UNITED STATES FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS

ADVISORY COMMITTEE MEETING

Gaithersburg, Maryland

Thursday, December 6, 2007

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P R O C E E D I N G S

(8:00 a.m.)

MR. GOLDSTEIN: Good morning. I'd like to call the Meeting of the Peripheral and Central Nervous System Advisory Committee for the FDA to order. My name is Larry Goldstein. I'm the acting chair of the committee for this meeting. To begin with, I need to say that for topics such as the ones being discussed at today's meeting, there are always a variety of opinions, some of which are often very strongly held.

Our goal today is, at today's meeting will be to have a fair and open forum for discussion of these issues in that individuals can express their views without interruption. So as a gentle reminder, individuals would be allowed to speak into the record only if recognized by the chair, and we're looking forward to a productive meeting so that the FDA can get the advice that they need.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, I need to ask the advisory committee members to take care not -- to have their conversations only on the record, or not to have any side discussions about anything that's discussed at the meeting. We are aware that members of the media are here and anxious to speak with the FDA about these proceedings.

The FDA will refrain from discussing any details of the meeting until the meeting's conclusion. Okay. As the -- also the committee is reminded to please refrain again from discussing the meeting topic or -- during the breaks or the lunch. Thank you all for being here and thank you to the members of the public that are going to be speaking to us later this afternoon.

I'd like now to allow the committee members to introduce themselves. We can start off with my right and work all the way

around.

MR. TWYMAN: Hi. My name is Roy Twyman, I'm the industry representative.

MS. MILEK: Hi. My name is Karen Milek. I represent Huntington's disease patient rep.

MS. KOSKI: Carolyn Koski, I'm the medical director for the GBS/CIDP Foundation, a retired professor of neurology from the University of Maryland.

MR. HOLMES: Greg Holmes, I am the chairman of neurology at Dartmouth Medical School.

MS. RUDNICKI: Stacy Rudnicki, a neurologist at the University of Arkansas.

MR. COUCH: James Couch, I'm the former chair of neurology at the University of Oklahoma, currently professor of neurology, University of Oklahoma.

MR. ANDERSON: Britt Anderson, I'm a neurologist and I'm currently at the University of Waterloo in Ontario.

MR. GOLDSTEIN: And you know, I'm Larry Goldstein, I'm professor of medicine at Duke University and director of the Stroke Center.

MR. LYONS: Darrell Lyons, the designated federal official for the committee.

MS. JUNG: Lily Jung --

MR. RIZZO: Mat Rizzo -- I'm not sure that everyone's spoken, but I'm on remotely, and I'm a professor of neurology at the University of Iowa and member of the committee.

MS. JUNG: Hi. I'm Lily Jung. I'm the consumer representative as well as a clinical associate professor of neurology at the University of Washington, and medical director of the neurology clinic at the Swedish Neuroscience Institute.

MR. GREEN: Hi. I'm Mark Green. I'm director of headache medicine and clinical professor of neurology,

anesthesiology, and dentistry at Columbia University.

MR. LU: Hi. I'm Ying Lu. I'm the professor of radiology and biostatistics from University of California, San Francisco.

MR. HURTIG: Howard Hurting, professor of neurology and co-director of the Parkinson's disease and Movement Disorders Center at the University of Pennsylvania in Philadelphia.

MS. HUGHES: Good morning. I'm Alice Hughes. I'm with the FDA. I'm the associate director for safety with the neurology division.

MR. KATZ: I'm Russell Katz, the director of the division of neurology products at the FDA.

MR. GOLDSTEIN: Mr. Lyons.

MR. LYONS: Before I read the Conflict of Interest Statement, I just want to say that if you have your cell phones on you can go ahead and silence your cell

phones, and then also for today's meeting our FDA press contact will be Sandy Walsh. She's here -- you can stand up and -- okay. Sandy Walsh will be our FDA contact for the press.

The Food and Drug Administration is convening today's Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee under the authority of Federal Advisory Committee Act of 1972 with the exceptions of the industry representative, all members and consultants of the committee, our special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict- of-interest laws covered by but not limited to those found in 18 U.S.C. 208 and 712 of the Federal Food, Drug, and Cosmetic Act are being provided to participants in today's meeting and to the

public. FDA has determined that members and consultants of this committee are in compliance with the federal ethics and conflict-of- interest laws.

And related to discussions of today's meeting, all members and consultants of this committee who are special government employees have been screened for potential financial conflict of interest of their own as well as those imputed to them, including those of their spouse or minor children, and for the purpose of 18 U.S.C. 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment. Today's topic -- today's agenda topic is the Prestwick Pharmaceuticals new drug application 21-894 proposed trade name "tetrabenazine" for the proposed indication

to treat chorea associated with Huntington's disease.

Based on the agenda for today's meeting and all financial interests reported by the committee members and consultants, it has been determined that all interests and firms regulated by the Center for Drug Evaluation and Research presents no potential for a conflict of interest.

We would like to note for the record that Dr. Howard Hurtig's employer, the Penn Neurological Institute, was a study site for Prestwick Pharmaceuticals' tetrabenazine. Although Dr. Hurtig was listed as a sub- investigator, he himself did no work on the study.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Roy Twyman is participating in this meeting as a nonvoting industry representative acting on behalf of regulated industry. Dr. Twyman's role on this

committee is to represent the industry interests in general and not any particular company. Dr. Twyman is employed by Johnson & Johnson.

We would like to remind members and consultants that if the discussions involve any other products of ours not already on the agenda for which the -- an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all participants to advise the committee of any financial relationships that they may have with any firms at issue. Thank you.

MR. GOLDSTEIN: Very good. So just to outline the day, what we're going to have in the morning is a series of sponsor presentations, a break, some comments then from the FDA and questions, then a lunch break, and then the public hearing in the

afternoon. Before we go on, I'd like to ask Dr. Katz to make some introductory statements from the standpoint of the FDA.

MR. KATZ: Thank you, Dr. Goldstein. And I want to -- I'll be very brief -- I want to first welcome the committee and welcome to the members of the public who -- some of whom have -- had a very difficult time getting here either yesterday or this morning. So we very much appreciate everyone's efforts to get here and what I think is a very important meeting.

And particularly I want to thank Dr. Goldstein for agreeing to be the acting chair for today's meeting and for -- Dr. Rizzo, I hope you can hear us throughout the day, and hope we're able to recognize you when you want to say something. It's -- I can imagine what it would be like to listen for 8 or 10 hours from a distant location. So hopefully we can accommodate you. Thanks for being available.

So anyway, as I said, I'll be brief. As you know, today we'll be asking the committee to consider NDA 21-894 submitted by Prestwick Pharmaceuticals for the use of tetrabenazine, essential dopamine-depleting agent as a treatment for chorea of Huntington's disease. And this application is actually the first new drug application that we have ever received for the treatment of any aspect of Huntington's disease.

And of course we're very eager to hear the committee's views as well as the views of the speakers from the public on several important issues that we believe need to be addressed before we can consider the application for approval. So briefly, as from the point of view of history, as you know, the agency issued an approvable letter to the sponsor on March 24, 2006.

And in that letter, we conveyed our conclusion to the sponsor that we had

concluded that they had provided substantial evidence of effectiveness for tetrabenazine's effect on chorea. But we did raise several concerns related to the drug's effects on non- chorea-related outcomes.

Specifically we noted that there appear to be a consistent tendency for the results of multiple secondary outcomes to favor placebo numerically, which in our experience for a drug that we believe to be effective, is quite unusual. And sometimes, not only numerically favoring placebo, but even normally statistically significantly favoring placebo on a few outcomes.

And in particular, various cognitive, behavioral, and functional measures favored placebo. And in addition, we were concerned that there was no patient rate at global assessment performed in the studies to clue us in on whether or not the changes in chorea were considered ultimately beneficial overall.

And it was unclear to us then, and I think it's still unclear to us now, whether the physician sets global rating, some of which did favor tetrabenazine. In fact, we're evaluating any behaviors above and beyond the chorea which we already knew to be favorably treated from the drug.

So it's important to note at this point that certainly we wouldn't require that a drug considered for approval for Huntington's disease treat all the symptoms of Huntington's disease successfully. But the findings taken as a whole raise serious concerns that at best the changes in chorea, which we do believe are real, might not actually be clinically meaningful.

And at worse, tetrabenazine might actually make patients worse in some important ways. And further an examination of the adverse reactions, also raise serious concerns. And specifically the use of tetrabenazine is associated with an increased

incidence of depression, extra pyramidal symptoms, and perhaps even dysphagia.

And these events, we believe, are not only potentially dangerous in and of themselves, but we were particularly concerned that they might not be easily recognized by a treating physician as drug related in any given patient, since these symptoms occur as part of the natural history of the disease itself.

So given these facts, we were and we still are concerned that physicians might continue to prescribe the drug in the face of these events under the belief that they are actually just the natural history of the underlying condition, and that it's -- in and of itself could have potentially significant clinical consequences.

I just should also point out for those of you who've read the approvable letter, that in that letter we asked the sponsor to address numerous non-clinical

issues prior to the approval of the application. Then we are not planning on formally asking the committee to address those issues. However, the timing of the required responses to those non-clinical issues will depend, in our view, on your answers to the questions that we will be asking you.

So as you know, the sponsor has responded to the approvable letter and we've reviewed that response. And later today, after the company presents their interpretation of the data, several of our staff will present our views or their views of the sponsor's response to the approvable letter. And it's important to point out that the agency has arrived at no final decision about the fate of this application.

In fact, that's clearly why we're here today to gain your views and the views of the public on these matters before we reach a final decision. So at this time, in

ending, I'd like to actually just read the questions that we would like you to formally vote on and/or discuss.

So the first question is: Do the findings on the secondary efficacy outcomes, in particular, the lack or the apparent lack of a beneficial effect of tetrabenazine on numerous measures of function, cognition, perhaps numerical superiority in favor of placebo on some of the other measures by themselves raise sufficient concerns about the utility of tetrabenazine's effect on chorea to justify not approving the application?

So here we're trying to get at whether or not even if you believe as we do that the chorea has been shown to be treated beneficially, whether the other efficacy outcomes, the lack of -- the apparent lack of an effect on function, whether that undermines the conclusion that this is a useful treatment for patients with

Huntington's disease.

And if not, if you find that that's not problem, is the panoply of adverse effects associated with tetrabenazine use sufficient to justify not approving the application? And when considering this question, we are particularly interested in hearing your views about whether or not a dosing regimen can be identified that would provide a benefit on chorea without an unacceptable risk of adverse events.

And failing that, we would be interested in hearing your views about any maneuvers that might mitigate these risks sufficiently to justify approval, for example, perhaps reducing the dose or discontinuing the drug or instituting concomitant treatments. For example, if there is an increase or the emergence of depression, whether or not treating with antidepressants would take care of that.

And we are also very interested in

your views on the previously mentioned concerns that it might be difficult for practitioners to discern if any clinical worsening in particular areas might in fact be related to the drug and not related to the underlying condition. And with the possibility that if it is drug related, continued treatment might lead to serious consequences and perhaps irreversible consequences.

The third question: If you determine that for any reason that the application shouldn't be approved, what studies if any could the sponsor do to establish the necessary either substantial evidence of effectiveness or safety in use?

And finally the fourth question: If you determine that the application should be approved, are there any studies that the sponsor should perform post- approval? Again, I just want to point out that we have not asked the committee to formally consider

the question of whether or not the sponsor has established substantial evidence of effectiveness for tetrabenazine's effect on chorea.

As I noted earlier, we have already concluded that they have, but of course if -- we are interested in any views you might have on this issue or any other issue we haven't specifically asked you about, and whether or not you think we need to consider additional factors in our consideration of the NDA. So with that again I just like to close.

I'd like to thank you for the work you've done in preparation for the meeting. We know that there is tremendous amount of material that we sent you and that the company sent you. So we appreciate your looking at that and thank you for your work today. And with that I'll turn it back to Dr. Goldstein.

MR. GOLDSTEIN: Thank you, Dr. Katz. Dr. Temple joined us. Maybe you could

just take a second just to introduce yourself.

MR. TEMPLE: Made a wrong turn. I'm Bob Temple. I'm director of the Office of Drug Evaluation I. Thanks.

MR. GOLDSTEIN: Thank you. So the next portion of the discussions will be presentations from the sponsor. It can well be going between now and about 10:00 o'clock. I asked the committee if they can, to hold questions aside from clarifying -- brief clarifying questions after each talk, and then we'll have time to discuss the presentation overall with the sponsor after they have completed their presentation.

MR. STOGNIEW: Thank you, Mr. Chairman. Members of the committee, ladies and gentlemen, good morning. My name is Martin Stogniew. On behalf of Prestwick we are honored to be here today to present our clinical data from the tetrabenazine clinical development program. Prestwick would like to

thank the FDA and the advisory committee members here today for giving us this opportunity.

And importantly, we'd like to also thank the investigators who led the tetrabenazine clinical trials and the patients who participated in them.

We are here today to walk you through some of the points raised by the FDA, and to explain to you why the data -- why we believe the data demonstrates the benefits shown by tetrabenazine is meaningful and critical for this patient population who have no FDA-approved treatment options for chorea, a serious medical condition. Like with other drugs, tetrabenazine has side effects.

However, we believe they are manageable with proper labeling and a risk-minimization action plan. Prestwick hopes that we can make important progress today in achieving our ultimate goal of delivering a risk- balanced treatment option

for Huntington's disease patients.

Today we are pleased to be joined by a few of the most experienced experts in the field of Huntington's disease who will help us present the data on the disease from our NDA. I will be presenting an overview of tetrabenazine regulatory history and some of the questions that have been raised about the data. Dr. Jankovic will give an overview of Huntington's disease and chorea.

Dr. Marshall will give a review of clinical efficacy, followed by Dr. Como, who would discuss the non- motor endpoints. Dr. Stamler will review the clinical safety profile and the RiskMAP. And finally, Dr. Shoulson will conclude today with an overall review of safety and efficacy. We have a number of additional experts who are on hand who will be available to address any other questions you may have.

Huntington's disease is a progressive neurodegenerative genetic

disorder with no known cure. HD is a true orphan disease affecting 30,000 patients in the United States per year. There are currently no FDA- approved treatment for chorea -- the most -- with most of the symptoms characterized by sudden, jerky, and voluntary movements, and is seen in about 90 percent of the patients.

Tetrabenazine has been known since the late 1950s to be a potent presynaptic depleter of monoamines. The effects of tetrabenazine are restricted to the central nervous system. CNS selectivity of tetrabenazine and its metabolites clearly differentiate it from reserpine, a drug that produces both central and peripheral depletion.

Tetrabenazine is a reversible inhibitor of VMAT2. This inhibition allows the monoamines to reside in the cytoplasm longer where they're degraded by monoamine oxidase. Tetrabenazine and its metabolites

have been shown to be approximately fivefold more selective for the depletion of Dopamine compared to norepinephrine and serotonin.

Following the oral administration of tetrabenazine, it's rapidly and completely -- almost completely absorbed. Tetrabenazine does undergo extensive hepatic metabolism. Tetrabenazine is metabolized via carbonyl reductase to form alpha and beta dihydrotetrabenazine or HTBZ. Alpha HTB is further metabolized via CYP2D6 and CYP3A4. Beta HTZB (sic) is metabolized by CYP2D6.

Prestwick conducted a drug-drug interaction study with paroxetine, a potent CYP2D6 inhibitor. The alpha HTBZ AUC increased by approximately threefold and the beta HTZ (sic) AUC increased by approximately ninefold. Protein binding is modest and there is no food effect. And tetrabenazine as primary tablets have short half lives which are consistent with three times a day dosing.

Tetrabenazine has been approved in 12 countries outside the United States. It's approved for chorea as well as some other indications all related to movement disorder. The first approval was in the United Kingdom in 1971, and of note in the last two years it has been approved in five countries in Western Europe as well as Israel.

We estimate that 5 to 10,000 patients per year are currently treated with tetrabenazine. The indication we are seeking for tetrabenazine is for the treatment of chorea associated with Huntington's disease.

I would like to now review quickly the regulatory history for tetrabenazine. In the United States an investigator, IND, was open in 1979 at Dr. Jankovic's research site. Prestwick followed an IND in 2003 shortly after we received Orphan designation, and in 2004 we were granted Fast Track due to the unmet medical need.

Our NDA was followed in 2005, and

we received an approvable letter in 2006. This approvable letter outlined a series of questions and concerns that we plan to address here today. We filed our complete response in April of this year. Today, we will be referring to a number of key studies that were conducted in the tetrabenazine development program and included in our NDA.

Study 004 is the double-blind registration trial, Study 007 is the long-term extension to this trial, Study 005 is a double-blind withdrawal trial, and Study 006 is the extension of the 005 trial. And the bottom three trials are from the investigator trials. On this slide we have outlined what we believe the key points raised by the FDA as in their approvable letter.

The FDA acknowledged efficacy and demonstrated for tetrabenazine for treating chorea. In addition, the FDA raised the question of whether there was a patient rated

measure of benefit in these trials. The FDA questioned the clinical significance of these non-motor endpoints and the fact that several favor placebo.

The FDA highlighted the following adverse events -- depression, parkinsonism, akathisia, and dysphagia, and whether they were recognizable. And finally, the FDA discussed the benefit risk analysis. Here I've outlined what our approach was in response to the approvable letter. Prestwick conducted a comprehensive analysis of the clinical database.

In regards to non-motor endpoints, we reanalyzed cognition and functional endpoints. Prestwick evaluated how these non-motor endpoints related to adverse events and to historical control data. In terms of safety, we looked at reverse, the reversibility of the side effects of tetrabenazine. And finally, we established a risk immunization action plan to enhance

monitoring and minimize risk.

Here I've outlined our conclusions based on our reanalysis of the FDA-raised issue. Patient rate of benefit was evident in the clinical trials. Functional changes were related to adverse events, and were consistent with the natural history of Huntington's disease, and patients' executive function remained intact.

Finally, we believe the adverse events are recognizable, reversible, and manageable. Today there are no drugs approved for chorea. Based on the data, we believe the benefit for certain patients is very important and very dramatic. The better they can be determined quickly for patients in the order of weeks, the adverse events are recognizable and manageable and reversible.

And importantly, with proper labeling, physician and patient education, Prestwick believes the risk can be managed, providing a safe and effective treatment for

this unmet medical need. We hope that after this morning's presentations on efficacy and safety and the risk benefit analysis, you will agree that tetrabenazine should be approved by the FDA for the treatment of chorea associated with Huntington's disease.

And now I'd like to introduce Dr. Joseph Jankovic, professor of neurology, Baylor College of Medicine. Thank you very much.

MR. JANKOVIC: Thank you. Mr. Chairman, members of the committee, ladies and gentlemen, thank you for the opportunity to briefly review with you some of the clinical features of Huntington's disease. Just by way of disclosure, I should point out that I obtained my IND in 1979. I received research grants from Prestwick. I'm a consultant for Prestwick, but I have no other personal/family/financial relationships with Prestwick.

I hope that today's presentation

will give you a little big of background that will serve useful -- that will be useful to you as we discuss other aspects of Huntington's disease and the treatment of chorea associated with Huntington's disease. Now, Huntington's disease is an autosomal dominant neurodegenerative disorder.

It is caused by genetic mutation, which consists of expansion of CAG repeats on chromosome 4 -- in the tip of the chromosome 4. Each offspring has a 50 percent chance of inheriting the gene mutation. Because of the high penetrance of this mutation, each individual has a 100 percent lifetime risk of exhibiting the neurologic and psychiatric symptoms associated with Huntington's disease, and eventually all patients die as a result of complication associated with the disease.

Here you can see the normal anatomy of a brain cut in cross section. You can see the cortex and part of the brain that is

involved in Huntington's disease, namely the striatum consisting chiefly of putamen caudate nucleon. On the left you see again the striatum; in comparison to the normal striatum it is markedly atrophied as a result of degeneration of the striatal neurons.

Now in the Huntington's disease there are a number of symptoms, and the epidemiology of Huntington's disease is not always easy, because it depends at what stage of the disease the patient is examined. Therefore the prevalence varies from population to population. On the average, the disease starts in the fourth decade.

It primarily occurs in Caucasians, and the prevalence in at least the United States is estimated to be 4 to 10 per 100,000 with about 30,000 patients affected with Huntington's disease in the United States. In addition to each patient diagnosed with Huntington's disease, there are other individuals of course who are at risk for

developing the disease who are not yet manifesting the symptoms.

Now, Huntington's disease is a progressive disease. Patients often become completely reliant on others, ultimately requiring long-term care. The disease terminates in death, typically 15 to 20 years after onset, and the disease is clearly more rapid in its progression in young onset or juvenile Huntington's disease, which collates with a higher CAG expansion.

There is currently no treatment available to halt, slow, or reverse progression of the disease. There are many symptoms associated with Huntington's disease, but most of them can be grouped into these four -- these three categories: movement disorders, behavioral symptoms, and cognitive decline.

Among movement disorders, chorea is clearly the most dominant feature, but there are many other movement disorders associated

with Huntington's disease including dystonia, tics, parkinsonism, gait, and partial problems as well as ataxia. And I will discuss some of these features later on.

Behavioral symptoms are chiefly associated with depression and anxiety and may be associated with suicide, which also is due not only to depression, but poor impulse control. And dementia is often the consequence of the more advanced stage of the disease. Now we want to focus on chorea which was used as the symptom that was targeted to be treated with tetrabenazine.

And I just want to briefly define for you what chorea is. It is considered a hyperkinetic movement disorder which is characterized by involuntary, continuous, abrupt, rapid, brief, unsustained, jerky, irregular movements that flow randomly from one body part to another.

I underscore the word "randomly," because it is the random nature of these

jerklike movements which help us differentiate chorea from some of the other hyperkinetic movement disorders, including dystonia and other hyperkinesias. Now chorea, just like other hyperkinetic disorders, worsens with stress, and may affect fine and gross motor function.

It impacts on the activities of daily living, gait and balance, and eventually impacts also on the quality of life of patients, and likely contributes to markedly increased morbidity. Now we assess chorea as well as other features of Huntington's disease by a tool that we refer to as Unified Huntington's Disease Rating Scale or UHDRS.

This test was developed by the Huntington Study Group to assess not only chorea, but a variety of other Huntingtonian symptoms. It consists of four major subscales that assess motor kinetic behavioral functional aspects of Huntington's

disease. But I will not go into any great detail, because subsequent speakers will refer to UHDRS in more detail in their presentations.

I do want to draw attention to the maximum chorea score, which was used as the measure to determine the primary outcome measure for the study that we're going to be discussing subsequently. This maximum chorea score has a range from 0 - 28, and it assesses chorea in various anatomic regions including the face, the bucco-oral- lingual area, trunk, and upper and lower extremities.

I'm now going to show you two videos, one video of a patient with mild chorea, which on the maximum chorea score was rated as having a score of 14 to illustrate some of the features of chorea. You can see the jerklike movements that again move randomly from one body part to another, and these movements not only affect the face and upper part and lower part of the body, but

also the trunk and interfere with the normal flow of the gait.

I now want to show you another patient with more severe chorea that we refer to as "moderate chorea," with UHDRS chorea score of 18. And again, she demonstrates choreatic movements in the face, the upper and lower extremities, as well as the trunk.

And I just want to point out that the difference between the first patient and the second patient is a 4 point difference, which is about the difference that we observe in the 004 Study that you -- we will be discussing later with respect to the improvement associated with tetrabenazine.

So you can see that these choreatic movements not only are obviously embarrassing to the patient, it may lead to social isolation, but would interfere with activities of daily living such as dressing, feeding, and so on. So chorea is not just a cosmetic-type problem, but clearly impacts on

the quality of life of patients with Huntington's disease.

Now, in addition to chorea, there are many other features of Huntington's disease, and one aspect of Huntington's disease that is of particular concern are the neuropsychiatric symptoms. I chose this particular study by Jane Paulsen which carefully examined 52 patients with Huntington's disease. And as you can see, the frequency of the various neuropsychiatric symptoms includes dysphoria, which was seen in about 69.2 percent of the patients.

In addition to dysphoria, depression, agitation, irritability, apathy, anxiety, disinhibition or poor impulse control, euphoria, delusions, hallucinations were some of the neuropsychiatric symptoms that were encountered in this population of patients with Huntington's disease.

Now, depression certainly is one of the major contributing factors to suicide,

but there are many other reasons why patients with Huntington's disease commit suicide, including poor impulse control and a variety of socio-economic factors associated with Huntington's disease. And I thought I would briefly review for you the suicide rate as an important feature of Huntington's disease.

So in this study of 506 individuals in whom 157 had an ascertained death, suicide accounted for 12.7 percent of all deaths. The most common cause of death was bronchopneumonia, which occur in almost a third of the patients. And then the second most common cause of death was heart disease, which accounted for about 15.3 percent of all the deaths.

Now, Tom Bird reviewed the literature on suicide rate in patients with Huntington's disease, and concluded that the suicide rate in patients with Huntington's disease is 138 per 100,000 person years, which compared to a 12 - 13 per 100,000

person years in general population. So therefore the risk of suicide in patients with Huntington's disease is about 10 times greater than what would be expected in general population.

Now Jane Paulsen reviewed the database of 4,171 patients who were included in the Huntington Study Group database, and concluded that the risk of suicidal ideation, not suicide rate, but suicidal ideation was about 22 percent, and it was highest at stage 2 of the disease. She divided the stages of Huntington's disease into five stages and during the stage 2 -- this is the time when the patients begin to recognize the troublesome symptoms that they are experiencing as well as for the first time they are learning about the diagnosis, which I think contributes to the unusually high suicide ideation at this stage of the disease.

Now, clearly there is an unmet need

to treat chorea, because chorea interferes with fine and gross motor coordination, speech, writing, typing, feeding, dressing, hygiene, and other activities of daily living. It presents an increased safety risk in that it contributes to falling, it worsens gait and postural instability, and it increases the need for supervision and assistance.

It probably also contributes to the weight loss as a result of increased energy expansion from the involuntary movements. It is a source of embarrassment which often leads to social isolation. It reduces employability and it increases dependence on others and may lead to institutionalization.

Now, currently, there is no safe and effective treatment available for chorea. There are some off-label treatments, but these are not terribly effective. Amantadine, for example, has been tested in patients with Huntington's disease, but has

been found to be seldom useful in treating chorea.

Traditionally, neuroleptics, or the dopamine- receptor-blocking drugs have been used to reduce chorea, but they can cause a variety of potentially severe adverse effects including sedation, Parkinsonism, weight gain, exacerbation of diabetes, and other side effects. The typical neuroleptics, in addition, can cause tardive dyskinesia and atypical neuroleptics, which possibly have a lower frequency of tardive dyskinesia, still are not terribly effective for the treatment of chorea.

Reserpine is another drug that has been used in the treatment of chorea. Reserpine, as you probably know, irreversibly bonds to VMAT, as opposed to tetrabenazine, which bonds to VMAT reversibly. It can cause hypertension, sedation, depression, a variety of other side effects, and it is not readily available.

So in summary, Huntington's disease is a progressive inherited neurodegenerative disorder. Chorea, which is the dominant motor feature of Huntington's disease, adversely impacts on activities of daily living and quality of life for patients with Huntington's disease. There are a variety of neuropsychiatric symptoms associated with Huntington's disease, including depression, and this, together with impulse control problems and other factors increases the risk of suicide.

There is a cognitive decline associated with Huntington's disease that contributes to overall disability. Pneumonia is the most common cause of Huntington's disease-related death. There is currently no known cure, and tetrabenazine, if it is approved, will become the first drug that will be approved for the treatment of chorea, and as we will demonstrate in our subsequent presentations, I think you will be convinced

that tetrabenazine clearly ameliorates chorea.

Now, in contrast to other neuroleptics, tetrabenazine has not being documented to cause tardive dyskinesia, which I consider one of the major advantages of tetrabenazine over other neuroleptics.

So it now gives me pleasure to introduce the next speaker, Dr. Fred Marshall.

MR. MARSHALL: Thank you very much, Mr. Chairman, and committee. It's a pleasure to present the efficacy data from trials 004 and 005 of the double-blind trials. By way of disclosure, I was the principal investigator of what we in the Huntington Study Group refer to as the TETRA-HD trial. We published the results of this trial in Neurology in 2006. This is Prestwick study 004. It was sponsored by Prestwick, via contractual agreements with my institution, and then subsequently, from our

institution to participating site institutions.

I have no personal or family financial relationships, equity interest, consulting fees with Prestwick, and -- although I did receive reimbursement to come down here and stay at the hotel. So with regard to studies 004 and 005, the 12-week 004 study enrolled 84 patients and the 005 study is a withdrawal study, which I will speak to after we've presented 004.

The steering committee for the studies gathered in Rochester beginning in about 2002, I believe, and is comprised of a number of really leading lights that I was honored to have an opportunity to work with on this trial -- leading lights in the field of movement disorder neurology.

The study design is double blind randomized 2 to placebo-controlled trial. We conducted it at 16 Huntington Study Group sites across the country, academic medical

centers with movement disorder specialists. The study was designed with a 14-day screening period, then patients are randomized, and there is a titration period -- which we will talk about in some detail, over the first 7 weeks of the study, during which drug can be escalated by the investigator, followed by a maintenance period of 5 weeks from week 7 to week 12, followed by a washout of 1 week.

The main inclusion criteria for 004 were that the patients needed to have manifest Huntington's disease with a career score greater than or equal to 10, meaning that they couldn't have mild chorea to get into the study, but significant chorea. They had to be independently ambulatory, which is a point I may come back to. And then the Hamilton Depression had to be less than 15, and we borrowed from the Unified Parkinson's Disease Rating Scale to judge dysphagia and dysarthria; patients needed to have no

significant swallowing difficulties or speech difficulties to enter our study.

They were also excluded if they had unstable concomitant medical illness or, in the judgment of the investigator, serious psychiatric illness. Concomitant use of the dopamine depletor such as Reserpine or the dopamine-blocking agents, the standard phenothiazines, the standard neuroleptics, and atypical neuroleptics, or the monoaminoxidase inhibitors or levodopa or dopamine agonists was excluded.

With regard to the titration, patients were started at 12.5 milligrams on day 1 and then on day 2 escalated to BID dosing for the rest of the first week. Thereafter, they increased by 12.5 milligrams per week and divided three times per daily dosings.

Importantly, the study drug increased on a weekly basis until either the investigator judged that adequate control

over the chorea had been achieved, they had reached the maximal allowed dosage of 100 milligrams per day, or intolerable side effects occurred. There were a number of instances in the study where a patient may have had what was deemed to be a mild side effect that the investigator nonetheless treated through. So it was intolerability that would have provoked either a suspension or a downward dosage adjustment.

The total chorea score was our primary endpoint; this is the mean change from baseline to the average of weeks 9 and 12. And the steering committee of experts had pre-specified that a 3-point change would be something that we would generally consider clinically meaningful benefit in a population of patients with chorea.

The sample size was based on previous Huntington Study Group studies. We had an 80-percent power to detect a mean difference of 2.7 points with an alpha 0.05.

Dr. Jankovic showed you the primary endpoint. I'm not going to linger on that slide. Baseline demographic characteristics were well balanced with regard to age and gender; and with regard to baseline illness characteristics, they had roughly equal total chorea scores at entrance, the disease duration was the same. The trinucleotide repeat burden was the same.

And I want to just note this, 56 percent and 67 percent respectively on tetrabenazine and placebo were being treated with concomitant antidepressants at entrance into the study, so the occurrence of depressive mood and the need for treatment with concomitant antidepressants is quite high in this population.

Here is our primary efficacy outcome demonstrating a robust effect on the reduction of the total maximal chorea score in the tetrabenazine group versus the placebo group with a treatment effect of 3.5 points

and a P value of.0001, which I believe in Dr. Katz's letter to the committee is characterized as extraordinary.

Reduction in the total chorea score over time; graphed here demonstrates that even by 3 weeks on 37.5 milligrams per day, these curves diverge and there is maintained efficacy through the 12-week period at a highly statistically significant level. And I think this slide, which then shows you the washout, is sort of internal replication of the primary efficacy outcome; that is to say, with washout the tetrabenazine group returns. There is no evidence of rebound effect here.

And another sort of, I think, somewhat reassuring finding to our steering committee was that this was a robust effect, really, across sites. Only one of the 16 sites failed to show a benefit in favor of drug.

The responder analysis with regard to a categorical analysis of the degree of

change in chorea, I think, also needs to be called to the attention of the committee. That is to say, although the mean result was a 3.5-point change, which would fall in this category, fully 50 percent of the patients enrolled had twice that effect or greater, with nearly 20 percent here -- 1 out of 5 patients showing a reduction in their chorea of greater than or equal to 10 points.

To put that into some clinical context, you saw two videos from Dr. Jankovic. One, the first gentleman had, I believe it was a score of 14, and the second, the lady that he showed had a score of 18. And so that's roughly a patient that would fall in this category here.

Now, I think, another internally important thing to recognize about the data is that the placebo group dosing at the end of the titration phase shows that most of these people were elevated to the highest possible number of tablets, eight tablets

here, whereas the tetrabenazine group is distributed across the dosing range allowable.

In addition to our interest in the impact on chorea, we had pre-specified as a committee a number of secondary efficacy endpoints, which were to be tested statistically in a hierarchical order in order to preserve alpha. That is to say, the pre-specified analysis plan was that clinical global impression was to be assessed first. If we were to achieve a significant result on that, we would feel comfortable proceeding to assess whether or not there was an impact on the total motor score et cetera. If there was no impact on total motor, we would then be shifting our thinking about going further down this list of secondary efficacy endpoints, thinking of them more at that point as exploratory outcomes, although I understand you'll be hearing more about that later. We're going to show you the data on

all of this.

I'll be speaking now to the clinical global impression. This is an effort to recognize that there is more to Huntington's disease than simply chorea. The investigators were specifically instructed to rate the overall change in their patients, in their subjects, based on all available clinical information, not merely on the change in chorea.

And indeed they did. If you look at individual cases in the study, it seemed to pick up on adverse events. The clinical global impression does change in a way that's responsive to the occurrence of adverse events. But in terms of how the study is conducted, no change is represented as a 4; anything less than 4 represents increasing benefit, and anything greater than 4 decreasing benefit; again, on this overall measure.

So here are the results on clinical

global impression. You can see here that actually there was a dramatic shift to the left in our curve with a P value of 0.0074 on the ANCOVA analysis, and fully 45 percent of the patients in the tetrabenazine group rated on a global measure as very much or much improved compared to only 7 percent of the patients in the placebo group.

At that point, we proceeded according to a hierarchical plan to look at the UHDRS total motor score, and although we approached a statistically significant result, the alpha -- the P value here is in excess of.05. And at that point, according to the pre-specified protocol, the steering committee did not proceed for inferential purposes to make claims as to efficacy.

Dr. Como will be showing you some of the other functional and other outcomes that you've heard about, but I want to speak to the question of whether or not there was a patient-rated measure of benefit. In the

Unified Huntington's Disease Rating Scale there is a question, item 79, "Since your last assessment does the patient report feeling improved, worsened, or about the same?"

Now, this is anchored to the last assessment, not to baseline, and so the only time when we could compare, in a clean way, the response of the patient was at washout from week 13 to week 12. So this is a little inverted; that is to say, the tetrabenazine patients are being washed out from 12 to 13 as are the placebo patients here. But the tetrabenazine patients rate that they're worse at a rate almost twice as much as the placebo patients do, and that value is statistically at 0.0013.

The withdrawal study is a randomized double- blind placebo controlled staggered withdrawal over 5 days, the objective to determine whether or not tetrabenazine recurs on withdrawal of the

drug. This was a single- center study conducted at Dr. Jankovic's site Baylor by our colleague Dr. Ondo. These are patients who had been treated under Dr. Jankovic's IND, and these are the doses that they had been on.

As planned, the study was to compare group 1 here that had been washed out for 2 days to combined group 2 and 3 that had not had any washout. As conducted, Dr. Ondo had a different interpretation of the protocol, mistakenly, and the patients actually in group 2 were washed out half a day early. But in any event, the primary analysis on day 3 reached a P value of 0.078. And if you look at the effect size in the analysis as planned, just looking at group 1 versus group 3, we still see the same general effect size of about 3.5 points on chorea.

We don't have a significant P value here -- it's 0.11 -- but take into consideration the fact that two- thirds of

the planned comparison group was un-analyzable due to a deviation in the actual conduct of the study.

So in conclusion, I would like to say that there is clear evidence of effectiveness for tetrabenazine for the treatment of chorea and Huntington's disease with a treatment effect that's 3.5 on average in some patients -- actually in half of patients it's twice that effect and in nearly 1 out of 5 people it's a 10-point or higher decline -- and that this is combined in the study with significant clinical benefit on the clinical global impression.

And then in terms of other internal replication, I think the fact that there is very low P values on these estimates of efficacy, the findings are consistent across centers. The washout from week 12 to 13 shows the same effect size. There is a response by dose that I didn't demonstrate, but that would be explicated by the FDA.

There is drug effect regardless of severity.

We did have the patient rated measure of patient benefit, and in studies 005, 006, and 007, which I'm not presenting in the interest of time today, but we can show you these curves if you're interested. There is a similar effect in the size of the withdrawal in study 005, and the pattern of the response in the patients re-treated in studies 006 and 007 demonstrates the same impact.

With that I would like to introduce my colleague from the University of Rochester, Dr. Peter Como, who will discuss some of the non-motor endpoints.

MR. COMO: Good morning. I too would like to thank Dr. Goldstein and the committee for the opportunity to address some of the concerns raised in the approvable letter by the agency. In the spirit of disclosure, I'm a consultant of Prestwick, but I have no other personal or family,

financial relationships with Prestwick.

This is the outline of my presentation. I've been involved in the care and clinical research of patients with Huntington's disease for over 23 years, and I was part of the research group that developed the Unified Huntington's Disease Rating Scale. I'm going to share a few observations about that. And then to talk about some of these so-called non-motor endpoints; of course, it's a bit of a misnomer to call these non-motor endpoints as we know that motor function contributes to things like feeding and dressing and even speaking, and other kinds of behavioral and functional and cognitive tasks.

So the Unified Huntington's Disease Rating Scale, which was published in 1996, over 11 years ago, as you've already heard, has four parts. There is a motor component that has 15 items that Dr. Jankovic has discussed. There is also a cognitive

section.

By way of introduction, I should point out that the UHDRS was really designed to track long-term changes and a natural cohort of Huntington's disease patients. It's by no means in particular, with the cognitive tests, no means a diagnostic instrument, that we really wanted to assess changes from pre-manifest to late stage disease on these various components.

The cognitive tests consist of three tests. I'll talk about those in just a few minutes. It's really inappropriately -- inappropriate from a neuropsychological perspective to sum all of those three tests. Actually those three tests yield 5 subscores, so it's inappropriate to just sum those 5 subscores and come up with the total cognition score on this particular test for a couple of reasons.

One is the Stroop test in particular has three of those subscores, and

the scales themselves have different ranges. If one wanted to come up with a total score, one of course would have to do some standardized score conversion in order to understand that better.

The behavioral items, the behavioral subtests consist of 11 items that assess the frequency and severity of some of the classic neuropsychiatric symptoms that you heard Dr. Jankovic talk about. And then finally, the UHDRS has three functional scales, an independent scale, a functional assessment scale, and the total functional capacity scale.

So this slide is really the slide that raised a lot of concerns in the approvable letter, so I'm just going to take a few moments to kind of familiarize the committee with this. So all of these scales, with the exception of the functional impact scale, are from the UHDRS. The steering committee of the TETRA-HD study, or study

004, wanted to pilot a functional impact scale primarily to address some of the inadequacies of some of these functional measures on the UHDRS.

For example, the functional assessment scale is really just a yes/no; it doesn't allow for any kind of degree of change. The rest of these are on the UHDRS.

So the other point that is worth raising is the fact that even though it looks like there is 11 independent tests up here on this slide, that's actually not quite correct. You really -- you have a behavioral assessment and then you really have four functional scales that are all highly inter-correlated with one another. And then you have a variety of cognitive test which also have significant inter-correlations among them. So you are really dealing with not 11 tests but really 3 groups of test that all have some correlations. And of course we also know that there is correlations among

these somewhat independent components of cognition, function, and behavior.

So to better understand and -- the concerns raised by the agencies, Prestwick conducted some additional analyses of these. I'll point out that there was really no differences between tetrabenazine and placebo with regard to the Behavioral Assessment Scale. And what I'd like to do now is focus in -- first on cognition so I'm breaking that slide down for you to make it easier to read.

In a particular -- the functional assessment checklist, that 25-question yes/no checklist from the UHDRS did favor placebo. And that was nominally statistically significant, so we wanted to understand that better. And the first thing we wanted to do is to actually look at observed cases rather than the last observation carried forward, in order to gain a better and clearer understanding of what might be going on on this particular functional -- on these

particular functional scales.

And the first thing I'd like to point out is the fact that the magnitude of change in both tetrabenazine and placebo is really quite small. And the clinical significance of these rather small changes on these scales is really uncertain and really difficult to determine. And as you can see, as they translate into what percent of the scale they actually represent these changes, it's actually quite modest.

Nonetheless, it was still important to try and understand these effects, so we wanted to do another analysis of the drug effects on the UHDRS functional scales. And Prestwick conducted analyses on the specific items of the UHDRS Behavioral Assessment Scale, and the Hamilton Depression inventory to see if there was anything that might be accounting for some of these functional changes.

And what was found in these

analyses was that on the Behavioral Assessment Scale there was a significant between-group difference and anxiety, favoring placebo. Certainly I think we all recognize that if you're extremely anxious that might interfere with your ability to carry out some functional activities. In addition, the anxiety and insomnia and agitation that was picked up on the Hamilton Depression inventory, which was more prevalent in the tetrabenazine group, also explains some of these differences.

Quite interestingly, on this Hamilton Depression inventory, the key item on the Hamilton depressed mood, there was no difference between drug -- between tetrabenazine and placebo.

This next slide further helps us understand these changes. And what this scale represents, or the slide represents is the change in functional scales by change in Hamilton Depression at week 12.

And if I can just walk people through, the orange are folks in which they improved on their Hamilton during the trial, the somewhat whitish or a light blue color are individuals that had very minimal change, and then this somewhat magenta color are individuals that their Hamilton score worsened.

And what you can see from this slide on, really, all of the functional -- all of the functional scales from the UHDRS, not this pilot scale, you saw that the Hamilton Depression inventory that as you worsened you really started to do less well on these various functional scales; again, suggesting that perhaps it's the anxiety, the agitation, and some of these other behavioral aspects that we see on this scale that might be driving some of these functional changes.

Nonetheless, it's still important to try and fully understand these changes since they were raised in the approvable

letter and they need to be addressed. So the next thing that Prestwick conducted was to compare these functional outcomes to historical data. Recognizing the limitations and caveats with doing that, it's still an appropriate thing to at least get a snapshot of these particular changes.

So the rationale behind this comparison to historical data and to use the CARE-HD clinical trial was that study 004 was really only 12 weeks and really didn't provide us any information about some of the long-term consequences of these functional outcomes. CARE-HD was published in Neurology in 2001; it was a large-scale -- and the largest prospective clinical trial in Huntington's disease that has been completed to date.

It was an interventional trial of some compounds, Coenzyme Q10 and Remacemide; subjects were not allowed to be on tetrabenazine. This was a large cohort of

patients, 347, that were followed for 2-1/2 years. And of particular interest to Prestwick was the 87 patients in the placebo group since they were not exposed to any intervention.

I might add that this trial was a negative trial, that there was really no effect of these compounds in the study, but nonetheless, it was important to look at the placebo group for comparison purposes. So this next slide has a lot of nice colors on it too. And as you can see I'm going to refer to my -- I have a little bit of colorblindness, so you could see the yellow bars is study 006, the orange -- I'm sorry, the -- yeah, the yellow is 006, the orange is 007, and again, this light bluish color is CARE-HD.

And again, these represent the changes in a relatively short term, 4 to 6 months, over a year, and then out to nearly 2 years. And again looking at the functional

assessment, the total functional capacity in the independent scale, you see quite nicely that for the most part the changes in the tetrabenazine studies in terms of its -- the decline in function are tracking quite nicely in CARE-HD with the Prestwick studies, which gives us summary assurances that these functional changes that was raised in the approvable letter is probably due to the natural history of the disease, as you've heard already.

So let me switch now, in concluding comments, about the cognitive measures; as I told you the three tests are in there to try and track cognitive changes. It's certainly by no means is a -- are scales to diagnose dementia. In Huntington's disease one would need a comprehensive neuropsychological test battery to really make diagnoses. The verbal fluency measure is a measure of mental flexibility, response generation, and fluency has a large attentional component to it.

These scales were picked particularly because we thought that they might be sensitive to some of the early changes in Huntington's disease and may track nicely during the course of the disease. Subjects have to generate words beginning with particular letters in 1 minute. The Symbol Digit Modalities Test is a test of working memory, psychomotor speed and has a visual attentional component to it. As you can see, the subject has to write in the number that matches the symbol. They are timed for 90 seconds and then the number correct is generated.

The Stroop test, which is another test of complex attention, that involves selective attention, mental flexibility, and information processing -- and this test is actually met -- administered in a very specific order. The subject is first handed a card that has the colors red, green, and blue on them. They're asked to read those

blocks of colors for 45 seconds and then they are stopped. They are then handed a card that has the words red, green, and blue printed in black and white. They go through a similar exercise after 45 seconds, and then we sort of throw a little mischief at the subject and we actually hand them a card in which the words red, green, and blue are printed in colors that they don't represent. And the subject is required to tell you the color of ink they see, not the word, which is a little bit more difficult to do since our natural tendency is to read.

Now, these three tests yield raw scores that together are not meaningful, because they can be influenced by a number of non-cognitive factors. So as a result, Professor Stroop, in his original 1935 paper, suggested that you really need to take these parts and calculate an interference score, if you want to get a true measure of what he called the Stroop Effect, which is associated

with executive function.

And the way you do that is that you have to do this formula -- and I apologize for the typo here. What you have to do is to you have to take the raw score that you got from this card, and subtract from it this ratio of the simpler test, the color and the word test, and calculate this ratio which gives you a predicted score.

What this takes into account is some of the non- cognitive factors that might be occurring on the simpler tests, like if you are a little slow, or you're a little sedated and you can't quite initiate your response, you've only got 45 seconds, so you're going to really miss a few words that may have nothing to do with cognition at all.

So to return to the outcome analysis, again, what was noticed here was that when you do this calculated interference score, there is really no difference between tetrabenazine and placebo; again, a more

robust measure of executive function as I tried to explain to you on the last slide. Nonetheless, there was some nominally statistical changes in favor of placebo on these individual subtest raw scores. So it's important to try and understand and explain those.

So we returned back to the baseline; Dr. Marshall presented to you some of the baseline data from 004, but he didn't show you the baseline cognitive measures, and a couple of things jump out immediately. With the exception of the verbal fluency Test, you can see that the tetrabenazine subjects are more impaired on these cognitive tests at baseline, and in particular, the Symbol Digit Modalities Test was statistically significantly different between the two.

Because of the high intercorrelations among the Stroop test and the Symbol Digit Test, we thought it would be

appropriate to do an analysis adjusting for these baseline imbalances, in particular, the baseline imbalance in symbol digit. And as you can see, when you do those analyses, the nominal statistical significance that was seen on the raw data, in the original analysis, is no longer present, mindful though that there still are trends favoring placebo. So even though it reduced 50 percent of the difference by doing this adjusting the baseline value and the symbol digit baseline value, we still see a trend here, which again the agency raised some concerns about that.

So even though this is a bit reassuring, again, we wanted to return back to the natural history comparison to the CARE-HD since these cognitive measures were also included in the CARE-HD trial. And so Prestwick conducted analyses of this Stroop interference score, again, just to remind you that a more robust measure of executive

function, similar to that what we did with the functional scales that I showed you a few minutes ago, and rather than show you all those colored bars again, I'll just tell you that the results were that the Stroop -- the changes in the Stroop interference score at 6, 12, and 20 months in the Prestwick studies were quite comparable to CARE. We certainly have those graphs if the committee would like to look at them later.

So let me conclude, the analyses of the non- motor endpoints, there was no difference in behavior between tetrabenazine and placebo. Tetrabenazine was associated with increased anxiety on the Behavioral Assessment Scale, and also associated with increased anxiety and agitation on the Hamilton Depression Scale. With regard to function, I hope to convince you that the changes were quite small and of certain clinical significance.

We think that some of this might be

explained by the anxiety and agitation that we showed you, that the long-term changes in these functional scales seem to be consistent with the natural history of Huntington's disease and shouldn't raise any concern.

And then, finally, with regards to cognition, again, the decline in that raw score on the Stroop word reading card, again, is small. It actually amounts to about a 0.3 standard deviation unit change, which in the field of neuropsychology, would not be considered clinically meaningful.

The absence of a tetrabenazine effect on both the verbal fluency and the Stroop interference score are evidence of no impairment to executive function. These folks were more impaired at baseline, which we think might account for some of the variance, some of the group -- the variance and the group difference on the Stroop. And then once again returning to a natural history database, these cognitive changes

seem to be highly consistent with the natural history of cognitive decline in Huntington's disease.

So I hope I enlightened the committee on some of these concerns raised by the agency in the approvable letter, and I'd now like to introduce Dr. David Stamler, chief scientific officer of Prestwick to talk about the safety and RiskMAP plan. Thank you.

MR. STAMLER: Mr. Chairman and members of the committee, thank you for the opportunity. I'll be presenting the clinical safety of tetrabenazine as well as our proposed Risk Minimization Action Plan that we have submitted to the agency.

To outline my talk, I'll briefly review the exposure of patients that contribute to our understanding of the tetrabenazine adverse event profile in our NDA.

I'll touch on study 004 and study

007. It's open-label extension regarding the incidents of adverse events between groups there. Included in this discussion, I'll highlight the differences in the rates of adverse event incidents between the titration and the maintenance phases. And I'll discuss some of the management of adverse events, specifically the adverse events of interest indicated below. I'll also touch on study 005 and 006 briefly as well as the main adverse events from the Baylor chorea experience.

And as mentioned, regarding adverse events of interest, I'll discuss the reversibility of these with dose reduction, dose discontinuation, or other medical management. And I would just point out regarding this, our analysis did focus on all these maneuvers of medical management, whereas I think the FDA analysis, at least in the briefing document, focused primarily on the effect of managing these with dose

reduction, so there is a bit of a different approach.

And finally, I will highlight the plan for our risk management plan. You don't have information on this plan in your briefing document, but the agency did ask us to give an overview of our plan at this meeting. In that they had not fully reviewed it, we didn't provide you with the plan itself.

Okay, so to turn to the number of patients that were treated within the NDA in the Prestwick studies, study 004, 54 patients received tetrabenazine, and you heard, an additional 30 received placebo. Of the total 84 enrolled in the study, 75 rolled over into the open-label extension which continued for up to 80 weeks.

Study 005 was the randomized withdrawal study that Dr. Marshall presented you. This is only a 5-day study, but then these 29 of these 30 subjects rolled over

into study 006 and they were treated for an additional 48 weeks.

So in addition to the Prestwick studies, we do have additional safety information from the investigator IND at Baylor -- at the Baylor College of Medicine, where about 150 patients were treated for chorea, either with or without Huntington's disease, and an additional 280 patients received tetrabenazine for other hyperkinetic movement disorders.

These data were collected under a compassionate use protocol and the data was recorded at Dr. Jankovic's site. These data were subsequently reviewed by Prestwick, audited, and entered into a database for analysis.

So to touch on the length of exposure in the NDA, we see in the Prestwick studies a total of 111 unique patients that were treated; 65 for about 6 months, and 58 for 1 year. Considerably more long-term

experience in the -- at the Baylor experience, where we have more than 250 patients that received drug for 6 months and 160 patients that received drug for more than 2 years.

Now, this slide summarizes the dosing during the maintenance phase of tetrabenazine in the Prestwick studies. And just take note that these greenish bars is study 004, the double-blind trial; the orange bars are 006, the long-term extension of 48 weeks, and this is the long-term extension to 80 weeks. The dosing intervals or the dose ranges are indicated down here, so if you look at the double-blind trial that Dr. Marshall presented, the model dose was between 75 -- greater than 75 to 100 milligrams. In study 006, the most common dose was 25 to 50 milligrams, and the same was true in the long-term extension 007. But you do see, because the other extension studies allowed the dose range to exceed 100

milligrams, that we have a lighter dose range than we did in the Prestwick double-blind trial.

Now, before I go on to describe the adverse events in greater detail, I wanted to acknowledge that there were some differences between the number of adverse events that are recorded and presented in our briefing document as compared to those in the FDA document. These discrepancies were largely due to coding issues, or in some cases, clinical judgment of what may or may not be akathisia or restlessness.

However, based on the information in the ancillary databases, there were a few instances where the FDA identified adverse events that were not actually recorded in our adverse event database. And we have reviewed these carefully, and we do agree with the FDA that some of these cases do meet the level of an adverse event. And I think, importantly, the committee should know that the

information that we had in our adverse event database was accurately reported in our numbers and no adverse events were intentionally overlooked.

Importantly, these additional cases that were identified by the agency do not change our overall understanding of the adverse event profile of tetrabenazine.

So turning to the double-blind study 004, this is a summary of the treatment-emergent adverse events that are present in at least 5 percent of subjects in either group. We see that most patients -- 91 percent in tetrabenazine, 70 in placebo -- experienced adverse events, which would not be surprising in this patient population. The most common adverse event was sedation reported in 31 percent, followed by insomnia and fatigue. Depression was reported in 8 percent of patients.

Falls were reported in a similar number of patients, but I would draw your

attention to the fact that similar, about 15 percent of patients in placebo also had falls. Falls are quite common in patients with Huntington's disease. Restlessness or restlessness increase was reported in 7 percent and we see that Parkinsonism or bradykinesia was reported in 5 percent. I should also point out, and this we'll discuss further, there were 5 reports of akathisia.

Continuing this list, anxiety or anxiety aggravated was reported in eight patients in study 004. Of note, half of these reports occurred during the washout period when patient's chorea was returning to baseline. And there were isolated injuries -- inflicted injuries such as lacerations associated with falls or tongue biting.

Okay, so just to remind you after completion of the double-blind trial, the 12-week trial, patients were to undergo a minimum 1-week washout and then they were eligible to roll over into the 007 study

which continued tetrabenazine administration for up to 80 weeks. This is a similar slide to the one I showed you for study 004, and this demonstrates the most frequent adverse events in descending order. So we see sedation/somnolence again topping the list at 43 percent followed by depression or depressive symptoms, falls, insomnia, anxiety, akathisia, and so on. And I think what we see is an adverse event profile that is quite consistent with what we observed in the double-blind trial.

Now, as I mentioned at the outset of my talk, we believe that the drug needs to be carefully titrated in order to minimize the risk of adverse events, and to detect these adverse events and manage them accordingly. So we thought it would be useful to examine the incidents, so new cases of these adverse events that occurred during titration or during maintenance. And although study 007 was an 80-week study, we

wanted to examine the incidents of these adverse events during the first 12 weeks versus the second 12 weeks of the study, which was when patients were to be on a stable dose.

Now, what we see on this slide is that for the important adverse events indicated along the bottom, that in titration, which is in green, that they're clearly more common during titration phase than during the maintenance, which is true for insomnia, sedation, depression, fatigue, anxiety. Less of a difference, an apparent difference, in akathisia, but the numbers were a bit low here.

Now, studies 005 and 006 are summarized briefly. I won't show you adverse events for these patients which were not very common. They were present in your briefing document, and I would note in the double-blind trial, that two patients developed dysphagia after discontinuation of

tetrabenazine. So it's not always clear if tetrabenazine dysphagia is associated with the drug itself or with the underlying disease.

Regarding study 006, the open-label extension, the adverse event profile, also in your briefing document I won't reproduce here, but is entirely consistent with what we observed in study 004 and study 007.

Now, as I mentioned about 150 patients have been treated under Dr. Jankovic's IND for chorea associated with either Huntington's disease or with other neurological disorders. And these patients were treated under his IND.

The most common adverse events reported in at least 10 percent of patients -- and some of these patients were treated for several years, so the numbers appear larger than in our shorter-term studies. But what we see is an adverse event profile that is really quite common or quite consistent

with our trials, with somnolence, depression or depressive symptoms, insomnia, accidental injury, dysphagia, Parkinsonism, and akathisia. So again, I think, the consistency across trials is indicated by these data as compared to our data.

Now, I would like to discuss the serious adverse events in the Prestwick studies. There were no serious adverse events in study 005, but in the other longer-term studies, we see that there were four falls, four malignancies, three pneumonias, and three patients with depression that were classified as serious, and so on, agitation, suicidal -- there were two patients with suicidal ideation.

There was one patient with a completed suicide. I'll give you a bit more information on this patient in a moment. There was one patient who had a suicidal attempt. She swallowed a couple of capfuls of Windex after an argument. And then we see

single cases of these additional adverse -- serious adverse events here.

Regarding the patient with suicide, this was a 40-year-old male with a history of Huntington's disease for 9 years. The patient was childless and unmarried and lived with his family. He had a prior history of suicidal ideation and a family history of suicide, but no abnormality was detected on the Hamilton Depression Scale a few weeks before the patient's death.

Following a decision to stop working due to Huntington's disease-related disability, the family reported that the patient became withdrawn, but regrettably this information was not conveyed to the study site, so they could not intervene. The family subsequently reported that the subject drowned the day before he was scheduled to have an appointment in his local disability office. The investigator judged that the suicide was possibly related to study

medication and the patient was receiving tetrabenazine.

Regarding other safety parameters assessed in the clinical trials there was no apparent effect on the cardiovascular parameter -- vital signs of blood pressure or pulse. There was no meaningful effects observed on hematology or chemistry parameters. There were five patients who had elevations in ALT, at least three times the upper limit of normal, and importantly, none of these episodes were associated with symptoms of hepatitis nor with elevations in total bilirubin.

Regarding electrocardiography, there was no increase in the rate of abnormal ECGs as compared to placebo subjects during the course of the clinical trials, and there was a small effect on the QT interval in a thorough QT study.

Now, I'll summarize the main results from the thorough QT study on this

slide as well as a 2D6 interaction study that Dr. Stogniew mentioned in his presentation.

So these three columns represent the thorough QT study, and we see this is the 25-milligram dose of tetrabenazine, 50 milligrams, and the positive control moxifloxacin. The 50-milligram dose was associated with a mean maximal change in QTcI of 7.7 milliseconds with a 90- percent confidence interval that just exceeded 10 milliseconds at 10.4. Moxifloxacin had an appropriate response of about 12 milliseconds.

In a subsequent 2D6 interaction study, where we also carefully examined the effect on QT, we see a significant increase in the exposure of tetrabenazine -- I'm sorry, alpha-dihydrotetrabenazine, one of the primary metabolites, and this is the CMAX and also a two-and-a-half-fold increase in the beta metabolite. And what we see here is that the maximum mean change between -- from

pre-dose is 6 milliseconds for tetrabenazine alone and with metabolic in addition with 6.7 milliseconds.

Of note, this was not a placebo-controlled trial in the same way that the thorough QT study was, but the results were consistent and we do have some internal data suggesting that there is assay sensitivity.

Now, I would now like to turn to the adverse events of interest. These were highlighted in our briefing document as well as the FDA's document, and I would point out that these adverse events were anticipated -- at least some of these were anticipated as possible adverse events based on the pharmacology of the drug, notably monoamine depletion presynaptically. And the -- accordingly, the steering committee built in objective measures to the protocol to try to systematically monitor for these possible adverse events.

So depression, akathisia, and Parkinsonism are certainly anticipated, and in the event of severe Parkinsonism or potentially based on dopaminergic neurotransmission interference with tetrabenazine, dysphagia was also examined.

So turning first to depression, or depressive symptoms, tetrabenazine is indicated in green, placebo in the dashed line, and we see the change from baseline to week 12 in the double-blind trail, and we actually see a decline in both groups, but obviously placebo is declining more, and there is a drug placebo difference.

As Dr. Como has indicated, this is largely explained by changes on the components relating to anxiety, agitation, and insomnia, and there was no evidence for depressed mood. And I might add that the adverse events of depression were those that were identified by the investigator. It's not clear if this is truly a clinical

depression or there was no requirement for the patient to have a Hamilton Depression Score greater than 15 in order to have that adverse event.

This slide summarizes patients with depressive symptoms across a clinical trial experience, and we see here by the studies that are listed here and in study 004, of the 54 patients there were 9 adverse events of depression, 7 of which were mild to moderate in severity. One of these patients did include the completed suicide. There were no reports of depression among the 30 placebo subjects. In study 006, we have seen nine cases, eight of which were mild to moderate in severity, and the same is true in the 007 long-term study.

And we see down below, the Baylor experience is really consistent with most adverse events of depression being mild to moderate in severity.

Now, this slide gives you details

on the reversibility of depression as I mentioned at the outset. We focused on patients who had no dose reduction, continued therapy, presumably in the setting of mild depression, or at those patients that had dose reduction or discontinuation.

So if you look at study 004, we see that eight or nine patients resolved depression with continued therapy, dose reduction, or with discontinuation of tetrabenazine. In study 006, there were four patients that had resolution with no dose reduction. One that resolved -- I'm sorry, that improved with dose reduction three that were ongoing with medical management.

And I would say that of these patients with ongoing adverse events that three had (off mike) changes only and two had an improvement in their Hamilton Depression Scale and one had a normal Hamilton Depression Scale at their end of therapy. And these numbers don't add up to eight --

don't add up to nine. There was one patient who had improved HAM-D with the dose reduction.

Now, study 007 shows a similar trend, that we see several patients 12 of 24 that resolved with one of these maneuvers, 5 improved with dose reduction, but you see here that there were 6 that were ongoing with medical management or dose reduction only. And of these 7 patients, I should say first the fix that had medical management, and went ahead and improved the HAM-D score.

Regarding the patient that had a persistent adverse event with a dose reduction, this patient was still receiving 150 milligrams a day of tetrabenazine.

So now just to complete this adverse-event constellation I would comment on suicide-related adverse events. I explained the patient with a completed suicide. There was one patient that Dr. Katz mentioned in his summary memo in your

briefing document of a patient that had a suicide at Baylor. This was a patient with Tourette syndrome with a complicated psychiatric history. And it's -- through recent information from Dr. Jankovic it appears this patient may have actually been on study medication. But he has also questioned whether or not there is clear evidence that the patient was a suicide.

Regarding suicide attempts I mentioned the one patient in my discussion of serious adverse events and then there were suicidal ideations over the course of the development program.

So to summarize, there is a high prevalence of depression in Huntington's disease. The adverse events of depression in our clinical trial were typically mild to moderate in therapy. They were more common during titration and during maintenance. They were largely responsible -- responsive to tetrabenazine dose reduction, but it