appears that increasing the antidepressant alone appears less effective in managing these. And accordingly, we'll propose -- I'll mention later some specific language on how we think these should be approached with proposed labeling.

This adverse event of course requires careful monitoring and intervention because of its potential seriousness, and accordingly, we have addressed this in detail in our proposed risk management plan, and I will discuss that plan at the end of my talk.

Okay, so turning to akathisia, we see here this is the Barnes akathisia score, this is the global score, and we see from baseline to week 7 and tetrabenazine- treated patients there is a group increase during the titration phase, but it does appear with dose adjustment and continued therapy that this does return to baseline.

Again, as with the adverse events of depression, these are summarized on --

across studies and we see that in study 004 that five of five patients with an adverse event of akathisia were mild to moderate. There were no cases in the '06 study, and 11 of 15 in the 007 study were also mild to moderate.

Regarding the reversibility of akathisia, we see that five of the five cases in study 004 were reversible -- I'm sorry -- resolved with either discontinuation or dose reduction. Study 007 showed the same finding. But there was a patient who had an unknown outcome, and a patient who prematurely discontinued and was lost to follow-up.

So now shifting to the adverse event of Parkinsonism, this is the UHDRS subscale which includes several items indicated on the bottom which capture symptoms and signs of Parkinsonism. And we see that from baseline to week 12 there is no apparent between-group differences. This is

the change from baseline in that Parkinson subscale, and there is no apparent between-group difference on the subscale.

Nonetheless, there were adverse events of Parkinsonism reported and these -- in the five patients in study 004, four or five were mild to moderate, and the same is true in the study 006 and 007. The reversibility of Parkinsonism is summarized here, four or five resolved with one of these maneuvers of dose reduction, discontinuation, or continued therapy.

One patient had an ongoing adverse event of Parkinsonism despite a dose reduction. This adverse event persisted and the patient entered study 007, but the patient was lost to follow-up 7 days after nursing home placement.

Study 006, we see two had persistent Parkinsonism despite medical management. These two patients had no dose reduction. The adverse event persisted.

Yet, both had Parkinsonism scores that were improved compared to baseline, so it's quite possible that these were reflected -- were reflecting their underlying disease.

Study 007, the one patient that improved with dose reduction but did not resolve was mild to moderate in severity, but again the Parkinson subscore returned to the baseline level.

Finally dysphagia; this is a similar curve showing the between-group changes from baseline in the dysphagia score. These are actually absolute scores, not change scores, and what we see is tetrabenazine here, placebo in the dashed line and no apparent between -- no clear apparent between-group difference in this objective measure.

Adverse events of dysphagia were relatively uncommon in the NDA. I would point out in the double- blind trial that there were -- there was no apparent signal

for increased rates of dysphagia. One of the adverse events that the FDA noted from ancillary databases was in the tetrabenazine group. So if there were two cases here with the 2 to 1 randomization, still there is no between-group difference in the incidence of dysphagia in the double-blind trial.

In study 006 there were cases -- in 007 there were cases, most of these were mild to moderate in severity.

Regarding reversibility of dysphagia; 004, the one patient resolved with dose reduction; in study 006, the two patients that had ongoing adverse events with medical management, one reported an adverse event of dysphagia on the last day of treatment, and one of these patients had a UPDRS dysphagia score consistent with rare choking.

Regarding study 007, the one patient who had an ongoing adverse event developed dysphagia 6 months after being on

tetrabenazine. This did progress to severe dysphagia requiring a feeding tube placement. However, this patient's dysphagia was present 6 months after discontinuation of the drug, and based on her overall disease progression we felt that this was more likely due to underlying disease than to drug.

So to conclude my presentation on the safety aspects of tetrabenazine, the adverse events do appear to be related to the pharmacological action of the drug. They are higher during the titration period than during maintenance. The adverse event profile is consistent across our studies as well as those that Dr. Jankovic cite. The most common drug-related adverse events observed in our clinical trials include sedations/somnolence, insomnia, restlessness or akathisia, anxiety, and depression or depressive symptoms. And there were no -- there was no evidence for acute withdrawal.

Regarding adverse events of

interest there was no evidence of increased dysphagia in tetrabenazine- treated patients in the double-blind trial. Depression over the NDA was generally mild to moderate in severity. There was one suicide in a patient with multiple risk factors at baseline.

And in general, depression, akathisia and Parkinsonism were reversible with dose reduction, discontinuation, or with medical management. Proposed labeling, which has not been discussed at length recently with the FDA, although we hope to do that in the future; we will certainly encourage very careful titration no faster than the titration scheme that was employed in study 004 and perhaps a slower titration scheme.

And we certainly will not recommend that adverse events or the titration continue in the setting of any adverse events. We'll clearly recommend dose reduction or discontinuation for adverse events that are likely related to tetrabenazine or adverse

events that may be confused with the underlying disease, of Huntington's disease, as Dr. Katz mentioned, if there is any concern that these can't be differentiated, the simplest way to have a safeguard is to stop or decrease the dose of the drug.

Finally we've told you about data from a 2D6 inhibitor study where we have significant increases in the primary metabolites of tetrabenazine. And we feel that the labeling needs to be very clear, that if a 2D6 inhibitor needs to be added to patients receiving stable therapy, the patient should stop tetrabenazine, start their 2D6 inhibitor, take that to a steady state and then to re-titrate tetrabenazine. This 2D6 inhibitor on the baseline really shouldn't affect tetrabenazine because if people are metabolically inhibited they'll start at a low dose and then they will titrate accordingly.

Finally, I want to comment on the

Risk Minimization Action Plan that the FDA asked us to give you an overview of. This plan was proposed in our NDA and it was revised following the receipt of the approval letter from the FDA. The starting point of our RiskMAP is going to be through registration of physicians and patients and controlled distribution.

We'll also focus on education and outreach to prescribers, patients, and caregivers about the important aspects of tetrabenazine such as dosing, careful titration, and the adverse events of interest. Evaluation of the program effectiveness is also a key component as well as patient monitoring of the program.

A little more detail here; as I mentioned, the first component is controlled distribution. This is through a specialty pharmacy hub which is a single specialty pharmacy that would be responsible for aggregating all relevant prescriber and

patient information and maintaining this database. Our proposal is that a prescription will only be filled if it complies with the label dosing, and patients will only receive a 4- week supply until they receive maintenance therapy after which they would eligible.

And I would underscore eligible because they would be assessed during this period by the -- by a nurse at the specialty pharmacy.

Regarding education, the prescribers will need to register and acknowledge when they register that they have carefully reviewed the tetrabenazine prescribing information and they must also agree to educate patients and the caregiver regarding titration, potential adverse events, and potential drug-drug interactions. I think this will -- we'll aim for the drug-drug interaction message to be very simple such that if a patient starts a new

medication regardless of what it is they should contract, contact the Central Pharmacy who can identify whether or not there is a potential drug-drug interaction.

Patient registration is another key component of -- that's associated with education and during this registration process patients must permit communication about prescriptions to the special pharmacy and they must also allow the special pharmacy to contact on the prescriber if there is an issue that they detect it in their screening. And a 24-hour hotline would be available for question and other educational issues.

Regarding the patient monitoring during the titration phase we have proposed that the call center nurse will contact the patient, I mean -- or a caregiver every 4 weeks to review specifically the dosing regimen, their compliance to find out if they've suspended or lowered their dose on their own suggestion of an adverse event.

Also question specifically for the presence of targeted adverse events such as depression or akathisia, and as I mentioned already, of drug-drug interactions are important. They will recommend physician referral as necessary and they can authorize a refill if indeed it is prescribed by the physician.

Finally the fourth component of the RiskMAP is the evaluation of the effectiveness of the program. And we will be monitoring the specialty pharmacy to ensure that it is compliant with only filling prescriptions for physicians who are registered. In addition we'll survey prescribers to see whether they have an adequate knowledge of the level of titration as well as the side-effect profile and management of these adverse events.

Next we'll also determine if prescribers are complying with distribution of the patient education materials to their

patients, and we will monitor prescription compliance. So we'll do this by monitoring the actual prescriptions to make it sure that they are being written in a way that is consistent with our proposed dosing in the label.

Now, the -- I know the FDA reviewer has raised some questions about the adequacy of the risk management plan to address depression, and while we haven't formally discussed this with the agency, these are a few examples of some additional enhancements that we could entertain to make the RiskMAP more robust.

So as examples, in addition to what we've already talked about we could kind of expand or enhance the call, the calls from the nurses to weekly during the titration phase as well as biweekly during the preliminary maintenance phase. And in addition there is certainly an option to administer a depression screening tool such

as PRIME-MD which is a subset of the physician's health questionnaire 9 at each relevant contact.

And also we could require, as an example, mandatory physician contact during the 12-week titration period in order to have prescriptions refilled. And in addition another example of what could be done to enhance a RiskMAP would be to limit the supply to 4 weeks beyond just the initial maintenance period.

So that concludes my talk, I thank you for your attention. And I would now like to introduce Dr. Ira Shoulson, who will give his views of the benefit risks.

MR. GOLDSTEIN: Thank you, I'd just like to remind the sponsor that we have to end their presentation promptly at 10:00, to allow the committee to have time to ask the questions.

MR. SHOULSON: Good morning, appreciate the opportunity to address the

panel. I will make my remarks brief.

Just a word about myself -- I've been a member of the faculty at the University of Rochester School of Medicine and Dentistry for 30 years now, and have actually had the opportunity and good fortune and honor to take care of Huntington's patients for even longer than that, almost 35 years.

In that period, I've -- either in a research setting or clinical setting, I've cared for hundreds of Huntington's patients and had the opportunity also to treat about 50 patients with Huntington's disease, either in a research setting or a clinical setting using tetrabenazine.

I also chair the Huntington Study Group, which is an independent not-for-profit consortium of clinical investigators, largely academic, in the U.S., Canada, Europe, and Australia. And our mission is to improve treatments for Huntington's disease. We have

a variety of sponsors, including government, NIH, and the FDA Orphan Products division, the foundations, and also industry sponsors.

As mentioned, I was a member of the steering committee. I should want to share with the group that I have no personal or family, financial relationship with Prestwick, and in the past 6 years, since the University of Rochester has been involved with Prestwick, I've not received any consulting fees, and I came down to this meeting on my own penny. The University of Rochester and the Huntington Study Group, however, have been recipients of grant support from Prestwick in keeping with continuing medical education guidelines.

First of all, chorea in Huntington's disease is disabling. There is a range of disability from bothersome to troublesome to, frankly, disabling. It's an unmet clinical need, and chorea affects nearly all adult Huntington's patients, and

once it appears, is progressive and disabling. It predisposes to imbalance, falls, injury and weight loss, and in the study published by Dr. Vicki Wheelock and her group at UC Davis, it's a harbinger of institutionalization. So increasing UHDRS motor scores have positive predictive value -- if I can use the word positive -- in terms of forecasting that an individual would be in a nursing home.

It contributes to social isolation and stigmatization and of course there's no approved treatments. And in addition there's no systematic knowledge about non-approved treatments for chorea of Huntington's disease.

First of all, we need to acknowledge the safety risk associated with tetrabenazine. These are not new; they've been known for years. The depression, somnolence, Parkinsonism, and akathisia are the major ones. These adverse effects, as

seen in the 004 study, are mild to moderate, and reversible.

They're not inevitable adverse effects of tetrabenazine, but I think the clinician and prescriber needs to anticipate these as signals for dosage reduction or discontinuation. Unlike the antipsychotic neuroleptic drugs, tetrabenazine has not been associated with the risk of tardive dyskinesia.

Now, anticipating and managing these adverse effects, the adjustment schedule used in the 004 study weekly was relatively aggressive, and I think, in a more clinical situation, a more gradual dose adjustment would be in order until antichoreic benefits are achieved or adverse effects supervene.

These benefits can usually be achieved before the adverse effects supervene, unlike the clinical trial where we had this relatively aggressive dose

adjustment schedule. If the adverse effects occur then one can reduce the dosage, or one should reduce the dosage, or discontinue tetrabenazine. And once safe and effective maintenance dosage is achieved, adverse effects are less common than during the adjustment phases pointed out, notwithstanding that treated patients with tetrabenazine need frequent and close monitoring.

So in my view the question, is tetrabenazine safe for Huntington's disease, I say, yes, when the clinician and the patient and family are mindful of and recognize the dosage-related adverse effects. We actually have a lot of information on the adverse effects that provide important signals for the clinician and for the patient and family. Is it safe? Yes, when the dosage is reduced or discontinued at the appearance of adverse effects, and yes, it's safe when the patient is closely monitored

especially during the initial dosage adjustment.

Just a few words -- I know this is not a point contention -- about efficacy, but I just want to mention a few points. One, the relief of chorea that's seen is clinically relevant. This average improvement of about 3- 1/2 units is consistent across all reported placebo-controlled trials, and in our study it's attended by an improvement in the Clinical Global Impression. And I'd also point out the clinical -- the instructions on the Clinical Global Impression is to take into account all information regarding the overall clinical status of the patient, all information, includes from patient and from caregiver, so the Clinical Global Impression was not just a mirror image of the change in chorea score, and also included information from the patients.

These clinical trial effects are

reproducible. I won't go through all the studies. There is a very nice review of -- evidence-based review of pharmacotherapy in Huntington's disease by Bonelli and Wenning published in 2006, and one thing in terms of reviewing the literature is there's really few, if any, surprises with tetrabenazine, which, nonetheless, should be administered with caution.

What would be the therapeutic mindset of the prescriber? Well, one is that the adverse effects and the effectiveness of tetrabenazine are both predictable consequences, given the mechanism of action of the dosage- related reduction in dopamine. Too much tetrabenazine may result in excess dopamine reduction in the striatal region, giving Parkinsonism, akathisia, in the limbic region, depression. It's really not too different from increasing dopaminergic neurotransmission, which we do for Parkinson's disease with dopaminergic agents,

and the predictable adverse effects of too much dopaminergic stimulation.

The optimal dosage of tetrabenazine reduces dopamine availability in the striatum, achieving the antichoreic effect without adverse effects.

So in summary, there is an unmet need that exists for the treatment of disabling chorea, and of course, there is no drug approved by the FDA for this invocation. I want to point out that the safety risks of tetrabenazine are discernible, they're recognizable, they're predictable, they're dosage-related, they're reversible, and they're manageable. And tetrabenazine also provides a clinically relevant relief of chorea that's consistent across all controlled trials that have been published. Thanks for your attention.

MR. GOLDSTEIN: Thank you, and thank you to the sponsors for the presentations. I'd like now to open the

floor to the committee for questions to the sponsor to clarify or address any issues that you would like them to address. As we do this I'd like to give everybody a chance to ask a question before asking a second question. Members of the committee.

MR. ANDERSON: I have a question.

MR. GOLDSTEIN: Yes, Dr. Anderson.

MR. ANDERSON: I had a question regarding the slide number 72, which was one of Dr. Como's slides, looking at the changes in the functional scales, and you partitioned based on the Hamilton Depression score. I was wondering if you had done something similar where you had used either the CGI or the chorea measure in the same way, to see if in fact sort of increased production of chorea might be associated with increased risk of functional decline, or in a sense that the motor manifestation might actually provide sort of a bio-index that you're sort of -- have depleted dopamine and are having

cognitive effects or something, which you're addressing functional issues.

MR. STAMLER: Yeah, I'm not sure if I should identify myself again, but I'm David Stamler of Prestwick. Yes, we did look at that, and regarding chorea, there did not appear to be a response like this in terms of reduction in chorea and change on the functional scales.

We're trying find a slide that looks at the CGI II and what we did see is -- or the CGI, the patients who had a decline that were either much worse or very much worse -- yeah, I think this is the slide -- that slide on please.

So this is the mean change in the functional parameters by the change in the CGI at week 12 for tetrabenazine-treated patients only. So recall for the functional assessment there was a half-point or a minus 0.4-point of reduction on the FA, and we see as people who improved had little or no

change in their functional assessment, whereas those that had a decline on their CGI II clearly had the largest change in the functional assessment.

Same is true for the independent scale. It seems flatter for the functional capacity and for the functional impact scale. So I think what this suggests is that the CGI does appear to be reflecting or capturing these declines in function as observed by the physicians.

MR. GOLDSTEIN: Dr. Lu.

MR. LU: Yeah, I have a question about the observed -- what you call the observed case-study, and so they basically use only the patient there who followed all the ways through the end, and do the analysis. I notice there are three patients who had depression and discontinued the medication. And so how do you know that what you observe is really not biased towards the better case and --

MR. STAMLER: Right, so the reason, just to give you some background on why we have used an observed-case analysis when examining the safety, is that we wanted to understand the impact both early and late on the effect of some of these measures. And when we looked at week 7 oftentimes -- and if you'd like we can show you some of the data -- the changes at week 7 were often the same as those at week 12. So it was specifically to try and figure out what was going on with patients at the end of therapy as opposed to carrying forward --

MR. LU: Yes, but that doesn't make sense because then that carry-forward should not carry the bias, because after the 7th week should we continue as, you know, you would expect, it will be a biased estimate.

MR. STAMLER: Yes.

MR. LU: And that's observation carried forward, right?

MR. STAMLER: Right, as you

mentioned there were three patients affected and we did -- when you compare those changes to the actual LOCF numbers that were presented in the briefing document, I think, in Dr. Como's presentation, the numbers are small. So if you looked at the functional assessment -- maybe we could have the core slide that presents the functional assessment back up the -- one of the first slides from Dr. Como's presentation, you see that the change from baseline to end treatment which was the average of week 9 and 12 using an LOCF -- note the big table from Dr. Como's presentation -- that the change was, I think, minus 0.79 -- yes, slide on.

So we see the functional assessment, the change from baseline to week 12 -- or I'm sorry, the average of week 12 using LOCF was minus 0.93 whereas in the observed- case analysis the change for tetrabenazine-treated patients was minus 0.4. So it was slightly larger, but the reason we

did that is because, as we mentioned, we wanted to analyze the change in this measure by some of the safety parameters that were only assessed at week 7 or week 12. So that was the background.

MR. LU: Yeah, the other analysis then when you show compared to the CARE-D study, that you show 006-007 versus CARE-D at week 0 to 12 weeks, right, and then 24 on.

MR. STAMLER: Right.

MR. LU: But you didn't show the -- in the plot -- you didn't plot the 004 there, right?

MR. STAMLER: Right, we have those data for 004 --

MR. LU: Yeah --

MR. STAMLER: -- compared -- you want -- would you like to see the functional measures?

MR. LU: Right, but the reason I ask you is that there is always 004 placebo group, obviously would be a better comparison

than historical comparison group and so when you show 004 over time versus, you know, historical control -- I mean, if you see the control group are not comparable to the control group of CARE-D, then you should -- to me, I will -- a statistician, I'll pay more confidence towards within-group randomization.

MR. STAMLER: Right, and I -- we fully agree that the placebo control data is where you start and the most important data. And we also agreed with the agency that this drug-placebo difference, you know, needed to be understood. So to try and do that -- and I think the agency was concerned, as were we, that this short-term consequence might mean something in the long term.

So we do recognize that there is something there in the short term, but we think the long-term data -- we tried to use the historical data to see if there was kind of progressive declines that we saw in the

short-term study.

MR. LU: Do we see any difference in the 004 placebo patients in the 007, you know, the difference between the -- so let me put it this way, the placebo grouping 007, do they behave differently from the treatment of 004 in the first 12 weeks, and also in the follow-up, do they agree with -- are they performed the same as patients who randomized the treatment and over -- followed the 007?

MR. STAMLER: Yeah, that's a -- I don't think we've done that analysis. If that's important we can try and examine your -- I think you're wondering about the changes in the functional measures.

MR. LU: About the behavior, yeah.

MR. STAMLER: -- of the 004 placebo patients as they rolled into 007?

MR. LU: Yeah, it's E2, yeah.

MR. STAMLER: So we can try and do that analysis and present that to you after the break, but I don't think we've done that

before.

MR. LU: Okay. Thanks.

MR. GOLDSTEIN: Thank you. Dr. Green.

MR. GREEN: Yeah, thank you. This may have been addressed. On slide 45, there is a bit of an imbalance on the percentage of those patients in study 004 who were on antidepressants -- fewer people who are in the tetrabenazine group on antidepressants. Do we have any data on the Hamilton scores of the two groups? Were they comparable, and do we have data on what antidepressants were used in the two groups to treat their depression in terms of which may have interacted?

MR. STAMLER: We're trying to get a slide that shows the comparison of the Hamilton scores at baseline. Most -- I don't have the specific drug names, I know that most of these were on SSRIs, but if you'd like the specific drug names then we can try

and get those for you at the break as well, but most of them were SSRIs.

So the slide that -- you can maybe refer to your core slide at the beginning of my discussion of adverse events of interest. There was a -- I'm not sure if that was a -- that may have actually been a change score and not a baseline score. So if that's -- I think that's the case, we'll -- and we can quickly check that while we're still doing Q and A, yeah, so on the slide I presented it was only a change score, so I'll get you the Hamilton scores at baseline.

MR. GREEN: You don't have the original?

MR. STAMLER: Yeah.

MR. GREEN: Okay.

MR. STAMLER: No, we have it. I just don't have it in the slide form.

MR. GREEN: Okay.

MR. STAMLER: So we'll get that for you.

MR. GREEN: Okay.
MR. GOLDSTEIN: Dr. Rudnicki.
MS. RUDNICKI: So in keeping with the depression question, did you analyze separately those who started on antidepressants versus those who were not, in terms of what happened with their depression over time and did that play a role upon their function, whether or not they had -- were taking antidepressants initially?
MR. STAMLER: No, we didn't actually evaluate them based on antidepressant treatment that was started during the trial.
MS. RUDNICKI: Not during the trial, but it -- whether or not they took it at baseline.
MR. STAMLER: I see, at baseline. I don't think we did that analysis either.
MR. GOLDSTEIN: Dr. --
MR. HURTIG: In the CGI, there were -- I gather there were three components,

there was the doctor, the patient, and the caregiver that were rolled into that assessment, is that correct?

MR. STAMLER: Actually I'd like to ask Dr. Marshall to comment on specifically the CGI. I think you may have read about three parts of the CGI from the FDA's material and that's actually not the case. There were -- the CGI that was -- that we presented was the Clinical Global Impression, so the physician's assessment, as Dr. Marshall explained. CGI I and CGI III, which I think are in the FDA's materials -- CGI I is assessment of disease severity and CGI III is an efficacy index that tries to quantify whether or not the patient is experiencing a clinical benefit that is interfered with or not interfered with by the adverse events of drug therapy.

MR. HURTIG: Well --

MR. STAMLER: I'm not sure if that answers your question.

MR. HURTIG: No.

MR. STAMLER: Okay. Is -- so if you're talking about the CGI that was presented --

MR. HURTIG: No, I'm trying to focus on the -- what went into making up the CGI, that's a Clinical Global Impression --

MR. STAMLER: Okay. All right, so I'll --

MR. HURTIG: -- scale, and I think in the briefing material we got from the FDA there was a statement, if I'm correct, that the caregiver input was not clarified and that's -- I guess, that's my question.

MR. STAMLER: Okay. I'll let Dr. Marshall comment on that.

MR. HURTIG: Because it relates to another thought I had about the degree of dementia in these patients and how much that would interfere with the patient's ability to assess their response.

MR. MARSHALL: Yes, I'm Fred

Marshall from University of Rochester. So with regard to the CGI, the instructions to the investigators, at the investigative coordinator initiating meeting, was that the CGI was to represent their global assessment of all available information at their disposal, that is to say, what they observed during the clinical encounter with the patient or the research encounter, I should say, as well as what the caregiver may have told them, what the patient told them, what staff, in the waiting room checking the patients in, may have told them.

They were really to use all the clinically available information, I believe, as Dr. Stamler had shown. There is an indication of validity of that measure, tracking function and predicting functional outcome.

I might -- can you give me E9? I just want to show the CGI III.

Dr. Stamler referred to the CGI

III, which was not a pre-specified measure of the outcome -- slide up, please -- but here's the CGI III, which is what he referred to as the efficacy index.

This is where the -- success here is defined as moderate or marked improvement in chorea, with side effects that were, in the opinion of the investigator, either none or not interfering, based on all available information. So you can see that on this measure the tetrabenazine compared to placebo is markedly effective on the CGI III as well, which is intended to take into account explicitly the balance between overall benefit and overall adversity.

MR. HURTIG: But it was the investigator who made the final decision?

MR. MARSHALL: That's true, that is true. And we did -- well, I'll leave it at that. If other questions regarding functionality come up --

MR. HURTIG: Yeah --

MR. MARSHALL: -- subsequently.

MR. HURTIG: Yeah, I mean, I'm just still not clear --

MR. MARSHALL: Yeah.

MR. HURTIG: -- whether you could actually measure the input from the caregiver who might be the most important --

MR. MARSHALL: We do have data with regard to the functional assessment tools and the total functional capacity ratings that tell us whether or not the information was taken from the patient alone or from the patient and the caregiver. And interestingly, in the FDA document with regard to the analysis of the functional assessments, there was a mal-distribution that was such that all the 33 percent of the patients at baseline were giving information so low, that is, without a caregiver.

In the placebo group at 12 weeks, 50 percent of the patients had a caregiver to provide information, whereas 25 percent of

the patients in the tetrabenazine group did. I make this point, and it's a bit of a subtlety that I think needs to be conveyed, which is, as Dr. Hurtig, I'm sure you're aware, many patients with advancing Huntington's disease, complicated by perhaps some dementia or executive dysfunction, have a certain form of agnosia for their deficit. It's very difficult for them to be precise with you about exactly what they can and cannot do.

And if we have an opportunity, I know perhaps the FDA reviewers are going to show us some of the analyses that they've done of the functional assessment. We've had an opportunity to look at that again, restricting the assessment to only those situations where we had caregiver input at baseline and at week 12, and indeed a lot of the signal on the functional adversity here disappears and seems to favor drug instead of placebo.

MR. GOLDSTEIN: Thank you. Dr. Twyman.

MR. TWYMAN: Yeah, just one -- could you please clarify the definition of the AE depression? And I presume that includes those with preexisting depression, who would be worsening depression?

MR. MARSHALL: That's right.

MR. TWYMAN: And number two, do you actually have the prevalence of depression versus the incidence in the maintenance phase?

MR. MARSHALL: I don't know that we've actually done prevalence numbers. We can -- and I'm not sure if you're talking about the double-blind study, or the --

MR. TWYMAN: Well, in maintenance, presumably the incidence is -- would be new cases of depression, I mean, that's --

MR. MARSHALL: Correct.

MR. TWYMAN: -- versus those cases who had depression in titration, and carried

over into the maintenance with depression.

MR. MARSHALL: Right.

MR. TWYMAN: That would be prevalence failure.

MR. MARSHALL: Right. We don't have the prevalence data in a slide, but actually -- could I get the duration of the adverse events?

We're going to pull up a slide that shows the duration of the adverse events, which I think will get to your question, but while we're getting that I just wanted to come to the question about the Hamilton Depression scores at baseline in study 004. And the mean baseline HAM-D for tetrabenazine treated patients was 4.5 and the mean baseline HAM-D score for placebo patients was 5.1 with a P value of 0.44.

Okay, yeah, slide on. So this gets to the question about the prevalence, somewhat indirectly, so if you look at depression and we have seven patients that

had an adverse event of depression during study 04 that had a median duration of 23 days with a range here. There was one patient who was ongoing at the end of therapy, so you see that actually most of these had resolved by day 44 in the study.

MR. GOLDSTEIN: Thank you. I hate to cut off discussion, but we're already over time for this portion of the session. I just want to remind the committee members who had second questions, or those who didn't have a chance to ask a question at this point that we will have ample opportunity for further questions and discussions in this afternoon's session.

So we break now until 10:30 on the dot, and then we will resume with the FDA's presentation. Thank you.

(Recess)

MR. GOLDSTEIN: Committee members, please. Okay let's reconvene, 10:30 on -- within 30 seconds of the dot. Next, is the

presentations by the FDA, I guess the first presentation is by Dr. Davis, who I hope is here.

MS. DAVIS: Hi, I'm Carole Davis, a clinical reviewer with the Department of Neurology at the FDA. I just wanted to go over with you a few of the challenges that tetrabenazine posed for us in the review process. First slide, please. Do I have a control here? I'm sorry, Alice do I have the control for this or does, do they --

SPEAKER: Yes, you have control for that.

MS. DAVIS: Okay, which --

SPEAKER: Let's see --

MS. DAVIS: Okay, first slide; this is just the overview of the studies that were included in the initial review process. The two clinical studies that were placebo controlled, as they've already noted are the --

SPEAKER: Can you get close to the

microphone --

MS. DAVIS: Sorry, okay.

SPEAKER: Can't hear you.

SPEAKER: Yeah.

MS. DAVIS: Sorry, is this any better?

SPEAKER: Better.

MS. DAVIS: Okay, thanks. The two placebo- controlled studies that we looked at initially were the 004, which was the 12-week study, and the 005, which was the 5-day withdrawal study. For the efficacy review we covered these, the two follow-on studies as well, the 007 and 006 respectively. And for the safety review all of them were covered. The -- I think that we wanted to point out primarily is just that we were looking at the primary end point, which was the reduction in chorea.

And as has already been mentioned, FDA agreed with the Sponsor that there was a statistically significant reduction in the

chorea, meeting, and surpassing their end point of the difference of three points on the UHRSD scale. The problem that we had was just looking at the -- some of the others, secondary -- you can see down the first column; the primary, secondary, and exploratory end points.

The -- during the review, we found that there was about, I think the 25 percent reduction in chorea was what the sponsor figured with the translation of the three points on the scale. What we usually look for in reviewing is that not only do they -- does the study meet the end point, ideally on two different studies. In this case, the second study, the withdrawal study did not meet its statistical endpoint, either because of differences in the timing or were not -- there were factors that interfered with the study.

So we had one study really to work with that actually did make its primary

endpoints. And with -- that was also the study that, because of its length of time and the additional assessments used in it, is the one that presented us with the questions that we are discussing here today.

On the far corner, column down here you are going to see the P values, but off to the side, in the yellow, is just whether or not the endpoint favored tetrabenazine, placebo, or in the case of FIS scale, unchanged. For the motor scores, the chorea score, gait score, those showed a favoring towards the placebo group. With the gait score, it was a little harder for us to interpret since most of the falls, adverse events, and things that we saw related to mobility seemed to be in the tetrabenazine treated group. The cognition score, I realize, this is like based on the total score and it is made up of three separate components -- on the initial review process they also use the Stroop as independent,

secondary endpoints.

Well, that was reevaluated later on and so there has been, you know, if you see different charts, you'll see different statistical evaluations for their end points. But in all cases, all of the components still favored placebo group. We -- one of the things that we are extremely concerned about is just that not only is the primary endpoint met, we'd like to have some internal reinforcement of that showing that there is an actual value to the treatment.

Well, one of the things we usually look at is the patient-oriented assessments, whether or not the patients themselves feel that there has been real benefit for having been on the drug. In this case, there were a few assessments that were done, but we did have problems with them during the review. The first was the question of the UHDRS, which was the week 13 visit. At this point the subjects had been off of the drug for one

week, and the question reads, "Since your last assessment does the participant feel improved, worse, or the same?" The endpoint showed that there was a difference however that favored tetrabenazine treated patients.

However, our problem with it was that there was no consistency in who was actually answering the question. It could have been caregiver, it could have been patient. Since the last assessment also had problems with their -- there was not a huge difference of a withdrawal effect, but there was a difference. There was an increase over baseline showing the withdrawal effect.

There was also an increase in the behavioral assessments score associated with anxiety, and it could've been that they were rating their anxiety level as opposed to their chorea level. It still left these open-end questions for us. On the CGI part two, which was their secondary endpoint, compared to baseline rate total improvement,

whether it's due entirely to the drug, you heard the sponsor describing the instructions that they believed, that the sites received, that it should have been a global assessment.

However, all we saw was just their instructions in writing, which is just simply as you see it on the screen. And when we looked at the assessments given by the investigators, this very same patients received exactly the same change in their chorea as they did on the CGI two. And it was hard to -- for us to distinguish whether or not it was really just the chorea change that was being evaluated.

CGI one; severity of illness, as we'll see in the next slide is virtually unchanged. Here are endpoints. Again, there is the CGI part two, did favor tetrabenazine, CGI one severity of illness, unchanged. And CGI three, part three; the efficacy index, we'll get to a little more in a minute. The efficacy index shows like this where your,

the investigator is supposed to be rating the therapeutic effect against the side effects of the medication, marked being -- marked and moderate being marked or moderate improvement.

The scores are in yellow at the top. Tetrabenazine, with an average score or 3.0, and placebo 3.75, which puts them between the point -- with between the 03 and 04, which in terms of the instructions for rating given to the investigator reads out, significantly interferes with side effects, significantly interfering with function or outweighing therapeutic benefit, which is very vague when they are trying to ask people to distinguish between these two factors.

The sponsor felt that the essence -- the functional scores were very, very broad, which we agree with. Most of these are big-scale issues such as employment, ability to drive, things that aren't going to change over a period of short study like 12

weeks. We tried to get around that issue by picking out the very few functional assessment factors that we thought would be the sort of, make it or break it difference for whether patients could be at home alone during the day if a caregiver was working, and that might be the most sensitive to short-term change. And we'll look at those separately in a minute.

Looking at an overview of the functional scales, again whether done on the initial review, or whether done on the re-review that was re-submitted, all of them still favored placebo expect for the functional impact scale which was unchanged. These are the ones that we came up with that we considered most essential in terms of functional abilities.

The ability to prepare a meal, a very, very simple, you know, at least to get it out of the refrigerator and feed yourself. The ability to use the telephone, to use

medications without help, to be able to feed oneself. There is another slide of this, but I think what you're -- is notable here is just that the numbers are extremely small, but they don't really show an improvement with tetrabenazine.

Same with these walk without falls, walk without help, chair to chair transfers, and in and out of bed, the ability to use the toilet. These are the ones that we consider the essentials. On the cognitive testing, there was a revaluation of this, because of the re- interpretation of this Stroop test. But no matter how we looked at it most of these also came out favoring placebo. They were not big, statistically significant differences, but it was persistent.

Our conclusions for the efficacy part of the review was just that what we had sort of needed from the review was some evidence that in addition to the reduction of chorea that we would see something in the way

of improved function for the patient, improved safety or gait stability, reduction in falls, improvement in ambulation, or improvement in quality of life.

And with the quality of life questions, because of the inconsistency as to whether or not it's the patient or the caregiver giving the responses, it was very hard for us to evaluate. If it's the caregiver, and in that case sometimes with the increased sedation, it may make the patient a little easier to manage, a little easier to care for, but that doesn't necessarily translate into a better quality of life for the patient, and we just needed some way to get at that information.

So the questions that we were left with for efficacy at the end of the revaluation was just that there was a reduction of chorea, we really were unable to find evidence for the secondary gains for that. And that's sort of what we have for

the committee, is just the challenges that poses for us in terms of trying to evaluate the benefits, to have for a benefit-risk analysis of the drug.

MR. BHATTARAM: Good morning, my name is Venkatesh Atul Bhattaram. I'm a pharmacometrics reviewer at the Office of Clinical Pharmacology, FDA. And I'll be presenting today on dose response analysis for effectiveness and safety for tetrabenazine. The reason why it is important is the knowledge of shape of dose-response relationship is useful to relate effects on chorea scores when dose is reduced.

So in my presentation, I will show you what the shape of dose-response relationship is. So our review focused on two questions; the first one is does the dose and change in total chorea scores relationship provide confirmatory evidence of effectiveness given that we have one positive

study and one failed study. And our finding says that, yes, there is a significant linear dose total chorea scores relationship for doses up to 100 milligrams.

And the changes in the total chorea scores are internally consistent across trials. The second one is what is the QT prolongation potential. The single dose studies at 50 milligram dose in a therapeutic study showed a maximum prolongation of 7.3 milliseconds. And shown in the brackets are the 90 percent confidence intervals. However, the prolongation after multiple doses with interacting drugs is not studied, so I will focus on these two questions in my presentation today.

I will briefly go over the pharmacokinetic characteristics of tetrabenazine, which has already been presented -- which has already been presented here. Tetrabenazine is well absorbed after oral administration is rapidly converted to

alpha and beta dihydrotetrabenazine, and which are predominantly further metabolized by CYP2D6. The half-life for the alpha and beta dihydrotetrabenazine is short; it's about four to five hours.

So let's now look at the first issue, which is the -- does the dose and change in total chorea score relationship provide confirmatory evidence of effectiveness. These are the four different studies that we analyzed to understand the shape of the dose-response relationship, and the various studies have been discussed in detail by presenters before.

This slide shows you that the changes in the total chorea scores are internally consistent across studies. Shown on the 'x' axis is the study week and on the 'y' axis is the mean total chorea scores, and in study 004, this is the changes in the total chorea scores in the placebo group, and the treatment group. Also overlaid on this

graph are the effects seen in the studies 006 and 007.

So this shows that the effects in the total chorea scores are internally consistent across studies. Now, to do dose-response analysis it's important to know that we have wide distribution of doses across patients. So this slide shows you the distribution of the tetrabenazine doses at week 12, which is the end of the study in 004. So shown here is the distribution of, or the percentage of patients and the total daily dose.

So for example, you see that about 39 percent of the patients were treated with 100 milligram total daily dose. That means we have at an individual level, affects on chorea scores across various doses until 100 milligrams, which is very useful in constructing the dose response relationship. However, the study 004, which is a titration study, it's important to ensure that dose and

time are not confounded for doing the analysis.

So there are three aspects, which we need to look at to ensure that the dose and time are not confounded. The first one is the pharmacokinetic half- life of tetrabenazine, which is five to six hours.

So essentially, the pharmacokinetic steady state is achieved after the first dose. The second one is the trends and changes in the placebo group, 26 out of 30 patients in the placebo group have no systematic changes in the total chorea scores over time. And we also analyze the change from the baseline in the placebo group at the end of the study, which was not statistically significant from zero.

The third point is the tetrabenazine elicits its effect on total chorea scores within one week of post dose change. And also in study 005 upon withdrawal of tetrabenazine, the total chorea

scores are at baseline levels within three days. So essentially, chorea scores at every weekly visit demonstrate full effect of the dose. So for the dose response analysis we did not need to include time in the analysis.

So this slide shows you the dose response shape based on the analysis that we did. So it shows that the relationship between dose and change in total chorea scores is linear between 12.5 and 100 milligrams. So I have created this graph, which shows on the 'x' axis the total daily dose in milligrams and on the 'y' axis the mean total chorea scores, in four groups of patients who have baseline score of 10, 15, 20, or 25, so you see that the patients who have a baseline score of 15, they have a drop of about five units on the average. And patients who have a baseline score of 25 they have on the average a drop of about 10 units in the total chorea scores.

This -- the last issue is the

effects of tetrabenazine on QT prolongation. There were two studies that we looked at to understand the QT prolongation potential, the first one is the study 015, which is the thorough QT study, which had placebo and moxifloxacin, where single doses of 25 and 50 milligrams were studied. The second one is the study 018, which is the single dose of 50 milligrams with multiple doses of paroxetine, paroxetine which is a CYP2D6 inhibitor.

So this slide summarizes the overall QT findings in the two studies and also a possible likely -- possible clinical scenario which was not studied. So here you see the different studies, study 015 and study 018 and the dose groups, placebo 25 milligrams single dose, 50 milligram single dose, and the Cmax, so for our analysis we use the sum of alpha and beta dihydrotetrabenazine. So shown here are the observed Cmax from the two studies, and the delta QTcF in the study 015 and study 018.

And here in the last column shown as the double delta QTcF, which is the baseline and placebo-subtracted prolongation. So we analyzed using QTcF and the mean is about 7.3 milliseconds and shown are the 90 percent confidence intervals. The second study showed that at higher exposures, the -- there is not much of an increase in the delta QTcF, but however this is not a thorough QT study.

There is one possible clinical scenario at which we don't know what is the likely QT prolongation potential, that is, if patients are taking 100 mg of total daily dose of tetrabenazine and using paroxetine, which is an antidepressant and also a CYP2D6 inhibitor, we have simulated and we are projecting a Cmax of about 285 nanogram/ml and we don't know what is going to be QT prolongation at this higher Cmax.

So to summarize our findings are that there is a significant linear dose total

chorea score relationship for doses up to 100 milligrams, and the changes in the total chorea scores are internally consistent across trials. And in terms of QT prolongation potentials, single-dose studies at 50 milligrams showed a maximum prolongation of 7.3 milliseconds. However, prolongation after multiple doses with interacting drugs is not studied. Thank you.

MS. VILLALBA: Okay, let me just try -- hello, is this okay? My name is Lourdes Villalba and I'm a medical officer in the division of neurology in the safety team, and I will be reviewing the safety of tetrabenazine. First of all this is an overview of my presentation, I will talk a little bit about the problems in interpreting data in these database, and I will focus on the safety in study 004, and will mention about the other studies one read about.

And I will talk mostly about the adverse events of interest that were

akathisia, parkinsonism, depression, and dysphagia. And these were events that were raised in the approval letter of March 2006. I would briefly mention other safety issues and touch upon the whether we can evaluate if the -- there is a difference in the benefit risk profile of the 50 and the 100 milligram dose. And I would have some comments to the sponsor's proposed risk minimization action plan and provide a summary.

First of all, one of the main limitations of this database is that it is small, and it was already described by the sponsor and -- so I won't go into details. But we are basically drawing our conclusions from the Prestwick studies, and particularly the placebo control study, the 12-week placebo control study, because the other placebo control study was a 5-day study.

And the other issue is the flexible dose design. By design, this was supposed to be, the dose was supposed to be titrated up

to the desired effect or to a maximum dose of 100 milligrams a day, or to intolerable adverse events over a 7-week period. However, there was no specific guidance as to what was the desired effect or what was intolerable, and that was different for each patient. And that was at the investigator's discretion to decide if the dose was supposed to be stopped or decreased, or even continue titration up in the presence of an adverse event.

In the other issue, this a complex disease, and some of the adverse effects associated with the tetrabenazine or potentially associated with tetrabenazine are difficult to distinguish from the underlying disease, and particularly depression, dysphagia, and bradykinesia in late HD. And this is a summary of the database; you already saw this slide, so I'm going to the next.

This is a summary of the safety in

study 004; there was one death, three non-fatal serious adverse events including one patient who had a fall and a subarachnoid hemorrhage, in a patient with suicidal ideation. And there were five discontinuations, the three events mentioned above in one case of akathisia, and 28 patients required dose reduction or stopping upward titration due to adverse event.

That is 52 percent of the patient and of course it was by study design that they needed to be stopped in the presence of certain adverse events. And there was only one case on placebo and that was a case of dizziness. This is the listing of the reasons of the specific and adverse events that led to stopping of titration or dose reduction and as you see the most common event was sedation and followed by akathisia, depression, et cetera.

Although some of these patients had more than one adverse event. Patient with

sedation also had depression or parkinsonism, et cetera. So the main questions that the approval letter raised were where these events recognized as a potentially drug related adverse events? Were they dose related? Did they respond to dose reduction? And what happened to the chorea score in these patients.

And I'm going to say TCS for total chorea score that was the primary end point. This is a summary of the adverse events of interest in the study 004 and as you see here, you have two columns for the tetrabenazine adverse events, and on the left side is the adverse events that the investigator -- the sponsor identified, on the right side the events that the FDA identified.

We found a couple of more cases of akathisia, three of parkinsonism, two of depression, and one additional case of dysphagia. And I am not showing these to

brag about the difference that we found but to emphasize that some of these adverse events were difficult to identify or to code. And so this is something to keep in mind, and there were no additional cases in the placebo group.

And this is the difference in the adverse events of interest in study 007, and 006. And as you see we didn't find any additional cases of akathisia or parkinsonism. They were a couple cases of, additional cases of depression and three additional cases of dysphagia. And this is a summary of all events in all three studies, and on the right-hand side you have the total number of events and for the three studies together. And the total number of patients who developed these events, because some patients developed more than one of these, I mean two patients had akathisia in 004 and then again in 007.

And seven patients had depression,

two of them in 004 and then recurrence in 007, and five patients had two separate episodes of depression in 007. And this is a little different from what you have in your background document, because I realized when rechecking all these numbers that some of these patients had had more than one event.

Regarding the cases of akathisia there were a total of seven in our analysis. Akathisia is a mode of restlessness associated with the inner desire to move, and it is an adverse event known to occur with other dopamine antagonists, such as the antipsychotics and actually tetrabenazine was initially developed as an antipsychotic, but eventually decided to be developed for the treatment of movement disorders.

The sponsor identified five cases and we identified two additional cases that one of them had been quoted as restlessness in the adverse events file, but as akathisia in an ancillary file, the so called UH file

and the other was in this ancillary file, but not entered as an adverse event. And again, I think that these points are to the, some time they provide -- in identifying and differentiating restlessness from akathisia. All these cases occur on tetrabenazine.

And this is the listing in the course of the disease in the adverse events, in patients with adverse events of akathisia, and please don't be scared. I'm just going to orient to you into the -- all the data that you can find in these tables, but I do have a summary table at the end of these events.

And these tables, in a similar format were provided by the sponsor at our request. They include the patient identification, the total chorea score at baseline, the adverse events, the dose at the onset and the day of the onset, which is D59; for example, in the dose at that time in parenthesis, you have the day when the

adverse event ended, so you can see to -- the duration of the event.

Then you know, if the patient underwent dose reduction, yes or no, and if the outcome was that the event resolved or not. The -- if there was to the completion or withdrawal, or if there was no data available because of loss of follow up. Then you have the total chorea score right after the adverse event or the next available information.

And a total chorea score at week 12, which is the approximate date 84. So here you will have all the information for all the patients, but I am going to show you the summary table. Of the seven patients, the median dose at onset was 75 milligrams, the median time to onset was -- I mean, 75 milligrams a day, the median time to onset was 43 days.

There were four cases that required dose reduction and one that led to withdrawal

and these, and here you have the outcome. Three resolved after dosage reduction, 1 to 21 days after dose reduction. Two resolved after the study completion, during the wash-up, 4 to 12 days after. One required withdrawal and recovered three weeks after withdrawal, and one we don't have the data, because it was not recorded as an adverse event.

And overall, two out of these seven patients who developed akathisia had a drop in total chorea score of at least three points at week 12. In addition to these cases of akathisia, there were four cases of restlessness. And here you have the cases of restlessness and again, I'm not going to go into detail, but it's important that after discussion with the sponsor, the sponsor looked back at the Barnes chorea -- the Barnes akathisia scores on those patients and they agreed that all these were consistent with akathisia.

So instead of 7, there were 11 cases of akathisia, but this doesn't change the conclusion, the overall conclusions regarding the event of akathisia, it doesn't change the number that much.

Regarding parkinsonism, there were eight cases in the FDA analysis, this is known to occur with dopamine antagonists; this is also a manifestation of late Huntington Disease. We identified five cases, I'm sorry the sponsors identified five cases, we identified three additional cases. And these are the terms that were listed either in the adverse event listing or in the ancillary listing source, and all of them occur on tetrabenazine.

Here is the summary of the cases and here is the summary of two of the cases of parkinsonism, the median dose at onset was 62.5 milligrams a day; the median time to onset was 28 days. And there were four cases who, that underwent dose reduction because of

parkinsonism, and in addition to these, three other patients with parkinsonism underwent dose reduction, but because of another adverse event, like depression, or sedation, or disorientation.

There were no cases of withdrawal due to parkinsonism, and they recover after dose reduction, five cases. One resolved after study completion, as you see, it is one day to three weeks after stopping the drug and three were not available. One was lost to follow-up after entering study 007, and requiring nursing home placement. One had no answer for the adverse event listing, and one was not listed as an adverse event and overall, six out of eight patients had a drop in total chorea score of at least three points at 12 weeks.

In addition to these cases, there were cases of balance difficulty. And again, these could be related to the disease itself or may be related to tetrabenazine. In the

-- all these three cases occur on tetrabenazine and here we have the results. In total, if we put together the cases of akathisia, parkinsonism, bradykinesia, all the terms that are consistent with the extrapyramidal symptoms, plus the problems of balance difficulty, and in- coordination, all those adverse events together.

We had a total 17 patients or 30 percent of patients who had some kind of events consistent with the extrapyramidal symptoms as compared to only one on placebo. And these kind of analyses of putting all these extrapyramidal symptoms together is common in the analysis in the layoffs for at least -- for most of the antipsychotic medications.

Regarding depression, worsening depression, there were 10 cases. The sponsor identified eight, we identified two additional cases. Of these 10 cases of depression, 7 occurred in patients who

already had a history of depression, and were taking antidepressant medication at entry, and three were in patients who were not taking the antidepressant medication.

And although depression is prevalent in patients with Huntington's disease, it is of note that there were no treatment-emergent cases on placebo, and there is some biological plausibility for this increase in -- in the risk of depression, because of the pharmacologic effects of tetrabenazine.

Here you have the cases of depression in case you want to look at them in detail, and I would like to spend a little time on these two cases. One was the case of a patient who committed suicide that actually has been already mentioned by the sponsor, but I want to point out that these two patients, 271 and 213, actually had a very good response in total chorea score.

So they had responded but they,

particularly the patient who committed suicide, despite having a good response in total chorea score, he felt that he couldn't work any longer and this could be because the total chorea score maybe is not really capturing what is important for the patient, or more likely, because the patient was already depressed, and if you look at the narrative, there were some evidence that the patient was depressed.

So it is very important for the patients and for their families to be informed of this potential adverse event. In the other case, the suicidal ideation occurred in a patient who had restlessness and had dropped the dose of tetrabenazine to 12.5, and at that dose, he developed depression and suicidal ideation, so these may or may have not been related to tetrabenazine.

But again, and you will see in the next slide in this summary, that the only way

to really know if this is dose related or not, if drug related or not, is stopping the drug. And in summary of the 10 cases, the medium dose was 62.5, but I would like to point out that there was one patient, or two who had the event that the dose was 25 milligrams daily, the median time to onset was 50. One of them had an event very early on day four.

And three underwent dose reduction, five underwent treatment change -- antidepressant treatment change, and all of them resolved accept for the case of suicide. But they resolved with different approaches. Some of them underwent dose reductions, other resolved after study was completed, other -- one case resolved after the early withdrawal, and one resolved after dose reduction and treatment.

And again, I think that the -- and actually, the sponsor has mentioned these in their presentation, was not as clear in the

application itself that the recommendation would be to stop the drug in case you suspect that something may be drug related. And regarding the drop in total chorea score, five out of these 10 patients had a drop in more than three point -- three or more points at week 3 -- at week 12, sorry.

Regarding dysphagia, dysphagia is recognized to be associated with tetrabenazine at doses above 100 milligrams daily, and there are some reports in the literature to support this. Now, we don't know if this -- if at this dose up to 100 milligrams a day, tetrabenazine is associated with dysphagia or not.

And in this -- in study 004, sponsor identified one case on tetrabenazine and one case on placebo, we identified one additional case and the cases are here, but this is such a small database, and there were few cases, so we cannot rule out a detrimental affect on -- of tetrabenazine on

dysphagia.

And another issue is whether the event was recognized or not as a potential adverse event, and altogether I think there were 11 cases of dysphagia and in half of the cases, they were considered by the investigator to be potentially related and in the other half they did not.

And actually, there was one study at Baylor, where an FDA investigation found that some patients who had had dysphagia in their clinical record, that was -- that information was not transferred into the case report forms, because the cases were thought to be related to the underlying disease. So this again points out to the difficulty of distinguishing whether this is drug related or not.

So these were the questions that we had. If they were recognized as adverse -- as drug related, if they were dose related and what were the effects in total chorea

score. And our conclusion after looking at the studies 004, as well as the other study 007, and 006, is that the events were not always recognized, or they were -- they might be -- they may have been recognized as an adverse event, but not drug related.

Of course, you wouldn't know that when you give your impression of it. And but also there were problems with coding, for example, restlessness versus akathisia, and in some cases of depression, the dose of the antidepressant was increased, but that was not entered as an adverse event of worsening depression in the database.

Is there a dose response for toxicity? We actually -- Dr. Bhattaram did an -- he is the FDA reviewer from the Pharmacometrics division. He did the analysis of dose response in terms of efficacy and that showed a strong dose response. He attempted to do the same for toxicity and looked at the different

measurements or parkinsonism scores, and dysphagia score, and Barnes akathisia scores, and really we couldn't find a dose response.

However, we have the issue of flexible dose study; therefore the doses were changed up and down because of different adverse events. That makes the analysis very difficult. What we know is that most events had an onset at doses of 50 milligrams a day or more except for depression that showed some adverse events at the dose of 25.

That way, there was response to dose reduction or discontinuation, particularly to discontinuation if they did not respond to dose reduction, they did respond to discontinuation. And that was not that clear for depression and dysphagia, because some of the events, not as much in 004, but in 007, and 006, some events of depression continued and did not resolve and they -- those may have been because the patients were going to have depression anyway

if they didn't receive the drug.

Again, without the placebo control, it's difficult to decide, similar with cases of dysphagia. Some of them were resolved, but took several months to resolve, so you wonder if that was drug related or not. And regarding the total chorea score after dose reduction, in general, patients who had responded before developing the adverse event, maintained at drop in total chorea score of three or more from baseline, if they did not discontinue because of the adverse event, so the affect was preserved.

The question that came up during this review is whether we really need to push the 50 milligram dose up to the point of toxicity, and whether the 50-milligrams-a-day dose may have a better benefit risk profile than the 100- milligrams-a-day dose.

And again, trying to do a formal statistical analysis didn't lead us to any final conclusions, so we tried to look in

different ways, and we looked at the number of patients who were responders with the dropping total chorea score of three or more by week 12, by dose, and there were 66 percent -- I'm sorry, let me go to the second column first. Here in the left column you have the dose -- the final dose, which is about 50 to 100 milligrams daily.

These would be, dose received 25 to 50 milligrams as a final dose and then we had patients with no data, and of the 54 patients on tetrabenazine, 54 percent ended up on doses above 50, 35 percent on doses of up to 50, and 11 percent had no data at week 12. Of those patients, 19 had a drug TCS more than three -- I mean, three or more, 15 in the 50 milligram group, and the percentage within the dose group would be 66 percent of patients on the high dose and 79 percent on the low dose.

This is the number of patients and this is another analysis that we tried to do

to look at responders at week 12 versus non-responders. And as you see, the responders already show the drop in total chorea scores, important drop, or clinically meaningful drop by week 3.

Let me explain this slide a little bit. This is the total chorea score, the medium total chorea score, changed from baseline by time and by responder status at week 12. On the y-axis, we have the delta -- changing chorea score. On the x-axis we have the time, 3 weeks, 7 weeks, or 12 weeks.

And by week 3, most patients were supposed to be around 50-milligram dose, and by week 7 most of them were supposed to be at 100 milligrams, unless they didn't tolerate it. So this analysis shows, again, that by week 3 there was already some response and that improved by week 7 and then it was kind of maintained to week 12. And in this analysis we separated those -- only those who responded.

The ones who responded to the high dose or to the low dose and actually those who responded to the lower dose, to doses up to 50 milligrams at week 12, had responded at week 3 already with a good response. Maybe somewhat better than the ones with the 100, and these are exactly patients who developed adverse events and required those reductions, so there seemed to be some patients who will require higher dose than others.

However, the question is, how much better you want the patient to get and what are you willing to accept as adverse events. So basically, with this database, because of the flexible study design, we cannot have an answer whether the 50 milligram has better benefit risk profile than the 100 milligrams a day.

Other safety issues were already mentioned by the sponsor. One of them was sedation that was clearly dose related. It was presented in approximately 30 percent of

the patients and is not unexpected because of the pharmacological effects, and actually sedation could have had something to do with the apparent decline or not improving in functional assessment, because given the impressive results in the motor component of the disease, one would expect that the function would improve too and actually we did have -- we saw some negative results and favorable results for function in cognition, and sedation may have something to do with it.

The other event that I thought it was interesting to look at was false because again, you are supposed to see some improvements and decrease in the number of falls, if the patient has improved so dramatically on the motor score. However, there was no reduction in the number of falls as compared to placebo, and this again maybe because the study was too short or too small to detect any differences, but we don't know.

Regarding hyperprolactinemia that was observed in clinical trials and that is consistent with the dopamine antagonist effect. It is common with the antipsychotics. Neuroleptic malignant syndrome and hypertension and orthostatic hypertension were not observed in the clinical trials. However, there have been post-marketing reports of these adverse events. These drugs have been approved in Europe, in other countries in 1971, so there are post- marketing reports of these events.

And actually, there were no cases of tardive dyskinesia in the trials or in post-marketing, but I don't see why this drug would be spared from that adverse event. I think the tested database is small to detect the tardive dyskinesia. Regarding QT prolongation, Dr. Bhattaram mentioned that there was a positive QTc study that was mildly prolonged. It was 7.3 or 7.7, and it's important to know that that value is on

the threshold of regulatory concern.

We usually with QT prolongations between 5 and milliseconds as a mean, we thought -- we think that the study is inconclusive and usually will require more data from the clinical trials, close monitoring, et cetera. However, in this case the database is not that large to be elucidated regarding potential aerogenic effects. We also -- as he mentioned we do not have data for higher doses that we don't have data for 100 milligrams a day, how the QTc will prolong in that case.

And the -- it was mentioned by the sponsor regarding the drug interaction we've -- to these six inhibitors, and they have proposed that in case that some of these drugs such as antidepressants are started, the tetrabenazine should be stopped and the titration should be restarted and we agree with that recommendation.

The sponsor has proposed a risk

minimization action plan. A risk map is a strategic safety program that tried to minimize specific risks. It could be more than one and uses different tools to achieve those goals. In the plan -- the sponsor proposed a plan to address the risk of depression and restless agitation or akathisia and promote appropriate titration and dosing.

I have some comments, but actually, the comments refer to the proposal of the sponsors at the time of the complete response, because the RiskMAP that was presented today is a little different, so I don't want to comment too much on the current proposal and I anticipate that there will be many more discussions about the ways to reduce the risk with tetrabenazine.

One of the main limitations that the Office of Surveillance and Epidemiology had found was that, well, the depression is one of the adverse events that used to be the

measure of when to continue or not on the drug -- on the drug titration. And the other one is that the monitoring seems to be done not by a physician, but done over the phone and this is very hard even in person sometimes to detect some of these adverse events.

So it's even harder to detect it over the phone. So we -- I think that we will need to discuss much more internally and if -- and you're welcome to propose any measurements that, or any approaches that may help to reduce the risks associated with the dose of -- the use of tetrabenazine.

In summary, Huntington's disease is a complex disease with a motor component, but also connected behavioral functional component. Tetrabenazine is effective, and we have no doubt that it is effective in reducing the motor component of the disease. However, it didn't show any improvement -- and also show some trends against an

improvement in functional assessment and cognitive assessments.

The safety profile is overall consistent with other dopamine antagonists. And the major issues are depression, suicidality, extrapyramidal symptoms, and that some of these adverse events may be difficult to recognize -- the adverse event as being drug related.

And I think that is it. Thank you very much.

MR. GOLDSTEIN: Thank you. I believe that's the last formal presentation for the morning. I'd like to, next, open the floor to the committee for questions for the FDA regarding their presentations or other issues that they ask for clarification. Dr. Lu.

MR. LU: I have a question for the first speaker, I think, Dr. Davis. The title -- the slides that showed, was the change from baseline to week 12, and the handout was

from baseline to average of week 9 and 12, and also the report was week 9 to 12. Was there any reason that you changed to week?

MS. DAVIS: There was the -- the initial review was done at the request of the sponsor based on all of the data at both, week 9 plus week 12. They figured that by week 9, they would be at least two weeks past the titration, and would be at a steady stage, and that the two different assessment dates together would give a better reading. And that's what we did for the initial evaluation phase. When they sent back in the complete response to approvable, they asked us to look at it, at week 12 only, thinking that that would have given them a longer time on their steady state, and would be a more realistic evaluation.

So we did that. We changed everything over, looked at just the week 12 alone. And the basic finding that we had was that it really didn't make any significant

difference in many of the outcomes. There were small statistical differences. None of them reached a level of significance, and none of them really showed any differences in the direction that drug treatment favored.

MR. LU: Yeah, I notice there are some number difference between the sponsored version and FDA's version.

MS. DAVIS: That's right.

MR. LU: And --

MS. DAVIS: Because there was a difference of the -- as you mentioned earlier, the patients that were dropped from last observation carried forward in the switch to observed cases. I think we stuck with the last observed, which carried forward and because of that, we ended up with the difference in the statistical -- and we wanted to stick with the way that we had looked at ours. We considered that the much more realistic way of statistically analyzing the data from our point of view. That's

where the discrepancy comes in.

MR. LU: And then a question that -- about the CGI. And is there any -- in your analysis, is there any dose response relationship with CGI and you know, if we group them by dose groups, do we have, you know, percentage of patient classifies a very much improved? And also the two that, I guess, two that very much improved in the placebo group without their dose, is there anyway we can know that?

MS. DAVIS: The -- I don't remember how closely we looked at that on the initial evaluation. The thing that came out very clearly for us was that -- first of all, it was very difficult to interpret who was giving us the responses. But when we looked at the CGI part II, what we saw consistently was that it's exactly the same patients that were being scored as "improved" by the investigator for their chorea score as being improved on the CGI II, same patients, every

time, about the same amount of change. And it just made it very difficult for us to interpret whether the investigators were actually looking closely at the set of instructions as to making it a global assessment or whether they were still looking at the amount of physical change that they were seeing in their patient, which was related to the chorea score, and judging them on the basis of that.

And as a result, I mean, I think the CGI scores are suggestive of improvement. But we couldn't really directly attribute it, because it's not directly related enough for our way of assessing to make sure that the patients are seeing benefit.

MR. LU: Yeah, I don't know if the sponsor can help me to plot those -- with dose group and the percentage of patients responded. The reason I ask that question was, you know, through the titration, there may be a (off mike) blindness, and the CGI

may be a, you know, assessment by a physician who unconsciously may be in favor of those with a lower dose, who has not achieved the 100, maximum dose levels. And particularly that, you know, seven percent of placebo group make me worry whether that seven percent happened to be the two that has not been -- and the placebo group has not been moving to the maximum dose. And that may show you some light -- I mean, I'm not questioning that. I think, you know, the validity against blind randomized double-blind. But unconsciously, I just want to check to make sure, you know, the CGI can be confidently trusted.

MR. GOLDSTEIN: Dr. Couch.

MR. COUCH: Just kind of a generic question asked in general for all of these complications or side effects that have been discussed, the FDA panel identified anywhere from 25 to maybe 60 percent additional cases. And I'd just like to ask you, is this an

unusual type of situation, or is this the usual type of situation that this many -- this percentage of additional cases are identified in the FDA analysis?

MR. KATZ: I don't know if it's usual. It's -- one thing that's unusual in general about this application is that the numbers are very small to begin with. And the control trial data is very small. So maybe it's unusual in a trial, you know, to detect those sorts of discrepancies in these sorts of small trials.

I don't really know that we know what the numbers are, what the range of discrepancies are across NDAs. I think we do see them, and they are typically due to coding problems, and lumping, and splitting, which is, I think, what you saw here when you add up, for example, the way that Lourdes presented, when you look up -- when you add up all the events that can reasonably be considered to be extrapyramidal symptoms, you

get 32 percent versus 3 percent, whereas if you look at it individually, it's 9 percent.

So that's common. That sort of thing is certainly -- we see that commonly. And we do see discrepancies, but we don't often have a chance necessarily to look through the entire database for all potential cases, because, usually with hundreds of thousands of patients, it's hard to do that. So --

MR. COUCH: But --

MR. KATZ: We could look at the complete dataset.

MR. TEMPLE: I mean, it's certainly not unheard of. And one of the things we do, because we do get case reports for everyone who leaves the study because of an adverse event, and we frequently ask for others. If you go nosing around the various pieces of description you have, you sometimes find adverse reactions that weren't noticed. There's a certain subjectivity to it. And

maybe we are looking with a different bias, you know. I don't know. But it's not -- it's not --

MR. KATZ: But again, just a sort of closed loop here, I think we are reasonably confident that now we have everything. Again, because we were able to inspect essentially the entire database, at least for the controlled trial.

MR. GOLDSTEIN: Dr. Anderson.

MR. ANDERSON: This might be for Dr. Bhattaram. In the briefing, we had a lot of, sort of, dose response curves and efforts looked at. And I was wondering if you could remind me if you had done one related to the cognitive components like the Stroop Interference Measure and the verbal fluency, and whether you had established any relationship between those measures and the dose that the patients were on.

MR. BHATTARAM: Yeah, we tried to do dose responsive analysis for all those