And I would submit to you this afternoon that chorea and not tetrabenazine is the major cause of depression in Huntington's patients. Mary told me the members of her support group at Cook County Hospital commented on her halted movement, before they knew that she as taking tetrabenazine. So that confirmed it as well.

Because of their movement disorder, sufferers from Huntington's live in constant fear of catastrophic accident. It might be a fall on the front steps, hematoma, and death. One of my fellow board members lost his wife in exactly this way. It might be aspirating food down the windpipe because of the

convulsive difficulty in swallowing.

We know tetrabenazine is no cure. Mary is not a better scrabble player than she was three years ago, although the other morning, she surprised me when she said "Dan, it is imperative that I have some bacon." Speaking as a caregiver in my view the treatment of the chorea is central, the central issue, not a peripheral matter. And so I would ask you, members of this advisory committee today, please take the rational and compassionate (off mike) recommend this drug for the FDA's approval, thank you very much.

MR. GOLDSTEIN: Thank you. Jonathan Monkemeyer, hope I didn't ruin your name.

MR. MONKEMEYER: I'm Jonathan Monkemeyer, and this my wife Sheryl and she has Huntington's. I'm here on behalf of my wife, my son, my family, and all the families affected by a disease that slowly and insidiously destroys life from generation to

generation. About 10 people die everyday from this incurable disease.

Today is Bill Fox's funeral, retired chairman of the Fox & Roach Realtors. He died as a result of complications from Huntington's disease. These complications become overwhelming burdens to their families who often place them in nursing homes, they die feeling isolated and rejected by society for the complicated way that they move and talk.

We are here today because people with Huntington's disease have a progressive inability to control their movements and this inability to control their movements, results in complications causing their death, the diaphragm complications because they can't control their swallowing, the diaphragm complications because they injure themselves by falling. My wife bites her lip, her tongue, and the sides of her mouth. She grinds her teeth together and smashes them

with her utensils.

She breaks toilet seats off the hinges, while sitting in a chair she bangs the back of her head into the wall. Unless she sits in the middle seat she smashes the side of her head into the passenger door window. She also sits in the backseat so that she can't accidentally push the transmission into reverse.

Even with my help and padded walls in our shower, she split open her head on the towel rack requiring a costly emergency room visit. She bashes her knees and elbows into everyone and everything. Her food goes everywhere from the floor to the ceiling. She accidentally throws here glasses off about once a day. She has managed to rip the soles of at least 10 pairs of boots and shoes.

The reason she can't speak or communicate well is because she can't control her muscles. My wife chokes on something in

just about ever meal. As Anne Pae can attest people with Huntington's insure themselves -- injure themselves as well as their care givers. This lack of motor control takes its toll both physically and mentally on all persons involved.

These physical movement problems accumulate until they eventually cause enough damaging complications to result in the cause of death. In spite of these difficulties, people with HD teach us that life is precious and worth fighting for. They warm our hearts by holding fast to that which they can. They go on in the face of suffering and adversity; they desire our love, not pity. By appreciating them, they give us a deeper understanding of the meaning of life.

The economic burden of this disease is overwhelming. We want tetrabenazine approved so that it can be included in prescription drug programs and made available to those like us who can't afford the cost of

importing it. Healthcare in America is about doing what is right, bringing a measure of comfort and control to those who are most in need.

Not for cosmetic reasons, but because movement- control difficulty is obviously a key cause of their deaths. My wife benefits from the effects of Prozac, creatine, fish oil, antioxidants, a Trader Joe's healthy diet, Namenda, and also the stop gap principle of use it or lose it. As a stop gap measure, we want tetrabenazine to allow to my wife to continue to be able to do the basic things in life that her chorea now complicates.

The technology to eventually cure this illness is being developed in researched laboratories in America. Interference RNA can target the mutant Huntington gene and be effectively delivered across the brain-blood barrier. These technologies exist in a large part due to the efforts and achievements of

Dr. Nancy Wexler, her colleagues, and fellow researchers.

The HD community, my Congressman Joe Sestak, and myself, want your support in approving this drug to help my wife and others survive until the cure becomes available. We trust in the findings of Dr. Nancy Wexler who is known the world over for her unbiased efforts to address the problems of Huntington's disease through her research and ceaseless lifetime dedication. Please help the people who suffer the most with complications from these now treatable symptoms by acting as (off mike) thank you.

MR. GOLDSTEIN: Thank you, the next speaker is Deborah Fine.

MS. FINE: Hi, I'm Debbie Fine. I'm the daughter, the granddaughter, the sister, and the aunt of Huntington's patients. I apologize in advance, tetrabenazine is the only treatment in existence worldwide with rational in an

evidence-based medicine for its efficiency. We know that it works, in the last 40 years it has been available worldwide and studied here in the U.S. We know that tetrabenazine is pretty safe. We know that it does not cause tardive dyskinesia.

Other side effects are treatable and predictable if they occur. I am urging you to approve tetrabenazine today to change the future for the -- more than 30,000 people in the United States who have HD and the 70,000 Americans who carry the abnormal version of the HD gene, and are destined impeccably by their DNA to develop HD.

We urge you to approve tetrabenazine and change their future. We deserve the gold standard that is available throughout the most of the developed world. Please change our future so that we do not follow in our parents' footsteps, thank you.

MR. GOLDSTEIN: Thank you. That was the last speaker who was registered for

the open public comment section. I want to thank each and every one of you for taking the time to come here and for the courage you each have shown by telling us your stories, thank you.

(Applause)

MR. GOLDSTEIN: The committee is going to take a 15 minute -- 15-minute break. We'll get back here -- let's make it a 20 after, so we can start to begin to address the questions laid before us by the FDA, thank you.

(Recess)

MR. GOLDSTEIN: Very good. Audience, please. Okay. We are ready to resume. Before we get started addressing the four questions -- we're on holiday, I guess, but the four questions posed to us by the FDA -- we had left a couple of issues for the sponsor to respond to when we left the morning session, I just wanted to give them the opportunity to present the data that we

were asking about.

MR. STAMLER: All right, thank you. I think we'll take slide QA2 please. Slide up. So this is to address the question posed by the agency, there are actually two answers on here. First is, what are the -- what was the incidence of depression in the double-blind trial dependent on antidepressant use at baseline? And we see that 6 of 29 patients who are receiving antidepressants at baseline had an adverse event of depression, and 2 of 20 patients who were not receiving antidepressants had an adverse event of depression at baseline.

Regarding the functional measures, it shows the same thing, red is antidepressant at baseline and blue is none, and we see that there appears to be no dramatic difference between the change in the functional assessment or the functional capacity, maybe a trend towards slightly greater declines, but I think probably the

patient numbers are relatively small, so no dramatic changes there. Okay, so the next slide QA4.

Yeah, slide up. This shows the change in the functional measures in patients in study 004 based on their prior treatment -- I'm sorry, this is their change in functional measures in study 07 based on their prior treatment in the double-blind trial. So recall that there were 54 patients in 004 that received tetrabenazine. So if they received tetrabenazine in 004, these are their functional measures, and -- at six months. And if they received placebo in 004, this is the change in their functional measure, once they all received tetrabenazine in the long term safety study.

So I think you don't see -- again, you see small changes from baseline over time, and there doesn't appear to be significant differences, and this is the functional assessment, the total functional

capacity, and the independent scale. QA5 please. Okay. Slide up. This is the change in weight for subjects that -- I mentioned I thought there was no difference between placebo and tetrabenazine over time. And this is based on their prior treatment in 004, the patients who rolled over into 007, this is their total exposure out to 84 weeks.

And at least there doesn't appear to be any material change between baseline and week 12 in the population, and then over time, no apparent between group difference based on their prior treatment, but what's interesting is they appear to be flat, so perhaps these patients' weight is somewhat preserved in the open extension.

There's obviously no placebo group in the long term exposure. Then I think the final slide I want to show is QA6, and this is a rather rough slide, I apologize, slide on. These are two overlay plots made from jump and what you see here is these -- this