DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS

ADVISORY COMMITTEE

NDA 20823, SE1-016, EXELON (rivastigmine tartrate) Capsules (1.5 mg, 3.0 mg, 4.5 mg and 6.0 mg), Novartis Pharmaceuticals Corporation, for the proposed indication of the treatment of mild to moderate dementia associated with Parkinson's disease.

Wednesday, May 17, 2006

8:00 a.m.

Hilton Washington D.C. North/Gaithersburg
Gaithersburg, Maryland

C O N T E N T S

C O N T E N T S (Continued)

PARTICIPANTS

Chair: Karl Kieburtz, M.D., MPA
Executive Secretary: LT Darrell Lyons

Committee Members
Michael D. Hughes, M.D.
Sandra F. Olson, M.D.
Ralph L. Sacco, M.D., M.S.

Temporary Voting Members
Eric Ahlskog, M.D., Ph.D.
Irene Litvan, M.D.
Marshall Loeb (Patient Representative)
Carol L. Koski, M.D.

Non-Voting Committee Member
Roger Porter, M.D. (Industry Representative)

FDA
Robert Temple, M.D.
Russell Katz, M.D.
Ranjit B. Mani, M.D.

P R O C E E D I N G S

Call to Order

DR. KIEBURTZ: Good morning. We will get started for this meeting of the Peripheral and Central Nervous System Drugs Advisory Committee.

We will start with presentations from the sponsor. We have an agenda. There are slight alterations to the agenda that I will talk about in a moment.

The first thing we will do is have the Conflict of Interest Statement read and then Dr. Katz will give some introductions to the meeting.

Conflict of Interest Statement

LT LYONS: The following announcement addresses the issue of conflict of interest and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an

appearance of a conflict of interest with the following exceptions.

In accordance with 18 U.S.C.208(b)(3), a full waiver has been granted to Dr. Karl Kieburtz for his membership on an unrelated Steering Committee for the sponsor, and an unrelated Data Safety Monitoring Board membership for a competitor. Dr. Kieburtz receives less than $10,001 per year from each firm for these activities.

Dr. Sandra Olson has been granted full waivers under 18 U.S.C.208(b)(3) and 21 U.S.C.355(n)(4) for her ownership of stock in two competitors. The stock values are between $25,001 to $50,000 each.

Mr. Marshall Loeb has been granted full waivers under 18 U.S.C.208(b)(3) and 21 U.S.C.355(n)(4) for his ownership of stock in a competitor. The stock value is between $50,001 to $100,000.

Finally, Dr. Carol Koski has been granted a waiver under 21 U.S.C.355(n)(4), an amendment of

the Food and Drug Administration Modernization Act, for ownership of stock in a competitor valued between $5,001 and $25,000. Because this stock interest falls below the de minimis exemption allowed under 5 C.F.R. 2640.202(a)(2), a waiver under 18 U.S.C. 208 is not required.

Waiver documents are available at FDA's docket web page. Specific instructions as to how to access the web page are available outside today's meeting room at the FDA information table. In addition, copies of all the waivers can be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Roger J. Porter has been invited to participate as an industry representative acting on behalf of regulated industry. Dr. Porter's role on this committee is to represent industry interests in general, and not any one particular company. Dr.

Porter is a retired employee of Wyeth Research.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

Thank you.

DR. KIEBURTZ: Thanks. I would like to take the opportunity to go around the table and have the committee members introduce themselves. If you want to add anything to the Conflict of Interest Statement or the material that has been read, please feel free to do so.

Dr. Porter, could you start and we will just go around the table.

DR. PORTER: Roger Porter, a neurologist,

20 years at NIH, 10 years at Wyeth, now a private consultant and a neurologist.

MR. LOEB: Marshall Loeb. I am a journalist, life-long journalist, and I am now with Marketwatts.com. Previously, I have been with Fortune Magazine, Money Magazine, and Time Magazine.

DR. LITVAN: I am Irene Litvan. I am a neurologist and director of the Movement Disorder program at the University of Louisville. I am specializing in Parkinson's Disease and dementia.

DR. KOSKI: Carol Lee Koski, Professor of Neurology, University of Maryland School of Medicine, previous head of the Division of Neuromuscular Disease.

LT LYONS: Lieutenant Darrell Lyons. I am the Designated Federal Officer for the committee.

DR. KIEBURTZ: Karl Kieburtz. I am a neurologist at the University of Rochester.

DR. OLSON: Sandy Olson. I am a neurologist at Northwestern in Chicago.

DR. SACCO: Ralph Sacco. I am Professor

of Neurology and Epidemiology and director of Stroke and Critical Care at Columbia University. I am a member of the panel.

DR. HUGHES: I am Michael Hughes. I am a member of the panel. I am Professor of Biostatistics at Harvard University.

DR. AHLSKOG: Eric Ahlskog. I am a neurologist at the Mayo Clinic in Rochester, Minnesota.

DR. MANI: Ranjit Mani, Division of Neurology Products, FDA.

DR. KATZ: Russ Katz, Division of Neurology Products, FDA.

DR. TEMPLE: I am Bob Temple. I am director of OD-1.

DR. KIEBURTZ: Dr. Katz, would you like to introduce the meeting, please.

Welcome and Introductory Comments

DR. KATZ: Thanks, Dr. Kieburtz.

I will be very brief. First, I would like to welcome the committee and, in particular, I would like to welcome our invited guests who are

not standing members of the committee, but who have agreed to come and help us deal with this interesting and important issue.

As you know, today, we are asking the committee to consider to a supplement to the Exelon New Drug Application. Exelon is a cholinesterase inhibitor currently approved as treatment for mild to moderate dementia of the Alzheimer's type. Now, the sponsor, Novartis, is proposing that Exelon also be approved as a treatment for the dementia associated with Parkinson's disease.

Their supplement contains the results of a single randomized trial in patients purportedly identified as having this latter dementia syndrome, but before we can consider the specifics of the supplemental New Drug Application, certain preliminary questions have to be addressed.

Specifically, we are going to ask the committee for your views on the question of whether or not there exists a dementia syndrome that is specific to patients with Parkinson's disease and that is distinct from other dementia syndromes and,

in particular, distinct from Alzheimer's disease.

Of course, there has been considerable discussion in the literature on the question of the existence of this Parkinson-specific dementia. Really, the only formal diagnostic criteria that exist are set out in DSM-IV, 294.1, which is quoted in the briefing books.

But I will just say it states that the essential feature of dementia due to Parkinson's disease is the presence of dementia that is judged to be of direct pathophysiological consequence of Parkinson's disease, but how the judgment is to be made that it is a direct pathophysiologic consequence of Parkinson's disease is not entirely clear, although the document does describe as does the literature several clinical features that are presumably distinct for this entity, including cognitive and motor slowing, impairment in memory retrieval, and executive dysfunction.

This morning, the sponsor will present evidence, both clinical and pathological, that in their view establishes the existence of the

distinct entity, and critically also establishes, again in their view, that the syndrome can reliably be diagnosed including being diagnosed by non-experts.

If the committee concludes that there is, in fact, a distinct dementia syndrome associated with Parkinson's disease, it is critical for us to know if the committee can conclude that the features of this syndrome are, in fact, sufficiently distinct, so that practitioners and importantly including non-experts can reliably identify patients with a specific dementia, and can distinguish the dementia of Parkinson's disease from other dementias purely on clinical grounds alone.

Further, we will want to know the committee's views on whether or not--and this is critical--the specific study that we will be hearing about today actually identified and enrolled only patients with the specific dementias associated with Parkinson's disease, and not, in particular, patients who had Alzheimer's disease.

These latter questions are critical for us for an adequate assessment of the application for the following reason: because Exelon is known to be effective as a treatment for Alzheimer's disease, we would expect the study to have been positive, as we believe it was by the protocol's specified rules, if the patients enrolled actually had Alzheimer's disease instead of Parkinson's dementia.

This is particularly true given that the primary outcome measures used in the study are the standard primary outcome measures that are used to assess treatments for Alzheimer's disease.

If patients in the study actually had Alzheimer's disease or perhaps a dementia syndrome characterized by overlapping pathology with Alzheimer's and Parkinson's disease, instead of Parkinson's dementia, it would be inappropriate to grant a claim for Exelon as a treatment for Parkinson's dementia on the basis of the results of this particular study.

So, for this reason, we need to know the

committee's views on the fundamental questions of whether or not Parkinson's dementia is distinct from Alzheimer's dementia, whether or not these two clinical entities are easily distinguished, and whether or not the appropriate patients in particular were enrolled in the study.

We have other questions, as well, including whether or not if the committee does answer the previous questions in the affirmative, a single study in this entity would suffice for approval.

On the one hand, if Parkinson's dementia is an entity distinct from Alzheimer's disease, perhaps the previous evidence of Exelon's effectiveness as a treatment for Alzheimer's disease offers no support for a Parkinson's dementia claim, and that therefore the usual standard for two independent sources of evidence should be required.

Another view, of course, would be that we can gain strength for various reasons that I am sure you will hear about later today from the

previous Alzheimer's data, and that therefore only a single study should suffice.

In addition, as noted earlier, the primary outcomes used in this study were the same as those used for studies of treatments for Alzheimer's disease, so we will want to know from you whether or not if the clinical features of Parkinson's dementia are sufficiently distinct from those of Alzheimer's dementia, these outcomes measures adequately assess the cognitive dysfunction presumably associated specifically with Parkinson's disease, or whether you believe, in fact, that a drug effect detected on these measures suggest instead that these patients were likely to have Alzheimer's disease concomitant with and not specifically as a consequence of Parkinson's disease.

So, those are the main issues we would like you to focus on. The specific questions are in the package, and we will want obviously, specific discussions about those or any other issue that you feel is relevant that we haven't already

raised.

They are complex questions, but they are very important from our point of view and have significant regulatory implications, so we are very grateful for your help, for coming, and I want to thank you for the work that you have done in preparation already and in advance for the work you will be doing today.

So, thanks, and I will stop there and I will hand it back to Dr. Kieburtz.

DR. KIEBURTZ: Thanks, Dr. Katz.

I would also like to add my thanks to the committee for reading the hundreds, if not thousands, of pages of briefing material on this particular hearing, and will continue with our information gathering task for the balance of the morning.

The agenda, as everyone should have access to, shows that we will have sponsor presentations for the balance of the morning. The way the agenda reads there is committee discussion. I would prefer, and I think the sponsor would too, to

actually have the presentations run fairly sequentially.

I would like the committee members to, at the conclusion of each presentation, if you have a question of clarification, if you misunderstood, had a pause in attention, or something, want to clarify a point, let's do that, but the discussions as to the meaning of the presentations or further in-depth discussion, I think perhaps would be best left to the conclusions of those presentations.

I don't see anyone feeling obstreperous about that, so we will go ahead with that plan.

We will have a break at 10 o'clock or thereabouts no matter where we are in the presentations, just so that people can have a chance to take a break. It will probably help people keep their attention focused.

At the conclusion of all of the presentations, the committee will have a chance to address the speakers from the sponsor and raise questions.

The discussion of the actual questions

among the committee follows the open public hearing. There will be a public hearing, and after that public hearing is closed, then, we will discuss among ourselves the questions, and vote on those questions.

We have the opportunity during that discussion to ask questions of the sponsor and of FDA, but the sponsor and FDA really, at that time, are not to offer information. It is not a chance for the sponsor to get up and speak again. We can ask people, though, for additional information, for backup slides or whatever.

Are people comfortable with that order of business?

Okay. Without further ado, from the sponsor, Dr. Struck, are you speaking first?

Sponsor Presentation

Exelon (rivastigmine)

Introduction and Regulatory Overview

DR. STRUCK: Professor Kieburtz, members of the committee, Dr. Temple, Dr. Katz, Dr. Mani, and FDA staff, colleagues, and guests: Good

morning. I am Martina Struck from Novartis Pharmaceuticals, Drug Regulatory Affairs.

[Slide.]

We are here today to talk about Parkinson's disease dementia and what role Exelon plays in ameliorating symptoms of this disease. Exelon is approved since April of 2000 for the treatment of mild to moderate dementia of the Alzheimer's type.

Alzheimer's disease is associated with a cholinergic deficit and Exelon is a cholinesterase inhibitor.

[Slide.]

The registration of Exelon in the treatment of Alzheimer's disease was based on the efficacy and safety of two well-controlled clinical studies. To date, the postmarketing exposure of Exelon is estimated to be 2.1 million patient years. Physicians, therefore, have extensive experience with Exelon and there exists a large safety database for Exelon.

[Slide.]

Novartis has further studied Exelon in another type of dementia, in Parkinson's disease dementia or abbreviated PDD.

As with Alzheimer's disease, PDD is also associated with a cholinergic deficit, however, the characteristic neuropathology in PDD and AD are distinct, and you will hear about this in greater detail in the following presentations by Professor Leverenz, Feldman, and Ballard.

Currently, there are no approved treatments in the U.S. for Parkinson's disease dementia, and at present, PDD is an unmet medical need.

A supplementary New Drug Application has been filed to the FDA last year, and the additional indication that we are seeking is for the treatment of mild to moderate dementia associated with Parkinson's disease.

Novartis has submitted this application to health authorities worldwide, and to date, Exelon in PDD is approved in 39 countries including all member states of the European Union.

[Slide.]

The application is based on the clinical study EXPRESS, which is a well-controlled study of Exelon in patients with PDD. The study met both co-primary endpoints of cognition and the global assessment.

Most of the secondary efficacy endpoints also reached statistical significance and included measures from different domains, such as activities of daily living, executive function, attention, and behavior.

[Slide.]

We contacted the FDA to seek advice for the additional indication of PDD in 2001 and in 2004. In both instances, the Agency communicated that they needed clarification on the following two points:

First, the Agency sought a more clear definition of PDD using widely accepted valid and reliable criteria; and second, the Agency sought a greater understanding of whether the patients with PDD differ from those with AD to whom the current

indication applies.

To respond to these questions, Novartis submitted a white paper written by a panel of movement disorder and dementia specialists. We then met with the FDA in May of 2005, and following those discussions, we filed the sNDA in August of last year with the agreement that we would present the sNDA to an advisory committee, and that is the reason why we are here today.

[Slide.]

We have two main objectives for today's meeting. The first is to address FDA's points for clarification as just outlined on the previous slide, and the second is to present the results of the EXPRESS study to demonstrate that Exelon in the treatment of patients with PDD is safe and efficacious, and therefore should so be indicated.

[Slide.]

To that end, let me introduce our program to you. Professor James Leverenz, from the University of Washington, Seattle, will present the neuropathology and cholinergic neurochemistry of

PDD.

Then, Professor Howard Feldman, from the University of British Columbia, Vancouver, will give a clinical overview of PDD.

Professor Clive Ballard, from King's College, London, will demonstrate that PDD is a distinct entity, which can be diagnosed in routine clinical practice.

[Slide.]

After the break, Dr. Roger Lane from Novartis will talk about the rationale and study design of Exelon PDD, followed by Dr. Sibel Tekin from Novartis who will present the results of the EXPRESS study.

The risk-benefit assessment for Exelon and PDD will be summarized by Professor Murat Emre from Istanbul University. Professor Emre was the principal investigator of the EXPRESS study, and he has published the results in the New England Journal of Medicine.

Thereafter, I will finalize the Novartis presentations with some regulatory considerations

on the new indication of Exelon and PDD.

[Slide.]

We have additional experts with us today. Professor Phil Harvey from Mount Sinai School of Medicine in New York. Professor Harvey is an expert in rating scales used in Europe psychologic assessments and measurement of outcomes in pharmacologic clinical trials.

Professor Howard Hurtig, he is Professor and Vice Chair, Department of Neurology, at the University of Pennsylvania in Philadelphia. He is our expert in Parkinson's disease.

Professor Woolson from the Medical University of South Carolina. He is our statistical consultant.

Now, I would like to welcome Professor Leverenz to give his presentation.

DR. KIEBURTZ: Any questions for Dr. Struck?

Just one point I forgot to make before. When we get through about 11:30 or so, we will be done.

DR. STRUCK: 11:30, okay.

The Neuropathology of Parkinson's Disease with Dementia

[Slide.]

DR. LEVERENZ: Good morning. My name is Jim Leverenz. I am a neurologist and neuropathologist from the University of Washington in Seattle.

[Slide.]

The two main points of my presentation this morning are that the dementia in elderly Parkinson's disease patients is primarily due to Lewy body pathology and not just coexistent Alzheimer's disease, and that PDD is associated with severe deficits in the cholinergic system.

To demonstrate these, I will share with you a review of the pathological changes observed in AD, PD, and PDD. I will also share with you data from biochemical and neuroimaging studies showing that there is a severe dysfunction of the cholinergic system in PDD.

[Slide.]

Before we go any further, I would like to define abbreviations and terminology that we will be using throughout our presentations.

PD will refer to Parkinson's disease without dementia. PDD will refer to Parkinson's disease with dementia, a syndrome in which a diagnosis of Parkinson's disease precedes onset of dementia by at least one year.

AD will refer to Alzheimer's disease. Lewy body pathology will refer to both "classic" Lewy body inclusions and alpha-synuclein immuno-positive inclusions and neurites.

CERAD refers to the Consortium to Establish a Registry for Alzheimer's Disease, a collaborative multicenter study from which the CERAD plaque staging originated.

[Slide.]

First, let's consider the pathology of AD patients. There are two primary pathological changes observed in AD. There are neuritic plaques and neurofibrillary tangles.

You can see neuritic plaques in these low-

and high-powered microscopic views. You can also see neurofibrillary tangles in low- and high-powered microscopic views.

[Slide.]

Staging of these pathologic changes of Alzheimer's disease are based on the density of neuritic plaques in the neocortex, and are staged from absent to frequent.

Neurofibrillary tangles are staged based on density and anatomical distribution ranging from limited medial temporal lobe pathology, Stage I, to severe diffuse neocortical tangle distribution, Stage VI.

Current pathological criteria for AD integrate staging for both pathological changes to assess the likelihood that these changes account for the clinical dementia, ranging from high likelihood with frequent plaques and neocortical, neurofibrillary tangles, to low likelihood with infrequent plaques and neurofibrillary tangles limited in number and distribution in the medial temporal lobe.

[Slide.]

It is important to recognize that these pathological changes of AD are common in normal elderly individuals.

David Knopman and his colleagues at the Mayo Clinic published their neuropathologic findings in 39 well-characterized non-demented elderly. They found that all but one case had neurofibrillary tangles although uncommonly beyond Stage III, and no case had Stage VI tangles, that is, severe neocortical tangles.

They also found neuritic plaques were generally sparse or absent.

They proposed a cutoff for the pathological diagnosis of Alzheimer's at Braak Stage IV to VI and neuritic plaque severity of moderate to frequent.

This cutoff allows us to classify a case as pathological AD or non-AD. We will use this cutoff to determine the presence or absence of pathological AD in studies examining the neuropathologic basis of dementia in PDD.

[Slide.]

Here is a graphical representation of the neurofibrillary tangle stages observed in this non-demented sample and the frequency of plaques. As you can see, mild to moderate pathological changes of Alzheimer's disease are relatively common in normal elderly.

[Slide.]

Unlike AD, the neuropathological diagnosis of PD is based on the presence of neuronal loss and Lewy body inclusions in the substantia nigra. As you can see on the left, we have a midbrain from a normal individual, on the right, a midbrain from a PD patient.

In the normal individual, there is preservation of substantia nigra neurons and therefore preservation of the normal pigmentation of this region. In the PD patient, there is significant loss of pigmented substantia nigra neurons leading to gross depigmentation of that region.

On the far right is a photomicrograph of a

pigmented substantia nigra neuron in a PD patient. Within that neuron you can see a pink inclusion with a clear halo, which is a classic Lewy body, as originally described by Freidrich Lewy.

[Slide.]

Within the last decade and with the discovery that Lewy bodies contain a synaptic protein alpha-synuclein, there has been a significant change in how Lewy body pathology is detected. This development was based on the discovery of mutations in the alpha-synuclein gene in certain forms of familial Parkinson's disease.

Subsequently, antibodies to alpha-synuclein were made, and it was discovered that these antibodies recognized not only classic brainstem Lewy bodies, but also cortical Lewy body inclusions and accumulation of alpha-synuclein in neuronal processes, often called Lewy neurites. Thus, the development of antibodies to alpha-synuclein has substantially improved our ability to detect Lewy body pathology throughout the brain.

[Slide.]

Using these methods, again we gain a more complete picture of Lewy body pathology in the brain of a PDD patient. On the left, we see Lewy body inclusions in the substantia nigra including one neuron with multiple inclusion bodies at the right arrow. In addition, we see a Lewy neurite in the section.

On the right, we see alpha-synuclein immunostaining of Lewy body inclusions in the deep layers of the cerebral cortex. As I will show you in a moment, these are the kinds of pathological changes that are commonly observed in PDD patients.

[Slide.]

Heiko Braak in Germany has suggested that Lewy body pathology can be staged in Parkinson's disease based on severity and distribution, much as he has done previously for neurofibrillary tangles in Alzheimer's disease.

He examined the brains of patients with Parkinson's disease in normal elderly for Lewy body pathology using antibodies to alpha-synuclein. His

results suggest the first Lewy body pathology appears in the medulla and olfactory bulb rather than the substantia nigra.

From there, the Lewy body pathology involves the remainder of the brainstem and then later the neocortical and limbic areas. As I will show you, it is at these later stages of more diffuse Lewy body pathology that the clinical signs of dementia appear in PD patients.

[Slide.]

So, with this background, what is the neuropathologic basis of dementia in Parkinson's disease?

[Slide.]

I think somewhat prophetic was Mel Ball's interpretation of his small study in 1984 looking for 80 pathologic changes in four cases of PDD. He found these cases had rare cortical neurofibrillary tangles, and stated, quote, "Contrary to published reports, most patients with parkinsonism who exhibit dementia do not have concomitant Alzheimer's disease. Some pathogenetic mechanism

must be sought to account for this increasingly common cause of cognitive decline in the sufferers of Parkinson's disease."

Of course, at that time he did not have access to alpha-synuclein antibodies to detect the diffuse Lewy body pathology commonly observed in patients with PDD.

[Slide.]

Multiple neuropathologic studies have demonstrated an association between the presence of cortical Lewy bodies and a clinical history of dementia in Parkinson's disease.

[Slide.]

A common misconception is that PD patients who later develop dementia simply have coexisting Alzheimer's disease. Recent carefully designed studies that have investigated this issue have demonstrated that dementia is due primarily to an extension of Lewy body pathology into the limbic system and neocortex.

In the past, many studies tried to address the issue of coexistent Alzheimer's disease in

patients with PDD. These studies have often had important methodologic problems. First, they have often included patients who developed dementia that preceded their clinical parkinsonism.

Second, many studies did not utilize alpha-synuclein immunostaining to detect the full extent of Lewy body pathology.

Finally, the pathological diagnosis of AD in these cases was often based on plaque pathology alone, and thus did not apply to up-to-date pathological criteria for Alzheimer's disease, that is, the presence of both neurofibrillary tangles and neuritic plaques.

[Slide.]

Three carefully designed clinical pathologic studies have demonstrated that PDD is not commonly associated with significant coexisting Alzheimer's disease pathology.

The first study is the Apaydin, et al. study from the Mayo Clinic group. In this study, they examined 13 cases of clinically diagnosed PDD. They were careful to only select cases in which the

clinical parkinsonism preceded the onset of dementia.

At autopsy, 12 of the 13 cases had Lewy body pathology. Only 1 of these cases had a coexistent pathologically confirmed Alzheimer's disease.

[Slide.]

In 2005, Heiko Braak published a study in which his group examined 88 clinical PD cases with autopsy confirmation of Lewy body pathology. Of these, 79 had some level of cognitive impairment ranging from mild to severe.

He found the severity of cognitive impairment as measured by the Mini-Mental State Examination score correlated inversely with the stage of Lewy body pathology, that is, the higher the stage of Lewy body pathology, the greater the severity of cognitive impairment.

This finding strongly suggests an association between the severity of Lewy body pathology and dementia.

Of interest in this group, only 2 cases

fulfilled the pathological criteria for Alzheimer's disease.

[Slide.]

Finally, Dag Aarsland, et al. examined the neuropathologic changes in a community-based sample of longitudinally followed Parkinson's disease patients. Twenty-two of these cases have come to autopsy, 18 with documented dementia prior to death.

They found the severity of dementia as documented by the Mini-Mental State Examination correlated with severity of Lewy body pathology, but not to the severity of AD pathology. In addition, coexistent pathological AD was limited.

[Slide.]

In summary, we have clinical pathologic data for 110 cases of PDD from 3 well-designed studies. Of note, all 3 studies used DSM-III or III-R criteria for the diagnosis of dementia compatible with DSM-IV criteria.

In addition, most of these people were in their late 70s at the time of death.

The presence and severity of limbic and neocortical Lewy body pathology correlated well with severity of dementia, and only 6 percent of these cases had coexistent pathological findings consistent with a diagnosis of Alzheimer's disease.

[Slide.]

In conclusion, the clinical diagnosis of PD with dementia, that is, PD subsequent development of cognitive impairment is highly predictive for Lewy body pathology at autopsy. In addition, in these cases, the presence of co-occurring Alzheimer's disease is relatively uncommon.

Thus, dementia in elderly PD patients is likely due to Lewy body pathology and not just coexistent Alzheimer's disease.

[Slide.]

The final question of this presentation is whether cholinergic system is dysfunctional in PDD.

[Slide.]

We know that in both PDD and AD, there is pathological involvement of the two main

cholinergic nuclei projecting to subcortical and cortical regions, specifically, the cholinergic basal forebrain and pedunculopontine nucleus, however, the type of involvement is fundamentally different.

In PD and PDD, we see neuronal loss and Lewy body pathology in both of these cholinergic nuclei. In fact, Friedrich Lewy originally described Lewy body inclusions in the basal forebrain.

While these cholinergic nuclei are also involved in Alzheimer's disease, the primary pathology is neurofibrillary tangle formation, and not Lewy body pathology.

[Slide.]

Thus, despite a difference in the fundamental pathology or pathobiology of PDD and AD, we observe a common outcome, which is a deficit in cholinergic function.

[Slide.]

Multiple neurochemical and neuroimaging studies have demonstrated a significant loss of

cholinergic markers in PDD.

In a summary slide, we see that a number of studies using both neurochemical analysis of autopsy tissue and PET imaging of patients have demonstrated a loss of cholinergic markers in PD and PDD. The loss of these cholinergic markers is generally the most severe in patients with a clinical history consistent with PDD.

[Slide.]

In this study, Bohnen and colleagues at the University of Pittsburgh reported a significant deficit in cortical acetylcholinesterase hydrolysis rates in AD, PD, and PDD. In the neocortex, the deficit was most severe in PDD.

[Slide.]

This same University of Pittsburgh group has also examined the relationship between severity of cholinergic deficit and level of cognitive impairment in patients with PD or PDD.

As shown in this slide, there was a significant correlation between cholinergic deficit, as measured by cortical

acetylcholinesterase hydrolysis rates and attentional and executive functioning. These data suggest a common link between the cholinergic deficit and executive dysfunction observed in PDD.

[Slide.]

To summarize, the two nuclei primarily responsible for cholinergic function in subcortical and cortical regions are pathologically involved in PDD.

Reduced cortical cholinergic activity is more severe in PDD than in mild AD.

Cholinergic dysfunction in PDD is associated with decreased performance on tests of attentional and executive functioning.

[Slide.]

So, in conclusion, the clinical syndrome of PDD is highly predictive for specific neuropathologic and neurochemical characteristics.

The neuropathology is characterized by the presence of Lewy body pathology and limited AD pathologic change, that is, PDD patients do not typically have the severity of neuritic plaque

deposition and neurofibrillary tangle formation necessary for a diagnosis of Alzheimer's disease.

Neurochemically, there are profound deficits in cortical cholinergic function that are associated with cognitive impairments known to occur in PDD.

Now, I would like to invite Dr. Feldman to the podium to present a clinical perspective on PDD.

DR. KIEBURTZ: Any points of clarification from the committee?

The Braak 2005 study, the 79 people with cognitive impairment, do we know about the temporal relationship to their diagnosis of PD?

DR. LEVERENZ: The PD preceded the dementia by greater than or equal to one year.

DR. KIEBURTZ: In all?

DR. LEVERENZ: That is what they reported, yes.

DR. KIEBURTZ: Thanks.

DR. PORTER: Just a quick clarification. I realize this is a neuropathological study, but in

your 110 patients, were there any subsets that were analyzed that were distinctive for PDD as opposed to AD?

DR. LEVERENZ: I am not sure I understand your question.

DR. PORTER: My question is whether there were subsets of the cognitive studies which defined PDD as opposed to AD in this neuropathological study.

DR. LEVERENZ: Those three neuropathological studies, to the best of my knowledge, did not try to make a differential based on the clinical neuropsych testing.

Parkinson's Disease Dementia (PDD)

A Clinical Perspective

[Slide.]

DR. FELDMAN: Good morning, ladies and gentlemen, and colleagues. My name is Dr. Howard Feldman. I am Professor and Head of the Division of Neurology at the University of British Columbia in Vancouver, Canada. I direct a clinic for Alzheimer's disease and related disorders, a

tertiary referral center for dementia care.

[Slide.]

In this next segment of our presentation, I am going to provide a clinical perspective of PDD. I will do this by addressing four major points.

First, I will illustrate the clinical presentation of PDD using a case clinical vignette.

Next, I will review the defining clinical features of PDD and compare them with those of Alzheimer's disease.

Then, I will outline some of the clinical and treatment challenges that arise in PDD, which is a relatively unique circumstance.

Finally, I will conclude by addressing the diagnosis of PDD in routine clinical practice.

[Slide.]

To set the stage for all of the discussions that will take place today, we need to consider the human face of this clinical problem of PDD. Here is an example of a typical PDD patient for presentation.

This gentleman was a 63-year-old male, had a 10-year history of Parkinson's disease. His initial presentation was that of an asymmetric tremor, rigidity and bradykinesia. He was identified to have idiopathic Parkinson's disease and treated with levodopa.

For a number of years, his motor symptoms were well handled before they became more challenging. He went on after a number of years to develop dyskinesia and motor fluctuations that led to the addition of bromocriptine and entacapone.

After approximately eight years of his illness, he began to experience a notable cognitive decline with behavioral changes and reported recurrent visual hallucinations. He described to his wife seeing small animals and children inside his home, a circumstance that you can imagine would be quite upsetting both to him and to his family.

[Slide.]

In his day-to-day functioning, his wife described a considerable change and uncharacteristic behaviors. He was described to be

less motivated, he appeared to be excessively sleepy, he was inattentive and forgetful particularly for recent events and conversations.

She remarked that his thought processing seemed slower, and she described him having topographic disorientation even inside his own home.

He withdrew from a number of his hobbies and increasingly required assistance in his instrumental and basic activities of daily living.

Hoping to settle his hallucinations, his physician reduced some of his dopaminergic medications. This led to a beneficial effect on the hallucinations, but his parkinsonism worsened.

In reviewing history, it came to light that he had evidence of a REM sleep behavioral disorder 10 years prior to the initial features of Parkinson's disease.

[Slide.]

At the time that he was assessed, he was cooperative and intermittently drowsy. He had global screening cognitive testing with a

Mini-Mental score of 21 of 30. His points were lost on the Mini-Mental and temporal disorientation where he lost 2 points, three-word recall 3 points, visual construction 1 point, and serial 7's 3 points.

He certainly had characteristic motor parkinsonian features, he now had resting tremor bilaterally, and a clearly festinating gait.

His diagnosis was Parkinson's disease with dementia.

[Slide.]

Our case illustrates a patient with longstanding Parkinson's disease who develops the cognitive and neuropsychiatric features of PDD. We see the key temporal relationship that identifies this disorder where the cognitive decline begins at least one year, and most often many years, after the initial PD diagnosis.

[Slide.]

Establishing PD is essential to the later consideration of PDD. In turn, it is worthwhile to spend a few moments reviewing the diagnostic

criteria for PD. There are a number of published criteria for PD. Within the clinical trial that will be discussed today, the validated PD diagnostic criteria of the UK Parkinson's Disease Society Brain Bank were used, and these are the ones that I will review.

According to these criterion, there is a three-step process for diagnosing PD. The initial step is the recognition of a parkinsonian syndrome, having features of bradykinesia, rigidity, resting tremor, or postural instability.

[Slide.]

The next step in establishing PD diagnosis is to exclude alternative disorders or atypical signs in the course of disease. As you can see, the list of exclusion ranges widely, covering things from stroke all the way through to neurotoxins, while additionally considering atypical clinical signs in between.

[Slide.]

The final diagnostic step involves longitudinal observation and confirmation where

three or more features are required for definite PD diagnosis. This will include features such as the asymmetry of onset, the course being progressive, and the levodopa responsiveness.

[Slide.]

Parkinson's disease is a significant health issue. The NINDS web site indicates that there are half a million Americans currently diagnosed or currently estimated to have PD with an additional 50,000 new cases diagnosed each year.

Among PD patients, it is estimated that between 24 and 40 percent have PDD. There is a significant increased risk estimated at 4 to 6 times for individuals with PD to develop dementia more so than their age-matched control peers.

[Slide.]

The societal burden of PDD is considerable. PDD predicts and decreases the time to nursing home placement. Changes in cognition and behavior are the strongest contributors of measurable caregiver distress. Mortality rate is increased with PDD by a factor of 2.

[Slide.]

As Dr. Leverenz has demonstrated, recent neuropathological studies indicate that PDD is most often associated with Lewy body pathology that spreads into the limbic system and neocortex, and is not commonly associated with full-blown Alzheimer's disease or diagnosable Alzheimer's disease.

In turn, the clinical phenomenology of PDD should be contrasted with AD both from the neuropsychological and behavioral viewpoints.

[Slide.]

There are some characteristic neuropsychological impairments in PDD within a number of domains. We can begin with memory processing where patients with early PDD will typically have greater difficulty in their retrieval of newly learned information than in its storage. They can respond to cueing and will generally have better preserved recognition memory.

By contrast, Alzheimer's disease patients have more severe dysfunction with both impaired

retrieval and impaired recognition memory. They do not respond to cueing. Different neuroanatomic bases can be ascribed to some of these differences.

In PDD, the memory difficulties will result from an underlying frontal striatal involvement accounting for the retrieval problem, while in AD, there will be greater impairment in the medial temporal lobe, hippocampus, and entorhinal cortical functions.

In PDD, executive dysfunction is prominent with difficulty across a range of functions that may include things like ability to set shift, to problem solve, and particularly to generate internally cued behavior. There is a characteristic slowing in cognitive speed that is not part of Alzheimer's disease.

There is an attentional impairment in PDD that frequently involves fluctuations that is characteristic of PDD and which again takes us back to the subcortical frontal axis.

Visuospatial impairment in PDD is also common and more affected at an early stage than in

Alzheimer's disease. This is seen particularly in tasks that require planning and sequencing within the visuospatial domain.

[Slide.]

From the AD perspective, there are a number of distinguishing features, as well. In language, there is greater impairment in Alzheimer's disease with anomia, decreased information content in spontaneous conversation, and impaired comprehension. These functions are less impaired in Parkinson's disease dementia.

Apraxia tends to be more impaired in Alzheimer's disease and relatively spared in PDD.

It should be appreciated, and I would emphasize, that these differences between AD and PDD are not absolute. They may be most readily identified early in both dementias. They may becomes less apparent as disease and dementia progresses.

By dementia definition, both AD and PDD have progressive functional decline, however, this can be more difficult to identify in PDD because of

the confounding effects of motoric problems.

[Slide.]

As our case vignette illustrated, behavioral changes are often prominent in PDD. Changes in personality are frequently reported. Depressive symptoms are common. Visual hallucinations can be particularly problematic, as our case illustrated.

They are two times more common in PDD than AD, in a series by Aarsland, 54 percent in PDD compared to 25 percent in AD. The REM sleep behavioral disorder is now appreciated to occur in about two-thirds of individuals even prior to a PD diagnosis.

[Slide.]

The presence of these behavioral symptoms is a particularly compelling therapeutic challenge in Parkinson's disease. Dopaminergic therapy may exacerbate or be associated with psychotic symptoms in PD.

The use of both atypical and typical neuroleptics, which are usually a mainstay for

psychotic symptoms, is problematic for a number of reasons.

First, it is recognized that patients with PDD are at an increased risk of significant hypersensitivity reaction to neuroleptics. Also, atypical antipsychotic medications have been associated with increased mortality rates in elderly patients who have behavioral symptoms.

Both cognition and motor function can worsen with their use.

Despite these challenges, the target behavioral symptoms are often upsetting to patients and their caregivers and they require treatment intervention.

[Slide.]

Turning our attention to diagnosing PDD using both formal diagnostic criteria, such as the DSM, as well as pragmatic approaches that need to be developed for usual care settings. We will begin with the DSM criterion.

The DSM-IV criterion provide both a general framework for diagnosing dementia, as well

as providing some guidance on the clinical characterization of PDD. The neuropathological correlate of studies that Dr. Leverenz just completed presenting have each used the DSM criteria to establish the clinical diagnosis of PDD prior to the neuropathological verification.

These data indeed provide some validation of the DSM PDD criteria and continuum.

[Slide.]

In the general framework for dementia diagnosis, which is put under the heading of Due to Other Medical Conditions, including Parkinson's disease, there is a specification that there should be significant impairment in memory and in a second cognitive domain.

Each of these cognitive domains should interfere with social or occupational functioning and should represent a decline from a previous level of competence.

Other potential causes, such as AD and cerebral vascular disease, as well as delirium, need to be excluded. This will generally require,

particularly delirium, a review of medications, a search for remediable medical illness, and neuroimaging.

[Slide.]

The DSM-IV also provides some additional characterization of PDD in Section 294.1, a copy of which is included in your packet. This section states that the dementia should be the direct pathophysiological consequence of PD.

The studies of Braak, Apaydin, Aarsland, that have been presented, underscore the ability of diagnosis of PD followed by DSM criteria IV dementia to predict accurately the presence of significant limbic and neocortical Lewy body neuropathology.

The clinical characterization that is offered provides a description of some of the neurocognitive and functional features to be looked for in PDD.

[Slide.]

In addition to the DSM-IV, there have been other validated criteria for other causes of

dementia that help shape PDD's delineation. For example, the NINCDS-ADRDA criteria for probable Alzheimer's disease specify that PD must be excluded to establish the diagnosis of Alzheimer's disease.

The working criteria proposed by McKeith and colleagues for dementia with Lewy bodies specify that for this diagnosis, the dementia should occur before, concurrent with, or within one year of the onset of parkinsonism.

[Slide.]

In routine clinical practice, physicians can apply the DSM-IV criteria based around clinical judgment. These criteria have the advantage that they are not tied to specific cut scores on psychometric tests, rather, they reside with the clinician's ability to evaluate the patient in front of them.

Finally, and importantly, there is a necessary temporal relationship of at least one year from the diagnosis of PD to the onset of dementia as can be determined by patient history.

[Slide.]

In conclusion, PDD is a clinically recognizable disorder that has some unique features. It is a dementia that begins with Parkinson's disease, with motor symptoms that are present for at least one year, and often many years, as in our illustrative case before the onset of dementia.

The dementia itself has both cognitive and neuropsychiatric symptoms that reflect on the underlying limbic and neocortical parkinsonian pathology.

This disorder can be identified and diagnosed in routine clinical practice according to current criteria, such as the DSM-IV, with attention added to the temporal relationships between PD and dementia onset.

There are currently no approved therapies for the symptoms of PDD in the U.S. This represents a significant unmet need for patients with this challenging disorder.

Thank you for your attention.

DR. KIEBURTZ: Any questions of Dr. Feldman? Dr. Temple.

DR. TEMPLE: I am probably asking this because I am not burdened with any knowledge of these conditions.

In presenting all this, you make it clear that to have Parkinson's dementia, you need to have Parkinson's disease. Okay, that's true, but it doesn't seem to help.

Could you pull out more the characteristics of the syndrome that make you think that it is not Alzheimer's disease occurring in the Parkinson's disease person versus Parkinson's dementia itself? You may have done that and maybe everybody knows it, and if you all understand all this already, just tell me and I will shut up, but I didn't find that clear.

Your index case, for example, sounded like someone with dementia all right, occurring eight years after--noted anyway eight years after Parkinson's disease, but how would you know even in retrospect that that wasn't just Alzheimer's

disease occurring in such a person?

DR. FELDMAN: The prospective studies that have been done neuropathologically used DSM criterion and then examined the pathology, and, in fact, the specification around the PDD in the DSM is actually reasonably limited. Yet, despite the relatively generic nature of the applied criterion, the pathology was quite uniform and, in fact, we see only 5 to 7 percent of full-blown Alzheimer's within those carefully followed cases.

So, we can get into the very specific characterization, and I touched on some of that in the neuropsychological differentiation, but the reality is that dementia that follows Parkinson's disease, you know, you have Parkinson's disease, then you develop dementia, and then you take it to autopsy. That continuum is highly predictive of the kind of neuropathology that we associate to PDD.

DR. TEMPLE: I understood the path argument, but I just wondered if you also thought the particular dementia syndromes could be

distinguished.

DR. FELDMAN: They can be distinguished, but I think that the question is, is it necessary is one question. If one is in expert hands, yes, definitely, there are phases of the illness where they are distinguishable, recognizing at the same time that as dementia progresses in severity, it gets increasingly difficult.

DR. KIEBURTZ: Dr. Katz.

DR. KATZ: Obviously, the point is made several times that when you see dementia in a Parkinson's patient, it is overwhelmingly likely that it not be Alzheimer's even if they are not exactly distinguishable clinically, or even if they are.

But in age and sex-matched sort of controls, how many cases of Alzheimer's disease would one expect to see in these sorts of samples that have been studied?

I am wondering whether or not the incidence of at least Alzheimer's pathology is markedly decreased in Parkinson's patients. Is

Parkinson's protective of Alzheimer's disease? Why don't you see more of it just randomly by chance?

DR. KIEBURTZ: I think we are straying from the clarifications in individual discussions, so can we just hold that?

DR. FELDMAN: We can.

DR. KIEBURTZ: Proceed, please.

DR. FELDMAN: I would like to introduce Professor Clive Ballard from the Institute of Psychiatry, King's College, London.

Clinical Summary

[Slide.]

DR. BALLARD: Thank you, Howard.

Good morning. As Howard said, I am Clive Ballard from the Institute of Psychiatry in London.

[Slide.]

Building upon the presentations of Dr. Leverenz and Dr. Feldman, I am going to cover three main areas: that PDD is a distinct dementia syndrome, that PDD can be diagnosed unambiguously in routine clinical practice, and that PDD is a rational target for treatment.

Along the way, I will also provide my perspective on both the commonalities and the unique differences between PDD and Alzheimer's disease.

[Slide.]

We have heard about the clinical and neuropathological features of PDD. I think a discussion of its genetic basis is also helpful. Although familial patients account for only a very small proportion of people with PDD, it is highly informative about the underlying disease substrate.

In reviewing the literature, it is very clear that the vast majority of familial PDD is associated with either a mutation of the alpha-synuclein gene or an abnormality leading to overproduction of alpha-synuclein.

None of these families have familial Alzheimer's disease genes, and none of them have normal synuclein genes that lead to familial Parkinson's disease, such as the LRRK2 gene or the parkin gene.

This indicates that in these families, it

is the alpha-synuclein abnormalities that underlie the development of Parkinson's disease dementia. In fact, if we look at the neuropathology in the cases that have come to autopsy, it is characterized by neocortical Lewy body disease.

[Slide.]

Distinguishing dementia syndromes occupies considerable attention. It is, however, important to understand that the overlap of different major pathologies is actually the usual clinical presentation for dementia patients.

For example, 40 to 50 percent of those individuals with Alzheimer's disease have fairly significant cerebrovascular disease. As would be expected, there is also some degree of overlap between Lewy body pathology and Alzheimer's pathology in PDD patients.

Neurofibrillary tangle pathology is actually infrequent across the spectrum of DLB and PDD with Braak Stage 5/6 pathology occurring in only about 10 percent of patients, but frequent plaque pathology, here defined using CERAD, is

actually quite common in dementia with Lewy bodies, but less frequent in PDD patients.

In fact, using the criteria explained by Dr. Leverenz, only 7 percent of PDD patients had sufficient pathology to meet diagnostic criteria for Alzheimer's disease.

This emphasizes the value of using PDD as a diagnostic entity, because although the temporal cutoff is arbitrary, it excludes the people with the most substantial overlap of Lewy body and Alzheimer pathology, and it therefore allows us to focus on the group where the predominant pathology underlying the condition is that of cortical Lewy body disease.

[Slide.]

As you can see from these data, as well as the data presented by Dr. Leverenz and Dr. Feldman, PDD is associated with a characteristic neuropathological and clinical profile.

To summarize some of these important points, Lewy body pathology is the predominant substrate of cognitive decline in PDD. Overlapping

Alzheimer plaque pathology is not the main correlate of dementia in PDD patients, and 93 to 94 percent of patients with PDD lack sufficient pathological changes to meet diagnostic criteria for Alzheimer's disease.

Dementia in PDD also has a characteristic profile of neuropsychiatric, cognitive, neurological, and autonomic features, which I would like to briefly illustrate over the next few minutes.

[Slide.]

In this study, we compared attentional performance in PDD and Alzheimer patients using a computerized test to look at reaction time and fluctuation. The words Yes or No are presented on a computer screen, and the patient is required to press the appropriate Yes or No button. This is repeated 30 times over 90 seconds.

The computer calculates the mean reaction time and the fluctuation of reaction time over the testing period. As you can see, the reaction times of PDD patients were twice as slow as those of

patients with Alzheimer's disease, and had four times as much fluctuation in response time. Furthermore, a significant difference was still evident after correcting for motor reaction time.

This is a clear indication of the slowed cognitive performance of patients with PDD and of the marked attentional impairments that are characteristic of these patients.

[Slide.]

The clinical presentation of PDD is also characteristic. We can see from a prospective clinical series where many patients came to autopsy that key clinical symptoms including major depression, fluctuating confusion, falls, visual hallucinations, and, of course, parkinsonism, were all significantly more common in Parkinson's disease dementia than in Alzheimer's disease.

[Slide.]

Another important clinical feature that distinguishes PDD from Alzheimer's disease is autonomic dysfunction. From the Braak staging of Parkinson's disease, we know that there is early

involvement of the brainstem and the sympathetic and parasympathetic ganglia including the vagus. Therefore, it is not surprising that autonomic dysfunction has been reported as a common problem in people with Parkinson's disease.

The data presented here from Rose Ann Kenny's work extend our understanding by comparing PDD patients and Alzheimer's disease patients. Using the Ewing battery, the simple clinical bedside test of parasympathetic autonomic function, Dr. Kenny demonstrated that the these functions are significantly more abnormal in PDD patients than amongst patients with Alzheimer's disease.

[Slide.]

What all of this data shows us is that PDD can be diagnosed simply and unambiguously in routine clinical practice using three simple principles: an established diagnosis of Parkinson's disease, development of dementia diagnosed using tools such as the generic criteria within DSM at least one or two years after the onset of Parkinson's disease, and exclusion of

other clear causes of dementia.

We know from prior autopsy studies that a clinician using these principles will accurately identify a group where more than 90 percent of the individuals have PDD.

Furthermore, we know that this group of individuals will have characteristic cognitive psychiatric and autonomic symptoms. However, this simple approach also has the advantage of avoiding complex assessments of individual symptoms, which can be difficult to identify in clinical practice.

[Slide.]

There are some distinct treatment issues related to PDD which emphasize the importance of considering it as a separate condition. For example, the high frequency of severe neuroleptic sensitivity reactions in PDD patients creates the need for a non-neuroleptic treatment option for psychiatric symptoms.

Similar to the neuroleptic malignant syndrome, neuroleptic sensitivity reactions in PDD patients are characterized by severe parkinsonism,

autonomic instability, increased confusion, and often death.

These reactions are seen in more than 30 percent of patients with PDD, but do not occur in patients with Alzheimer's disease.

[Slide.]

As highlighted by Dr. Leverenz, there is, however, a clear cortical cholinergic deficit in PDD patients similar to or greater in severity than that seen in Alzheimer's disease.

In addition, there is emerging evidence linking the severity of these cholinergic deficits to some of the key cognitive and neuropsychiatric symptoms in these patients, emphasizing the importance of cholinergic deficits as a treatment target.

[Slide.]

So, in conclusion, Lewy body pathology is the main substrate of cognitive impairment and cognitive decline in Parkinson's disease dementia. Parkinson's disease dementia can be most effectively diagnosed using simple clinical

criteria based on the presence of Parkinson's disease and the time course to the development of subsequent dementia.

Although there are distinct treatment issues related to PDD which emphasize the importance of considering it as a separate condition, both PDD and Alzheimer's disease share a common cholinergic deficit, which is am important treatment target in both conditions.

Now, I would like to introduce Dr. Roger Lane from Novartis who will take further questions.

DR. KIEBURTZ: Before you switch over, Dr. Katz.

DR. KATZ: Just one question. There is a high rate of this severe neuroleptic sensitivity reactions in patients with PDD and Lewy body dementia, and not in Alzheimer's disease.

Is there any information about Parkinson's patients without dementia?

DR. BALLARD: Yes. The Aarsland study also looked at that group of individuals and found about 20 percent of people did have these

reactions, so it was less frequent than in Parkinson's dementia, but more frequent than in Alzheimer's disease.

DR. KATZ: What was the incidence in Parkinson's dementia?

DR. BALLARD: Thirty-nine percent.

DR. KATZ: People thought that was a significant difference between the patients with and without dementia, Parkinson's patients?

DR. BALLARD: Yes.

DR. KATZ: How many Parkinson's patients did they look at in that study, without dementia?

DR. BALLARD: I think it was about 40.

DR. KATZ: Thank you.

DR. KIEBURTZ: Dr. Porter.

DR. PORTER: Yes. In your choice reaction time studies, is it important to stage the patients with PDD or AD as opposed to, say, as to mild or severe, and did you do that, or is this a phenomenon that is across the board independent of the severity of the disease?

DR. BALLARD: Looking at the severity, it

is certainly associated with the overall severity of the dementia, the more severe the cognitive impairment, the more slow the reaction times.

With respect to the severity of the parkinsonism, the surprisingly small relationship between the severity of the parkinsonism and the severity of impairment of reaction times.

To clarify that these differences were actually differences in cognitive reaction time, we did also measure simple reaction times and subtract those from the choice reaction times to give a cognitive reaction time, and there was still a significant difference between the groups.

DR. PORTER: Thank you.

DR. KIEBURTZ: Dr. Olson.

DR. OLSON: Actually, my question is similar. In the reaction time in the fluctuation of choice reaction time, how were the severities of the dementia compared, in other words, how were they measured, and were they comparable as far as the severity of the dementia?

DR. BALLARD: The severity of dementia in

the Alzheimer patients and the PDD patients were very closely matched. We also looked at it in MSSE bands within each diagnosis, and each band had a similar difference in reaction time, as well.

DR. KIEBURTZ: Dr. Katz.

DR. KATZ: A number of folks have said that there is a--you obviously talked about the presumed distinctness on clinical grounds of Alzheimer's and Parkinson's disease dementia--maybe that actually doesn't even matter, because it seems to be that if you have dementia, if you have Parkinson's disease and then in a few years you get dementia, it is not Alzheimer's, but that needs to be discussed.

What is the actual evidence that a non-expert can actually tell the difference on clinical grounds?

DR. BALLARD: I think the evidence is that the symptom profile is different. I mean some of the key symptoms like visual hallucinations, for example, are a lot more frequent in Parkinson's disease dementia than in Alzheimer's disease.

I think the point is, though, that no individual symptom distinguishes 100 percent between the condition, so although the overall profile is different, you can't separate the two groups of people on the specific individual symptoms, and that is why really the most pragmatic approach to diagnosis I think is to diagnose the Parkinson's disease and then diagnose the subsequent dementia, and that group of people will have those characteristic differences.

DR. KIEBURTZ: I think I am hearing separation between the notion of there is a distinct neuropsychologic test performance profile of these dementias, which is different than a clinical ability to discriminate between them based on routine clinical features. Is that what you are drawing out?

DR. KATZ: I am thinking back to an advisory committee meeting we had a number of years ago where we talked about how do you diagnose MCI in mild cognitive impairment, and can people who are not experts do that.

One of the things the committee recommended was before we approved a drug for MCI that a study ought to be done in the community, in other words, where non-experts are enrolled as investigators to see whether or not they can capture the right patients.

So, I am just trying to figure out whether or not the non-expert, if this were to be approved for this condition, would be able to reliably identify who these people are.

Now, maybe it's ultimately not going to matter, because again it's a very operational definition that seems to be evolving. You have Parkinson's, you have dementia, then, you don't have Alzheimer's, you have the Parkinson's disease dementia.

So, maybe it's even a moot point, but I am just trying to figure out whether or not the average clinician out there could detect these people.

DR. KIEBURTZ: Dr. Sacco, then, Dr. Temple.

DR. FELDMAN: Could I respond to Dr. Katz's comment?

DR. KIEBURTZ: Sure.

DR. FELDMAN: I would just offer the perspective, having been heavily involved in MCI for a lot of years, MCI is an extremely heterogenous entity, and I think we are talking this morning about an entity that is much more unified in the sense that what binds this all together is Parkinson's disease.

So, unlike MCI, which has every kind of dementia in its prodromal stage, we are talking about a distinct disease today that starts as Parkinson's disease and then a dementia evolves from that.

So, I would just respond by saying that there is a much greater homogeneity of what we are talking about this morning in relationship to phenotypes than with MCI.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: Rather than talk about the simple clinician definition of dementia right now,

I wanted to just ask for clarification from Dr. Ballard. You showed the attention and the reaction time.

I presume there were other things tested in neuropsychometric measurements, and where were there similarities, and are there any other differences between the groups of patients in the neuropsychological assessment?

DR. BALLARD: I showed the attentional data as an example really rather than going through the whole gamut of things, but clearly, if you look at detailed tests, visuospatial performance is significantly more impaired in Parkinson's disease dementia than in Alzheimer's disease, that is, simply copying and drawing tasks are more impaired, executive function tasks are also more impaired. On memory tasks, there is perhaps slightly less impairment of memory, and if you tease it out, there may be some differences in the aspects of memory that are affected, as well.

DR. TEMPLE: I guess what I heard probably 10 times was that none of these distinctions, while

perhaps real, matter much, because if you take someone who has Parkinson's disease for sure, which is probably not that hard to diagnose, and find that he is demented in some way, only 5 or 6 percent of those people, based on the pathology, have Alzheimer's disease, so the rest have Parkinson's disease, which I guess one might say the specificity and sensitivity of doing it the way you described is not so bad, although you will obviously include a few people who really do have Alzheimer's disease, most of them won't.

But the fundamental argument there that I hear is the pathologic one, not anything else, and given who has got to make this diagnosis in many cases, maybe that is reasonable. But that is the argument, isn't it, principally?

DR. BALLARD: That is the argument, because I think although the clinical syndrome is different, and the neuropsychology is different, that would require probably a higher degree of expertise in the assessment to tease those apart.

What we are suggesting is because of the

pathological data, that level of expert diagnosis probably isn't necessary.

DR. KIEBURTZ: Thank you. We will move on.

Dr. Lane.

Rationale for Indication of Parkinson's Disease Dementia (PDD) and Study Design

DR. LANE: I am Roger Lane. I am the Disease Area Section Head for Dementia at Novartis, and I will be helping moderate the sponsor's response, I mean if there are any questions. Do you want to move on with the next presentation? All right.

[Slide.]

Good morning, ladies and gentlemen. As I said, I am Roger Lane. I am the Disease Area Section Head for Dementia at Novartis. I am going to give you a brief overview of the rationale for, and the design of, the core and extension studies.

[Slide.]

Exelon and other cholinesterase inhibitors are not considered as treatments for the

neuropathology of Alzheimer's or Parkinson's disease. Rather, they ameliorate the cholinergic deficit that underlies many symptoms of the dementia syndrome.

This cholinergic deficit is associated with the distinct neuropathologies of these separate disorders. Dementia arising in the context of established Parkinson's disease predicts a characteristic symptom profile in addition to alpha-synuclein related neuropathology.

These distinct features and the unmet medical need provide the motivation and the scientific basis for the Exelon treatment program in Parkinson's disease dementia.

In this presentation, we will look at evidence from previous uncontrolled studies in patients with Parkinson's disease dementia, at the established pharmacological profile of Exelon and at the design of the pivotal study.

[Slide.]

The results of three open, uncontrolled studies of Exelon in patients with Parkinson's

disease dementia were available to us when we designed the double-blind study. Some of these studies were unpublished at the time.

Patients entering these studies had a PD diagnosis for approximately 10 years, an average baseline MMSE score of 20 points.

[Slide.]

These small, uncontrolled studies suggested that Exelon was efficacious in patients with PDD, and did not induce unexpected safety problems. There was some suggestion that tremor emerged at high doses of Exelon. This has also been observed in a small proportion of patients with Alzheimer's disease. Other than that, there was no evidence that motor symptoms of Parkinson's disease were adversely affected.

[Slide.]

Pharmacological profiling studies suggest that Exelon may preferentially inhibit cholinesterase isoforms that are involved in neurodegeneration, and that Exelon may be less likely to induce unwanted effects in the brainstem

and striatum.

From clinical experience in Alzheimer's disease, Exelon appears to have a low potential to induce cardiotoxicity, sleep disturbance, and extrapyramidal symptoms.

[Slide.]

Before discussing the study design, I will summarize the rationale for investigating Exelon in patients with PDD. First, dementia arising in the context of an established PD diagnosis is highly predictive for alpha-synuclein related neuropathology.

Second, the distinct neuropathology underlying PDD is associated with a cholinergic deficit that is generally earlier, more widespread, and more severe than that associated with Alzheimer neuropathology.

Third, clinical data from three uncontrolled, open study studies indicate efficacy without unexpected safety concerns.

Lastly, the pharmacological profile of Exelon might be well suited to the treatment of

dementia symptoms in patients with PDD.

[Slide.]

The design of the EXPRESS study, the pivotal study, followed existing dementia guidelines and the precedent set by previous pivotal registration studies in dementia associated with a cholinergic deficit, such as Alzheimer's disease.

Patients were randomized to Exelon or placebo in a 2:1 ratio which permitted the collection of more Exelon treatment safety data. The study comprised a 16-week dose escalation phase to reach maximum tolerated doses up to 12 mg/day. This does was then maintained for a further 8 weeks.

[Slide.]

This is a schematic of the study design. Patients could consent and enter the separate open-label, 24-week extension study. In the extension study, Exelon treatment was titrated or re-titrated in a similar manner as in the core study. In the next presentation from Dr. Tekin,

two groups of patients are identified in the open-label extension study.

Those who received Exelon in the double-blind core study are called Exe-Exelon patients, and those who received placebo in the previous study are called Placebo-Exelon patients.

[Slide.]

The study aimed to recruit patients whose dementia was due to PDD, and not to any other cause. The publications last year from Dag Aarsland's group, from Craybill [ph], et al., and from Braak and colleagues add to existing evidence that selection of patients with established PD, who subsequently developed dementia, without requirement for any distinctive dementia symptoms identifies patients with one, a symptom profile that is characteristic of PDD, and secondly, these criteria are highly predictive for distinct alpha-synuclein related neuropathology that correlates with the dementia syndrome severity.

[Slide.]

This slide shows the most important study

inclusion criteria. The PD diagnosis used UK Parkinson's Disease Society Brain Bank criteria, which have a high specificity for idiopathic Parkinson's disease, and distinguish this diagnosis from, for example, vascular PD.

The generic dementia criteria associated with PDD in DSM-IV give a memory impairment of the cardinal symptom of PDD. This must be associated with a deficit in at least one other cognitive domain, such as executive dysfunction, and these deficits must be sufficient to cause significant social or occupational impairment.

An MMSE score of between 10 and 24 points is generally regarded as mild to moderate severity of dementia. The onset of symptoms of dementia was to be at least two years after the PD diagnosis. This ensured that we recruited patients with an established PD diagnosis who subsequently developed symptoms of dementia. Therefore, there was no enrollment of patients with Lewy body dementia.

[Slide.]

Patients with probable or possible

vascular dementia were also excluded. MRI or CT scan at screening or within 6 months prior to screening was required in all patients to appropriately operationalize UK Brain Bank criteria for PD, and to exclude vascular dementia and structural lesions associated with dementia.

No patients with Alzheimer's disease could enter the study as the diagnosis of AD cannot be made if a patient has Parkinson's disease. Therefore, all pre-approval efficacy studies in Alzheimer's disease excluded patients with PD.

So, this study enrolled patients that have not been included in previous large placebo-controlled studies in dementia.

[Slide.]

The dementia syndrome assessments at week 16 and again at week 24 used instruments that were validated and widely used in dementia associated with cholinergic deficit, such as AD. However, at the time the study was designed, very few efficacy outcome scales have been systematically validated in PDD.

There are good reasons why the study outcome measures were similar to those in previous dementia studies. Although the underlying neuropathology may be very different, PDD is associated with a cholinergic deficit.

Much dementia symptomatology may overlap between AD and PDD due to this shared cholinergic deficit. As is usual in dementia clinical studies, there is a co-primary global assessment, a 7-point ADCS Clinical Global Impression of Change that assessed relative to a baseline evaluation whether patients had minimal, moderate, or marked change, for better or worse, or were unchanged during the course of the study.

This global measure encompasses cognition, functioning, and behavior with caregiver input and was assessed independently of the ADAS-cog by an experienced clinician who was blind to other clinical and motor evaluations in the study.

The purpose of this co-primary clinician-rated global change measure is to assess whether cognitive changes seen on the ADAS-cog are

clinically meaningful in terms of their global impacts on patient performance.

The study was powered on the estimated treatment differences with the standard deviations shown in this slide. In the next presentation, you will see that Exelon actually produced greater treatment differences than these estimates. Superiority of the drug over placebo was to be demonstrated separately on the two primary efficacy measures both with p values less than 5 percent and with no correction for multiplicity.

[Slide.]

The ADAS-cog is the gold standard assessment scale of general cognitive function in dementia. At the time the study was designed, the ADAS-cog had not been well validated in PDD, but it was a widely used and well validated general cognitive assessment across dementia associated with a cholinergic deficit, such as AD.

Although specific cognitive domains, such as executive functions may be more impaired in PDD than in AD, showing effects in specific cognitive

domains may be less meaningful than showing general cognitive effects.

Deficits in executive function and attention are not directly assessed by specific ADAS-cog items, but impairment in these domains will affect performance on the ADAS-cog.

The pilot open study of Giladi, et al. that you saw earlier suggested that the ADAS-cog was sensitive to Exelon treatment effects in PDD patients. In addition, the Exelon PDD program featured a supplementary cross-sectional, non-interventional study in patients with PDD or AD.

This study showed that the ADAS-cog was sensitive to changes in dementia severity and showed a similar degree of test-retest reliability in patients with PDD as in patients with AD.

[Slide.]

Secondary efficacy measures included activities of daily living on the well-validated ADCS-ADL scale and neuropsychiatric symptoms on the neuropsychiatric inventory or NPI.

In order to perform specific subanalyses in patients with visual hallucinations, those with hallucinations on the relevant NPI item at baseline were further identified by a case report form tick box that queried if these hallucinations were visual.

At attempt was made to assess executive function and attention. At the investigator meeting prior to the initiation of the study, consulting and Stroop-like word color interference tests were considered too difficult for most PDD patients to perform, but a few highly experienced centers still wanted to conduct these tests in some of their patients. A Ten-Point Clock Test was suggested as an easier outcome measure to replace these tests, and with an amendment, it was later added to the protocol.

Letter fluency was assessed at most centers in this study. A computerized assessment battery examined attention and motor processing speed.

[Slide.]

The study's safety evaluation were similar to those in previous dementia studies with the exception of the motor symptom subscale of the unified Parkinson's disease rating scale. This scale assessed any impactive treatment on the underlying movement disorder of Parkinson's disease.

[Slide.]

In conclusion, there was a strong rationale to definitively assess the efficacy, tolerability, and safety of Exelon treatment in patients with Parkinson's disease dementia. There was a major unmet medical need for any treatment that would go some way to meaningfully impact dementia symptoms in PDD.

A compelling scientific rationale was supported by clinical evidence from open studies suggesting that Exelon may be effective in PDD with unexpected safety concerns.

Study design and primary outcome measures were similar to those of previous pivotal studies in dementia indications. The study population had

an established PD diagnosis at least two years before the onset of dementia symptoms.

The simple, easy to operationalize enrollment criteria identified patients with characteristic Parkinson's disease dementia deficits whose cholinergic deficit is primarily associated without alpha-synuclein related neuropathology.

Reliable dementia scales and validated in other dementias associated with cholinergic deficits were employed, and in the next presentation, Dr. Sibel Tekin will discuss the results of this pivotal study.

DR. KIEBURTZ: Questions before we move on? Dr. Hughes.

DR. HUGHES: I would just like to ask the question as to why you thought only one study was necessary and not two.

DR. KIEBURTZ: Can we just hold on that question of reproducibility just because that is a discussion question.

Other questions?

DR. LITVAN: It seems like dopaminergic agonists were allowed to be used in this population.

DR. LANE: They were. Patients were permitted to be on those medications at baseline.

DR. LITVAN: That is not the usual practice, however, to do that in patients with Parkinson's disease and dementia.

DR. LANE: I have to ask the experts to comment on that, but we did recruit patients who were on dopaminergic agonists into the study.

DR. KIEBURTZ: Is that a question or a comment, Dr. Litvan?

DR. LITVAN: Both.

DR. KIEBURTZ: There are imaging results within six months of entry on all subjects?

DR. LANE: That was the requirement at the beginning of the protocol. There were a few violators of that criterion, but that was a requirement of the protocol, yes.

DR. KIEBURTZ: I wonder if everyone in the room could actually sketch out the questions that

are on the Alzheimer's disease assessment scale cognitive subscale. My guess would be maybe two or three could.

Do you have a slide showing us what it is, since that is the primary outcome measure, or could we get one within a little bit?

DR. LANE: Yes.

DR. KIEBURTZ: Very good, because I think that might help people understand what the primary outcome measure is here.

DR. LANE: Would you like Dr. Harvey to go through it now?

DR. KIEBURTZ: It would be probably useful to have the visuals, so maybe at some point at the break, we could make copies. I think at some point it is going to come up for the committee. It's a little abstract if you have never actually walked through it.

I have a recollection that TRALES or symbol digit were done as part of the KEFS battery. Letter fluency I know was done, was there not?

DR. LANE: The TRALES A was done in the

validation study, but not in the actual study itself.

DR. KIEBURTZ: Okay. Other questions? Dr. Katz.

DR. KATZ: Again, with regard to the question of the specific clinical syndrome, even though I recognize that maybe it's not that important, I am still not clear, were the investigators required to identify clinically the alleged specific clinical features of Parkinson's disease, or was it just did they use 294.1, which says generic dementia clinically and some medical condition, in this case Parkinson's disease, so that is the first question.

And if they weren't, if it was just sort of generic dementia in the context of Parkinson's disease, you said that the simple-to-use diagnostic criteria that were employed in the study identified patients, you know, ultimately resulted in identification of patients with the specific syndrome. How do you know that if the inclusion criteria didn't require it?

DR. LANE: Well, the answer to your first question, the investigators were certainly exposed to the full DSM-IV criteria for general medical conditions and the subscription of features that characterize populations of patients with Parkinson's disease dementia, which excludes executive dysfunction, and so forth, but they weren't required to operationalize those criteria. They merely had to ensure that patients fulfilled the sort of generic criteria for dementia.

The population that we recruited into the study, you will see in the next presentation from Dr. Tekin, did have marked attentional deficits, marked executive dysfunction. Forty-four percent of them had hallucinations, 35 percent had visual hallucinations, so that they did on the population level fulfill the characteristics you would expect of Parkinson's disease dementia.

DR. MANI: I would just like to get back to that question that Dr. Kieburtz raised about patients being required to have imaging within six months of study entry. First of all, I didn't see

that specified in the protocol and I may have missed it.

My understanding is that the imaging requirement was more inferred than specified in the sense that to satisfy the UK Brain Bank criteria for Parkinson's, you needed imaging to exclude the diagnosis of normal pressure hydrocephalus. That is Step 2. Number two, to exclude the diagnosis of vascular dementia, you needed imaging.

Is my understanding correct, or did the protocol actually specify that imaging had to be done, because it wasn't listed as a study procedure, similar to what we might see in studies for Alzheimer's where it is very, very clear that imaging has to be done within 6 to 12 months--

DR. LANE: We were surprised that the FDA got that impression, but when we read what we had sent you, we understood how it may have come across as a little vague, but certainly that was the requirement for the diagnosis of DSM-IV dementia and also for the PD criteria, also for the exclusion of patients with probable or possible

vascular dementia.

I could ask Dr. Murat Emre, who was the principal investigator and actually conducted the study, to comment on that.

DR. EMRE: It was mentioned in the exclusion criteria, I think No. 6, which says vascular dementia must be excluded, and then it continues and imaging must be available in the last six months, at least the report as far as verification, should be available. That is where it is mentioned specifically.

DR. KIEBURTZ: I see where I got confused. So, single digit, color word interference, card sorting done in selected French- and English-speaking centers, and only the verbal fluency was done in all centers. The magnitude of the availability of single digit, card sorting, color word interference. How many?

DR. LANE: About 60 patients. We did achieve some levels of statistical significance in some of the outcomes that are calculated from these tests, but we haven't featured them, because the

same size was too small.

DR. KIEBURTZ: Thank you.

DR. LANE: Do you want Professor Harvey to run over the ADAS-cog now, because we have the slide here?

DR. KIEBURTZ: That would be great actually, because unless people have an objection, it would be useful to see that before the results.

DR. HARVEY: Phil Harvey from Mount Sinai School of Medicine in New York.

The ADAS-cog administered in this trial was the 11 item ADAS-cog, which includes subdomains of memory and new learning, language, and praxis. Word recall is a list-learning test. It's a multitrial list-learning test. Orientation is the standard assessment of orientation to time, place, and person.

Word recognition is a separate recall procedure whereby the subjects are read a new list of words and subsequently asked to recognize which of the words occurred on the list that they had just heard or were extra-list.

Language is the ability to remember and respond to commands. Spoken language ability is rated on the ability of the person to interact. Naming objects and fingers is the standard confrontation naming procedure.

Word finding difficulty is rated. Comprehension is also a performance-based measure. Constructional praxis involves copying designs that range from very simple, like a circle, to complex, which is a Q. So, the argument could be raised that the praxis items measure both simple copying ability, as well as executive functioning particularly in an impaired population like this.

An ideational praxis is the ability to perform complex sets of actions based on overlearned acts. So, what we are seeing is it is wide ranging, and the one deficiency of the ADAS-cog in general is it is not possible to separate delayed recall from delayed recognition abnormalities because there is no such rapid forgetting assessment with a long delay.

DR. KIEBURTZ: How many words in the word

list?

DR. HARVEY: The word list recall is 10.

DR. KIEBURTZ: And how many trials?

DR. HARVEY: There are three.

DR. KIEBURTZ: This sounds routine, but I am sure many people don't know this.

DR. HARVEY: Absolutely, it's important for clarification.

DR. KIEBURTZ: And the recognition process is a list of 20 words out of which you have to recognize?

DR. HARVEY: Actually, the recognition is the number of incorrect responses out of a 12-item presented list and 12 possible foils. Scores on the ADAS-cog are higher for people who are more impaired, in contrast to the Mini-Mental where a higher score is better. A score of zero on the ADAS-cog is the best score you can get.

DR. KIEBURTZ: I am sorry, I was being concrete. So, there are 10 words in the list that you repeated three times, and the distracter list that includes some of the words from the original

10 and some distracters is?

DR. HARVEY: There is no distracter for the word list learning. There is a distracter list for the word list recall, which is a separate list and separate procedure, so it is not like, for example, the Ray Auditory Verbal Learning Test or the CBLT, where you learn, interfere, recall, and recognize.

Here, you just learn over multiple trials, and you forget about that. You go back again, you go through another list, and you recognize intra- and extra-list words after.

DR. KIEBURTZ: That helps. The ideational praxis?

DR. HARVEY: Ideation praxis is you instruct the person to perform a complex, five-step command. The idea of writing a letter, folding it, putting it in envelope, sealing it, addressing it to yourself, and showing where you would put the stamp, which is you give the person instructions, and they are supposed to go through the motor activities.

DR. KIEBURTZ: It is like in some ways like a Mini-Mental status, but it clearly has other tasks, and there is verbal learning, and then there are these other aspects. The middle part about language, you articulated.

Dr. Ahlskog.

DR. AHLSKOG: If a psychometrician were going to design a scale that would really capture all the essence features of Parkinson's disease dementia, what would he or she add to this?

DR. HARVEY: Not being as much of an expert on Parkinson's disease as the other experts here, I will give an answer, which could be supplemented by them.

Clearly, it would be nice to have a measure, a clear measure, uncomplicated measure of executive functioning that could be performed by people with substantial cognitive impairments.

DR. AHLSKOG: Does that exist?

DR. HARVEY: Not in any really meaningful way at this point. We all know that when you give the Wisconsin Card Sorting Test to someone who

Mini-Mental is 28, it's a very different test than when your Mini-Mental is 10.

The closest you come, I would believe, is, for instance, administering the TRALE-making test, parts A and B, and comparing performance under alternation demands to simple speed demands to get some index of the added alternation requirement.

DR. KIEBURTZ: For TRALES A, you connect 1, 2, 3, 4, 5, 6, 7. TRALES B is 1A, 2B, 3C, 4D, so you are alternating letters and numbers.

DR. HARVEY: You are actually explicitly instructed to alternate, so it is a test of alternation, as well as sort of remembering the instructions as you go along with errors corrected, but not counted as part of the dependent variable.

DR. KIEBURTZ: Professor Emre would like to add something.

DR. EMRE: In answer to Dr. Ahlskog's question, I would add verbal fluency, letter fluency, clock-drawing test, and TRALES A/B, and maybe line orientation, which is very easy, so three, four additional simple tests, what I can do.

DR. AHLSKOG: Some of those you performed.

DR. EMRE: Yes.

DR. LITVAN: I think that another possibility would be also to add a frontal assessment battery. That is something that has been done in many other parkinsonian disorders, as well, on frontal dementias, and certainly measures of frontal ability in different ways.

DR. EMRE: There is a specific reason why I did not include in this one, for example, this inhibition part of FAB is not necessarily a practice in these patients, so we tried to have a validated scale with good normative and large normative value, and the complemented by simple scales to be performed by this rather affected population, that is, letter fluency, clock-drawing test.

DR. KIEBURTZ: My intent in putting up the ADAS-cog was not to say it's good or bad, but just so that everybody knows that it is. I think any scale could be improved probably.

Maybe we should break and then proceed

with the presentation of results. The committee is giving me a nod. We will reconvene in 15 minutes. That would be ten after 10:00, please. Thank you.

[Break.]

EXPRESS Results

[Slide.]

DR. TEKIN: Good morning again. My name is Sibel Tekin. I am the Clinical Program Leader with Exelon for Novartis Pharmaceuticals Corporation.

This morning I will present the results of the EXPRESS study that was conducted to investigate efficacy, safety, and tolerability of Exelon in patients with Parkinson's disease dementia.

[Slide.]

I will begin my presentation with an overview of patient disposition and baseline characteristics. I will then discuss the efficacy results of the double-blind core study, followed by the safety findings of both core and extension phases of the study.

[Slide.]

In the double-blind core study, 650 patients were screened and 541 patients were randomized. 362 patients were randomized to Exelon and 179 to placebo. Seventy-three percent of the Exelon-treated patients and 82 percent of the placebo group completed the double-blind phase of the study.

211 patients from the Exelon group and 123 patients from the placebo group the entered the extension phase. Of those patients, 84 percent in the Exe-Exelon group and 78 percent in the Placebo-Exelon group completed the extension phase of the study.

[Slide.]

The main reasons for discontinuation were similar to those reported in previous dementia trials. Across both treatment groups, adverse events were the most common reason for discontinuation.

[Slide.]

Baseline characteristics in terms of age, gender, and race were well matched across both

treatment groups. Two-thirds of the patients randomized to this study were males, representing the demographic characteristics underlying Parkinson's disease.

[Slide.]

Computerized tomography or MRI imaging was required as a screening tool for enrollment eligibility into EXPRESS study. The imaging reports were retained at sites as source documentation only.

Recent source document verification revealed that there were no reports of patients not undergoing imaging, and 85 percent of the cases collected to date had imaging with six months prior to screening visits.

[Slide.]

The baseline disease characteristics were also well matched across treatment groups and supported the diagnosis of Parkinson's disease dementia. On average, patients had a nine-year disease history, demonstrating the presence of established Parkinson's disease.

Parkinson's disease was of moderate severity based on the Hoehn and Yahr mean score of 2.8 and UPDRS part III score of 33.

The mean MMSE score was 19, and it indicated the presence of mild to moderate severity dementia at baseline.

Finally, the mean duration of seven years between diagnosis of Parkinson's disease and for symptoms of dementia clearly indicated that in the randomized population, Parkinson's disease preceded the onset of dementia.

[Slide.]

The baseline scores of dementia assessment scores further confirmed the characteristic deficits of Parkinson's disease dementia. The baseline scores revealed deficits in cognition as demonstrated on ADAS-cog, executive functioning as demonstrated on D-KEFS letter fluency test, and functional activity as demonstrated on the ADCS-ADL scale.

[Slide.]

Similarly, the observed typical behavioral

dysfunction at baseline in the form of frequent apathy, depression, anxiety, and hallucinations, which were also representative of the behavioral profile of patients with Parkinson's disease dementia.

[Slide.]

As expected, virtually all patients were being treated with dopamine preparations, L-dopa preparations, for the management of motor symptoms of underlying Parkinson's disease.

At baseline, the mean daily doses of L-dopa were 660 mg and 700 mg in two treatment groups was comparable.

[Slide.]

I will now present the efficacy results of the double-blind core phase of the EXPRESS study.

[Slide.]

Recall that there were two primary outcome measures: assessment of cognition by ADAS-cog and overall assessment of dementia symptoms by the ADCS-CGIC scale.

The primary efficacy analysis were based

on change from baseline on these scales at week 24 in the intent-to-treat and retreat dropout population.

[Slide.]

Here you see the results for the ADAS-COG scale. In terms of cognition, Exelon provided statistically significant improvement over placebo at week 24. In fact, the mean treatment difference between Exelon and placebo was 2.9 points, which was slightly greater than the treatment difference demonstrated in previous studies conducted with Exelon in Alzheimer's disease.

[Slide.]

We saw similar statistically significant results for the overall dementia assessment. Using the ADCS-CGIC, a 7-point clinical rating scale, it was demonstrated that there were consistently more patients in the Exelon group, who showed an improvement compared with the placebo group at week 24.

Conversely, more placebo-treated patients were reported as worsening at the study endpoint.

[Slide.]

The results shown for the primary endpoints were consistent throughout other pre-planned analysis populations including ITT last observation carried forward and observed cases. The improvements on the ADAS-cog in all three of these populations were statistically significant in favor of Exelon at week 24.

[Slide.]

Similarly, the results for the ADCS-CGIC were also statistically significant in favor of Exelon across the study populations at week 24.

[Slide.]

Having met the two prospectively defined primary endpoints, we next evaluated the secondary efficacy outcome measures. These included assessment of functional activity, behavior, attention, and executive functioning.

[Slide.]

Here, you see the results for the assessment of functional activity. Change from baseline in the ADCS-ADL score at week 24 showed

that compared with placebo, Exelon-treated patients experienced significantly less deterioration in the activities of daily living.

[Slide.]

In regards to behavior, the neuropsychiatric inventory, which assesses multiple behavioral domains associated with dementia, showed an improvement from baseline at week 24 for the Exelon-treated patients whereas, placebo-treated patients showed worsening on this scale.

These results were also statistically significant in favor of Exelon at study endpoint.

[Slide.]

Attention deficit is a prominent characteristic of patients with Parkinson's disease dementia. In the EXPRESS study, power of attention, which was the composite score for simple reaction time, digit vigilance, and choice reaction time was assessed by a computerized test battery that is called CDR.

As you can see, at study endpoint, patients in the Exelon group demonstrated a

statistically significant improvement in the composite score of power of attention compared to the placebo group.

[Slide.]

A similar pattern was observed in executive function assessment by the D-KEFS letter fluency test. At week 24, patients treated with Exelon showed statistically significant improvement on the scale while the patients treated with placebo worsened.

[Slide.]

In addition to analysis related to the primary and secondary endpoints, we also conducted post-hoc analysis to show consistency of the results across age, gender, and baseline disease characteristics.

[Slide.]

As you see here, the results of the analysis of treatment difference between Exelon and placebo on ADAS-cog at week 24 show that benefits were consistently in favor of Exelon, and not limited to a particular subgroup that was

investigated.

[Slide.]

The subgroup of patients with visual hallucinations at baseline was of particular interest based on prior evidence of a possible correlation between visual hallucinations and cortical cholinergic deficits. In addition, management of visual hallucinations in Parkinson's disease dementia present challenges to both clinicians and caregivers.

The assessment of ADAS-cog in patients with and without hallucinations at baseline showed that these patients also derived significant benefits in cognition similar to the overall study population.

[Slide.]

In addition, improvement in behavioral symptoms of dementia, as assessed by the neuropsychiatric inventory, was also in favor of Exelon-treated patients with visual hallucinations at baseline compared to the placebo group.

[Slide.]

Analysis of antipsychotic use in this subgroup of patients showed that compared to placebo group, patients in the Exelon treatment group had less newly introduced antipsychotics. Similar results were also observed for the total study population.

Although the duration and dose of antipsychotic treatment have not been accounted for in this analysis, the data suggested that Exelon treatment did not increase the need for antipsychotic use in this subgroup of patients.

[Slide.]

In summary, Exelon treatment demonstrated statistically significant improvements compared to placebo. In the two prospectively defined primary endpoints assessing cognition and overall dementia, the results were statistically significant across all three analysis populations both at weeks 16 and 24.

The results were also in favor of Exelon across demographic and disease characteristic subgroups that were investigated.

Secondary efficacy outcome measures assessing functional activity, executive functioning, attention, and behavior were also statistically significant at week 24.

The results across these endpoints demonstrate the consistency of the study's efficacy findings.

[Slide.]

I will now present the safety findings both the double-blind and open-label extension phases of the study.

[Slide.]

A review of Exelon dosage showed that 76 percent of patients in the Exelon treatment group received 6 to 12 mg/day of Exelon as their last dose in the study.

[Slide.]

Here, on this slide, you see the frequent adverse events reported during the double-blind core study. The most frequently reported adverse events were nausea, vomiting, tremor, diarrhea, and anorexia. There were cholinergic events and, in

general, consistent with the previously known tolerability profile of Exelon.

Interestingly, the rate of some of the adverse events, such as hypotension, hallucination, constipation were less frequent in the Exelon treatment group compared to the placebo group.

In the extension study, the profile of adverse events reports was similar to what has been reported in the double-blind phase.

[Slide.]

Looking at the incidence of serious adverse events, we find that in the core study, there were fewer serious adverse events and fewer deaths in the Exelon group compared to the placebo group.

These events were typical of what is expected in elderly patients with Parkinson's disease, and none of the deaths were reported to be related to the study medication by the investigators.

During the extension study, the profile of serious adverse events were similar to what has

been reported in the core study.

[Slide.]

Compared to the overall incidence of adverse events in the Exelon treatment group, discontinuations due to adverse events were very low. The most common event leading to discontinuation was nausea, followed by vomiting and tremor, and tremor led to discontinuation only in 1.7 percent of the patients.

In the extension study, the discontinuation rates due to these events were again very low.

[Slide.]

To provide a more in-depth understanding of the safety profile, we looked at those system organ classes that tend to be impacted by the underlying Parkinson's disease. Events reported in the cardiac and vascular organ system classes were less frequent in the Exelon treatment group compared to the placebo group.

Treatment with Exelon in these patients did not seem to be associated with any new

cardiovascular safety findings. Furthermore, there was no increase in the frequency of psychiatric adverse events or adverse events such as syncope or constipation in the Exelon group compared to the placebo group.

In the extension study, the frequency of adverse events in these system organ classes were again similar to what has been reported in the double-blind phase.

[Slide.]

Because of the cholinergic effects of Exelon, we paid particular attention to monitoring the motor symptoms of Parkinson's disease. We prospectively defined and grouped these 22 adverse event preferred terms as adverse events potentially associated with Parkinson's disease for the safety analysis purposes.

I would like to mention that investigators did not report these adverse events in a special Parkinson's disease related category, but just as a regular adverse event report.

[Slide.]

In the core study, 27 percent of patients in the Exelon group and 15 percent in the placebo group reported such adverse events. The overall rate of these predefined adverse events in the Exelon treatment group was mostly driven by the 10 percent incidence rate of tremor.

The other cardinal extrapyramidal motor symptoms were slightly higher in the Exelon group, but were infrequently reported. Reports for the other adverse events in this category are provided in the briefing book.

In the extension study, the profile of this group of adverse events was again similar to what has been reported in the double-blind phase of the study.

[Slide.]

When examined the consequences of these adverse events, we found that none were classified as serious. They were generally mild or moderate in severity, rarely required use of concomitant medication, and infrequently led to discontinuations. The majority of the events were

reported to be resolved while the patient still treated in the study.

In conclusion, these events were generally manageable and did not lead to serious consequences for the patients.

[Slide.]

Furthermore, these events did not result in a deterioration in the motor symptoms as measured by the objective assessment of UPDRS Part III scale.

As we see here, at week 24 of the core study, Exelon-treated patients showed similar mean changes from baseline to patients in the placebo group.

In the extension study, for patients who remained on Exelon, the magnitude of decline in motor system assessment was only 1.1 points.

[Slide.]

In terms of the overall safety profile, we have reached the following conclusions.

The most frequent adverse events in the Exelon-treated patients, both in the core and

extension studies, were nausea, vomiting, and tremor. The majority of these cholinergic events were mild to moderate in severity, and they rarely led to discontinuations.

Compared to placebo, there were fewer serious adverse events and fewer deaths in the Exelon group, and none of these events were considered to be study drug related. Reasons of death were consistent with the patient population studied.

Exelon was not associated with any cardiovascular safety findings that were different from the previous experience with Exelon. There was no worsening on frequent symptoms of Parkinson's disease, such as falls or psychotic symptoms.

[Slide.]

The mean adverse events associated with Parkinson's disease during the study was tremor. Adverse events of tremor were also mild and moderate in severity. They did not induce significant consequences. They resulted in few

discontinuations, and they were not reflected in changes on the total UPDRS Part III scale.

Finally, exposure to long-term treatment with Exelon in 24-week extension study revealed a similar safety profile to what has been observed in the double-blind phase, indicating no additional safety concerns with one-year treatment with Exelon.

Thank you for your attention.

DR. KIEBURTZ: Questions?

DR. KOSKI: I have two questions actually. Obviously, there was a little bit of difference in the amount of depression between the two groups with a slightly higher amount of depression being noted in the placebo group.

Were there any measures of how severe the depression was or the amount of antidepressant drugs they were taking relatively between the two groups?

DR. TEKIN: One of the exclusion criteria of the study was exclusion of major depression based on the DSM criteria, so there were no

protocol violators identified based on that item. However, the data that I have presented was based on the neuropsychiatric inventory assessments at baseline, which also captures depressive symptoms, but based on the exclusion criteria, we interpret that they were not sufficient to fulfill for the clinical major depression diagnosis.

DR. KOSKI: The other thing I wanted to know is in those patients that decided to extend in the open label, those particularly that had been on the study drug, were there certain characteristics of those patients, in other words, did they tend to be the more mildly cognitively impaired, or it was a random thing?

DR. TEKIN: We could present to you the baseline demographic characteristics for patients who entered the extension study. As far as I remember, they were similar to the core demographic characteristics, but we will verify the data.

DR. AHLSKOG: Clarify one thing for me. The total number of people in the core study that dropped out, the total percent, wasn't that 17

percent? I recall seeing that on one of your early slide. The percent of people in the core study that dropped out due to adverse events, or if it wasn't 17 percent, tell me what the percentage was.

DR. TEKIN: Yes, that was 17 percent.

DR. AHLSKOG: And then in a subsequent slide, it seemed that when you looked at the central conditions that led to dropouts, which is tremor, nausea, and vomiting, the numbers didn't add up to anything really close to 17 percent.

What exactly was the percent of people that dropped out due to tremor, nausea, and vomiting?

DR. TEKIN: The most frequent reasons or adverse events that led to discontinuation were, as you stated, nausea, vomiting, and tremor. Tremor, it was 1.7 percent, and I can present the remaining.

If you could project the slide for me, please.

[Slide.]

Nausea, it was 3.6 percent in the Exelon,

and for vomiting, it was 1.9 percent discontinuation rates specifically due to these adverse events.

DR. AHLSKOG: So, there really were a myriad of other things that led these dropouts to discontinue.

[Slide.]

DR. TEKIN: Here, on this slide, you see the most frequent reasons that were about 1 percent incidence, so there were additional number of adverse events that ended up in discontinuation, however, in terms of incidence rate, they were less than 1 percent, so individual cases with different adverse events.

DR. TEMPLE: That's about half.

DR. KIEBURTZ: Dr. Katz.

DR. KATZ: You mentioned that the adverse events associated with Parkinson's disease and, in particular, tremor, about half of them resolved or I forget what the numbers were exactly.

Can you say something about some of these more frequent adverse events, whether it's the

tremor or nausea, does most of that resolve, do you know anything about the time course of these things? Do they have it for a week, and they accommodate to it? I just wonder about that.

DR. TEKIN: I understand the question is duration of the adverse events.

DR. KATZ: Yes, and also, by the way, when we say "resolved," was there some maneuver that induced the resolution, like the dose was lowered or something like that?

DR. TEKIN: The resolution was based on the completion date of the adverse event as recorded by the investigator and the patients. In terms of the duration of the adverse events, the majority of the events, again based on their start date and end date of reporting, the majority were of short duration for tremor. I can provide you this data.

If you could project the slide for me.

[Slide.]

Forty percent of nausea cases, the duration was one to seven days, so the duration was

for one week.

For vomiting, it was similar. Forty-seven percent of the cases, the duration was one week.

If you could go back to the tremor slide, please, the previous slide, for me.

[Slide.]

The same applied to adverse events of tremor. The duration was within one week for almost 40 percent of the patients.

To address your second question about what measures were taken in the resolution, we looked at the doses of study medication at the time of the event. The majority of the tremor cases were actually on lower doses of Exelon when they experienced the event, lower meaning less than 6 mg per daily doses.

Then, when we looked at individual cases, the majority of the cases, when they experienced these events, actually decreased the Exelon dosage, and that helped the resolution of the event in our interpretation.

DR. KATZ: Were those lower doses

maintained in those patients for the rest of the trial, or were they able to go back up to a higher dose?

DR. TEKIN: I have to look closely to the data to answer that question accurately.

DR. KIEBURTZ: Dr. Hughes, then Dr. Olson, then Dr. Ahlskog.

DR. HUGHES: If I recall rightly, this study wasn't done at any sites in the United States. Do you have any information about variability in response across different geographic locations, and is there any reason to believe that these results wouldn't hold up in a U.S. population?

DR. TEKIN: Yes, the study sites were mainly in Europe and Canada and North America, and we have looked at the sites for the primary outcome measures and the treatment difference, the distribution per site.

[Slide.]

In general, the results that we have received from different countries were consistent

except for several countries, such as Portugal and Austria, but the number of patients recruited from these sites were very small.

DR. KIEBURTZ: Would you leave the slides up a little longer. The one on tremor was there about three seconds.

DR. HUGHES: Just to follow on, I agree with you about the small numbers in certain countries. So, more generally, in other studies, has there been evidence of variation geographically in studies of Parkinson's disease?

DR. TEKIN: I maybe turn to our experts in the group. Dr. Emre or Dr. Hurtig, would you like to comment on that?

DR. EMRE: In terms of Parkinson's disease, I remember two recent studies with the same compound rasagaline, and the results were very comparable in a comparable population of Parkinson patients with motor complications.

DR. HUGHES: And with other compounds, just generally, there is not a geographic issue?

DR. EMRE: As far as I am aware of, with

Western Europe and North America, there are no pharmacogenetic differences.

DR. LANE: It might be useful to add that we haven't seen any variation between patients studied who have got Alzheimer's disease in the U.S. or in the rest of the world in terms of the Exelon studies we have previously performed.

DR. OLSON: The number of serious adverse events, as you have reported here, was 47 in the Exelon patients in the core study, as we see in Table 6-24 on page 39, however, on page 38, in the core study on Table 6-23, patients with severe adverse events were listed as 59 or 16.3 percent.

Perhaps I missed something, but could you explain that discrepancy?

DR. TEKIN: I understand you are referring to the briefing book pages for a total number of serious adverse events?

DR. OLSON: So, there was different terminology.

DR. TEKIN: Severe and serious, yes. Adverse events were rated as mild, moderate, and

severe, and in a different category, we also collected information on serious adverse events. The criteria was slightly different than what is for severe adverse events.

DR. OLSON: Thank you.

DR. KIEBURTZ: Dr. Ahlskog.

DR. AHLSKOG: Theoretically, this class of drug can cause bradycardia, and I just wrote down the number here, bradycardia 1.4 percent in the core Exelon group, and 0.6 percent in the other.

Can you tell me something about those few patients that did develop bradycardia, the rates? And I assume that it wasn't serious, because they weren't listed as serious in another entry, but tell me a little more about that.

DR. TEKIN: Yes. As far as I recall, none of them were serious, and they did not lead to discontinuations. In terms of the inclusion criteria to the study, we did not include patients who have baseline abnormalities in terms of heart rate less than 50 per minute, so we did not want to expose these patients in particular to the drug

because of non-risks of the drug as outlined in the package insert.

DR. AHLSKOG: I did see that in the exclusion criteria, there was a list of several different things, any kinds of conduction problems, so if this drug were approved for use in PDD, what kind of a package insert would be included with reference to the potential for cardiac induction problems and specifically bradycardia? What would you tell the prescribing physician in the package insert as to which patients should be excluded from use of this drug?

DR. TEKIN: Based on the safety data collected from the study, we did not observe any different incidence rates for conduction abnormalities or bradycardia compared to Alzheimer's disease population.

Yes?

DR. LANE: We have already got those precautions in our current label, so that the inclusion/exclusion criteria followed the instructions as per our current label in

Alzheimer's disease, so it wouldn't change.

DR. TEKIN: So, the conclusion is based on the safety information collected in the EXPRESS study. The cardiac safety profile is similar to what it has been for Alzheimer's disease, so we do not anticipate any particular additional warning in regards to cardiac events.

DR. KIEBURTZ: From the imaging, what was the frequency of structural or vascular abnormalities?

DR. TEKIN: The limitation of the imaging conducted in the study was this was used as a screening tool, and this was assessed by the investigators as one of the exclusion criteria, however, in the CRF, we don't have standard documentation of what actually the imaging data demonstrated, so although we can confirm that the patients had imaging, and based on the imaging data they fulfilled the entry criteria by investigator's assessment or judgment, we are not able to provide you standard information as to what has been shown in the imaging analysis.

DR. KIEBURTZ: So, we can't have the standard information. Do we have any information?

DR. TEKIN: In terms of screen-failed patients, we had reports for 25 patients who did not fulfill the entry criteria based on investigations, which included imaging.

So, this is one indirect information that we could provide, that 25 patients. This could also apply to other diagnostic entry criteria, such as MMSE range, but we know that some of these patients among 25 also did not fulfill for the imaging criteria.

DR. KIEBURTZ: Let me just make sure I understand. So, 84.5 percent of the people, there was imaging, but less than six months prior to screening, and you know that based on whatever that imaging showed, the enrolling investigator felt they met entry criteria, but you don't know what that imaging showed.

DR. TEKIN: Correct. We didn't collect the imaging information as part of the study data.

DR. KIEBURTZ: Just that it happened, you

collected the information that it happened.

DR. TEKIN: Yes, based on source data verification. We went back to sites and asked them to provide us a copy of the reports, however, these reports are in different languages, and they weren't reported by a standardized central imaging center. Those were done at individual country basis.

DR. KIEBURTZ: So, there is clinical interpretation of imaging, you don't have any sense about?

DR. TEKIN: It has been based on the judgment of clinicians to exclude other reasons of Parkinson's disease.

DR. KIEBURTZ: Okay.

Other questions?

DR. KIEBURTZ: Thank you.

Benefit-Risk Assessment

DR. EMRE: Mr. Chairman, honorable members of the panel, ladies and gentlemen: Good morning.

[Slide.]

My name is Murat Emre. I am Professor of

Neurology, Istanbul Faculty of Medicine, Department of Neurology, where I had a unit for movement disorders and behavioral neurology, dealing with patients with Alzheimer's disease and Parkinson's disease basically.

My objective today is to wrap up this session by giving you an assessment of the risks and benefits provided by Exelon in Parkinson's disease patients with dementia. I have assumed this role as the principal investigator of the study just presented and as a clinician who has been caring for patients with Parkinson's disease dementia, and Alzheimer's disease for many years.

[Slide.]

Just to recapitulate, we have heard from Professor Feldman that Parkinson's disease dementia a readily diagnosable clinical condition. Dementia in this population develops in the context of established Parkinson's disease.

There is a typical cognitive profile characterized by impairment in attention, memory, visuospatial, and executive functions, frequent

neuropsychiatric symptoms, all of which result in functional disability.

As in other forms of degenerative dementias, symptomatic forms need to be excluded for a proper diagnosis. We know from epidemiological studies that dementia leads to an increased burden for patients and families, is a frequent cause of nursing home placement, and there is considerable unmet need for this patient population.

[Slide.]

What is the statement of need in Parkinson's disease patients with dementia? Ideally, the symptomatic intervention should benefit all symptom domains including cognition, behavior, and function. In terms of tolerability, this treatment should not cause any adverse impact on motor symptoms, nor on autonomic or cardiovascular functions, areas of specific concern in this patient population.

[Slide.]

As. Dr. Tekin explained earlier, Exelon

has been found to be associated with statistically significant and clinically relevant benefits in both primary endpoints including the composite score of cognition ADAS-cog, as well as the scale for overall evaluation, the Clinical Global Impression of Change.

In addition to the primary endpoints, all secondary efficacy measures showed differences favoring Exelon. These included measures of attention, executive function, behavioral symptoms, as well as ADL.

[Slide.]

Now, we can look at these results from a different angle in terms of the main symptom domains of this condition, Parkinson's disease dementia.

Overall, the effect sizes were moderate, but consistent throughout the different domains. If you take cognition, for example, the overall measure, ADAS-cog showed significant improvement.

Likewise, cognitive domains, which are typically impaired in PDD, such as executive

function and attention, also showed consistent improvements when measured by verbal fluency, clock-drawing, and computerized attention test batteries.

Behavior or neuropsychiatric symptoms, as measured by NPI, improved under Exelon, and in terms of ADL, there was less decline in the Exelon group as compared to patients under placebo.

Finally, the overall evaluation, taking into account changes in all these domains showed that as a group, patients exposed to Exelon were doing better than patients exposed to placebo.

[Slide.]

Now, this table summarizes the results of all primary and secondary efficacy measures in the EXPRESS study. As you can see, there were statistically significant differences favoring Exelon for all parameters, and, in fact, this is one of the most robust and consistent sets of data I have ever seen in any dementia trial.

[Slide.]

So, what are, then, the risks, what are

the potential safety and tolerability problems? The leading adverse events were those related to the gastrointestinal system, and this is something we know from Alzheimer's disease studies.

These occurred mostly during titration. The majority were mild or moderate in severity, and did not lead to discontinuation. For example, the most frequent adverse event, nausea, was reported in 29 percent of the patients, but only 4 percent chose to discontinue because of nausea.

If one compares this to historical data from past Alzheimer's disease studies, the incidence and discontinuation rates in the PDD study were lower. This may partly have been due to the slower titration rate used in the EXPRESS study.

[Slide.]

Anti-cholinergic drugs have been used for decades to treat motor symptoms of Parkinson's disease, so one question, one concern we had in designing the study was whether cholinergic stimulation may cause worsening of motor symptoms,

and that is why, therefore, we placed special emphasis on monitoring patients' motor function, as well as adverse events, that could potentially be associated with worsening of Parkinson's disease symptoms. Such were 11 percent more frequent in the Exelon population with tremor basically driving this difference.

These were, however, mostly single episodes of mild or moderate severity, and the incidence of newly emerging adverse events decreased after the completion of dose titration in the core and extension studies.

Worsening of tremor was reported as an adverse event in 10 percent of the patients in the Exelon group as compared to 4 percent in the placebo, however, only 1.7, that is, about 2 out of 100 patients, chose to discontinue because of worsening tremor.

In addition, the objective measure of motor function, the total united Parkinson's disease rating scale score didn't show any difference between placebo and Exelon. There was

also no difference in UPDRS scores of patients exposed to Exelon over 48 weeks as compared to those who were exposed for 24 weeks.

[Slide.]

Another group of adverse events typically of concern in this patient population are those related to cardiovascular and autonomic functions. In this study, there were no such safety issues identified with the use of Exelon.

In fact, orthostatic hypotension and syncope, which are frequent autonomic problems in this population, were reported less frequently with Exelon. In addition, there were fewer serious adverse events and deaths in the Exelon than in the placebo group.

So, we can conclude that Exelon is not associated with a risk beyond what has been known and what has been described in the product label for patients with Alzheimer's disease.

[Slide.]

What is the clinical relevance of the benefits? First, let us look at how efficacy

results compare to what we have seen in Alzheimer's population earlier.

In the previous trials with cholinesterase inhibitors in Alzheimer's disease, the change in ADAS-cog ranged from 2 to 4 points. In this particular study, the change in ADAS-cog from baseline compared to placebo was 2.9 scores. This compares to 2.1 in the AD study with Exelon.

In this study, there was more improvement above baseline in the active group, and less decline under placebo as compared to less improvement from baseline in the active, and more decline under placebo in the Alzheimer's disease studies.

In other words, the difference between Exelon and placebo in this study was driven by more improvement above baseline in the active group, and less decline in the placebo.

[Slide.]

In terms of clinical global impression of change, the global evaluation based on clinician's judgment of changes in cognition, in behavior and

in function, patients treated with Exelon as a group showed an improvement from baseline, whereas, patients exposed to placebo as a group showed deterioration.

Now, remember that this is a symmetrical 7-point scale, 4 is no change, lower than 4 is improvement, and higher is deterioration.

With regard to percentage of patients with a change from baseline, there were 11 percent more patients who showed any improvement in the Exelon group as compared to placebo, and 9 percent fewer patients in the Exelon group had any worsening.

Finally, considering the number of patients who had a clinically relevant change from baseline, which was defined as marked or moderate improvement, or marked moderate worsening, there was a 16 percent difference between the two groups in favor of Exelon, 6 percent more patients improved, and 10 percent fewer patients worsened in the Exelon group to a marked or moderate extent.

[Slide.]

Let me then summarize. In this study, we

saw benefits that were moderate, but they were consistent across all primary and secondary measures in all symptom domains.

Adverse events were consistent with the established safety profile for Exelon, and there was a risk of worsening tremor in 10 percent of the patients, which led to discontinuation in only a few.

There were no additional safety concerns beyond those described in the current label for cholinesterase inhibitors in particular with regards to autonomic or cardiovascular function.

[Slide.]

Let me then conclude. There is currently no approved treatment for Parkinson's disease dementia patients in this country. Exelon in this study has demonstrated benefits in cognition, behavior, and function.

Adverse events were consistent with its established safety profile. Tolerability problems seen in this study, such as nausea or worsening of tremor, can easily be monitored clinically, and

they are easy to manage by reducing the dose or withdrawing the medication.

If we put everything together, the benefits of Exelon treatment in patients with Parkinson's disease dementia outweigh the risks.

Ladies and gentlemen, I don't think Exelon is the ultimate therapeutic solution for these patients, but while the benefits with Exelon are moderate, I believe they are clinically relevant, the results are robust and consistent, and the risks are acceptable.

Therefore, I think that patients with PDD should be given a chance to have access to this treatment.

Thank you, Mr. Chairman.

DR. KIEBURTZ: Questions?

Could I ask you a couple questions more about the tremor? Do we know whether this appeared to be worsening of resting tremor, or was an action or postural tremor, any sense about that?

DR. EMRE: In most of the cases, this was not specified. It was recorded as an adverse

event. I don't know if they went into the details of was it resting tremor or was it action tremor. There was no further specification on the adverse event report form.

DR. KIEBURTZ: I just want to get clarification on a point. All titration was done by 16 weeks. Do we know about the incidence of tremor in those who never had tremor, or who did not have tremor in the titration period, in the post-titration period, did you tell me that?

DR. EMRE: That would probably be the number of patients who developed tremor de novo.

DR. TEKIN: In general, the adverse event reports for tremor were higher during the titration phase, and in the maintenance phases, the incidence rates were lower.

[Slide.]

Here, you see on the lefthand side, the adverse event reports for the core phase, and on the righthand side is for the extension phase. The incidence rates were broken down to four weekly periods, and we have 16 week titration periods, and

an additional 8 weeks for maintenance. The incidence rates were as seen.

The highest incidence rates we observed between week 8 to 12.

DR. KIEBURTZ: Did you show us this already, am I blanking?

DR. TEKIN: This wasn't part of the core presentation.

DR. KIEBURTZ: Could I ask another question? I know we are not putting a great deal of emphasis, or I haven't heard you putting a great deal of emphasis on the neuropsychological test performance or cognitive profile of Parkinson's disease dementia, but just saying we were interested in that, and know what the ADAS-cog actually measures, rather than a composite score, are there subelements of it that you would have anticipated in advance would be the most sensitive to improvement, and was there any look at those?

DR. EMRE: Well, if we consider the neuropsychologic profile of Parkinson's dementia patients, impairment in attention and executive

functions being more prominent than in primary memory, for example, one would expect that tests for verbal fluency and clock-drawing tests should show differences, and they did.

In the ADAS-cog, I personally think the word recognition tests may be a little bit overwhelming with its 12 words for especially impaired patients. Dr. Ahlskog asked me how I would redefine or redesign ADAS-cog, I would probably reduce the number of words, for example, that is manageable also for these patients, but I would expect to see differences in word recall, word recognition.

There is a sub-analysis, and that can be provided, I guess, by Phil Harvey.

DR. HARVEY: Thanks. The analysis actually was done. We can put the slide up here.

DR. KATZ: Do you have a similar slide for the pattern of responses for these various subparts of the ADAS-cog for Alzheimer's patients, as well? Across-study comparisons are treacherous, but I am just trying to figure out if there is

something--again, assuming, as Karl said, that we are interested in this question--the uniqueness of the pattern of responses across the two different types of dementia.

DR. HARVEY: Well, the one thing I can tell you is that, surprisingly enough, in most of the Alzheimer's pivotal trials, the memory elements of the ADAS-cog have not stood out in terms of their particular response to cholinesterase inhibitors.

What you see here is that word recall and commands, as well as naming, the ideational praxis item, which is clearly an executive item, remembering instructions, spoken language ability, and comprehension, all showed statistically significant improvements.

So, this shows that it is not just an item or two that is pulling this overall significant effect, and while the individual item changes themselves are not huge, they do some to a level of total change from baseline that was greater than in any of the Alzheimer's pivotal trials.

So, it does seem to be a cognitive response that makes sense given what we know about Parkinson's dementia.

DR. KATZ: Again, do you have a similar display for what it would look like in Alzheimer's patients?

DR. HARVEY: Not available here.

DR. KATZ: Well, all right. So, does anybody have a recollection? Again, under the heading of is this unique, do they respond to different things, is it the right outcome measure, does anybody know?

DR. HARVEY: We are going to do some looking up and see if we can get back to you on that.

DR. TEKIN: We will be able to provide the information.

DR. KIEBURTZ: Thank you.

DR. EMRE: Dr. Struck will close it.

Exelon (rivastigmine) PDD Indication

Regulatory Considerations

DR. STRUCK: To conclude our

presentations, let me address FDA's question of whether the EXPRESS study results require replication for a claim of PDD to be granted.

[Slide.]

Exelon is already approved for the treatment of dementia of the Alzheimer's type based on two well-controlled studies. Exelon therefore is no longer a new molecular entity. In fact, as I have mentioned this morning, the postmarketing exposure of Exelon is about 2.1 million patient years.

Novartis has filed the supplementary NDA to request an expansion of the indication of the currently approved indication of Exelon to include another type of dementia, namely, the dementia associated with Parkinson's disease.

[Slide.]

We have heard this morning that PDD is a distinct disease entity that can be diagnosed in routine clinical practice. Therefore, the treatment of patients with PDD should be accepted as a separate claim or indication in the label.

We have also heard today that both Alzheimer's disease and Parkinson's disease dementia are associated with a cholinergic deficit, suggesting that Exelon treatment of Alzheimer's disease and Parkinson's disease dementia is based on the same mechanism of action.

There is no need for additional studies for a claim of PDD to be granted, because Exelon has already shown benefits in a dementia associated with a cholinergic deficit in our trials of Alzheimer's disease.

[Slide.]

This is according to the guidance for industry providing clinical evidence of effectiveness for human drug and biological products. Section 2 of this guidance address the situations in which a single adequate and well-controlled study of a specific new use can be supported by information from other related, adequate and well-controlled studies.

So, in our case, the EXPRESS study in the new use of PDD can be supported by the

well-controlled studies of Exelon in Alzheimer's disease.

As we have heard, the EXPRESS study in the new use of PDD is an adequate and well-controlled, multicenter study. The results are statistically persuasive with internal consistency across analysis populations and multiple efficacy endpoints from different domains.

[Slide.]

Therefore, let me conclude from our regulatory perspective Exelon is already approved for one type of dementia associated with a cholinergic deficit, and we are requesting registration in another type of dementia based on the same mechanism of action.

The EXPRESS study results are robust and consistent with no additional safety concerns other than the ones already known from the large safety database of Exelon in Alzheimer's disease.

For these reasons, Exelon should be indicated for the treatment of mild to moderate dementia associated with Parkinson's disease.

I thank you for your attention.

DR. KIEBURTZ: Thank you.

DR. STRUCK: And I think we are still on time.

DR. KIEBURTZ: Yes, very nicely done, thank you, and we even ate up some of your time with our questions, so appreciate the presentations from the sponsor.

Do we have questions directed specifically to the last presentation?

Dr. Hughes, I squelched you a little earlier. Do you still have your question you would like to ask?

DR. HUGHES: I guess they expressed their opinion during the last presentation.

DR. KIEBURTZ: Anything you want to pursue on that?

DR. HUGHES: No.

DR. KIEBURTZ: Other questions for our sponsors?]

[No response.]

DR. KIEBURTZ: Well, we are in a little

bit of a pickle. If you have got something you would like to say, you have a moment.

DR. LANE: Well, I think we have already said it, but we think this is an adequate and well-controlled study that demonstrates a range of benefits on symptoms of PDD across a number of symptom domains, general cognitive, attention, executive function, neuropsychiatric activities of daily living, and the global impact on the patient performance, and the adverse events seen in the study aren't unexpected. They are what we see in Alzheimer's disease.

If anything, the adverse events of nausea and vomiting seem to be a little lower, and the adverse events are manageable, and so we see the treatment manages cholinergic deficit. It manages cholinergic deficit in AD, and it manages the cholinergic deficit in PDD, so we think on that basis, one study should be sufficient for approval.

DR. KIEBURTZ: Thanks.

Here is our little bit of a pickle. I don't think we have our public speakers here.

Is anyone here who registered to speak at the public hearing?

No. This is just a procedural thing. In the Federal Register that is part of this meeting, we announced that there will be an open public hearing at 1 o'clock, and people are requested to sign up in advance, and we have one such speaker, who is not here.

Typically, we hold the presentations and then the public hearing, and then close the public hearing and go into our deliberations, and that is the standard process. However, there is some flexibility in that, and I am extremely loathe to lose time and also not quite keen on eating lunch at 11:15, so I think I will take a little bit of an unusual circumstance, and hopefully, it will not degrade the quality of the public hearing by closing this phase and moving on to some of the discussion, at least of Question 1, which I don't think the public hearing person is addressing.

Is that no-no? Discussion, very good. We won't vote any questions for sure. Just

discussion. I understand.

Committee Discussion

DR. KIEBURTZ: So, let's discuss without addressing any specific questions. Again, this discussion is for the committee. This is a committee discussion, and we can ask the sponsor and FDA.

This issue about whether--and I would be particularly interested in hearing from Dr. Ahlskog and Dr. Litvan--the question in my mind, or at least that's running around here, not these questions, but a question, is there such a thing as Parkinson's disease dementia.

Is there consensus on there being such a thing, is it really ambiguous?

DR. AHLSKOG: Well, you are looking at me as you are asking that question. I think there have been enough studies now that really have been pretty uniform in addressing that there is a specific PDD with a specific neuropathology, and that is the proliferation of Lewy body disease.

You know, these are things that have

really come to fruition and changed our thinking in the last decade. When our group published our paper on patients who initially had Parkinson's disease and subsequently developed dementia, I had gone back and read all of the older papers that had looked at the neuropathology in that group, and I can tell you that those papers were really very heterogeneous.

This is a problem for most neuropathology studies, it is very hard for a neuropathologist to get a clinical history. That was certainly one of the problems.

Obviously, there is a problem of inadequate immunohistochemical techniques before they were invented, and there was a huge breakthrough that developed about six or seven years ago, the development of alpha-synuclein immunohistochemistry.

In the past of using hematoxylin and eosin, there really is a paucity of things that you can discover using that type of a technique.

Also, when you look at the histories, you

know, I went back and looked at who exactly were these patients that were being described in some of these older papers, some of which said, well, it's Alzheimer's disease, and some said other things. Some said it's a specific nucleus.

The histories really didn't even tell you basic things like did the dementia precede Parkinson's disease or come after, and in most of those papers, that was really very problematic.

So, I think we have entered into a new era. Dr. Hurtig, who is here, Dr. Hurtig wrote probably one of the first papers, our group wrote a paper, Aarsland wrote a paper, Martello wrote a paper, and now Heiko Braak wrote a paper, they are all coming to the same conclusion.

I think this also speaks to the issue of should we be focusing on a specific neurocognitive profile in isolation. Well, first of all, I would say that clinical practitioners--and that includes general neurologists--aren't real good at kind of sorting these things out on a busy day in the clinic, you know, do you have a little bit of

executive dysfunction, and so on.

These things aren't going to happen in the clinic, but it's a pretty simple issue here - do you have Parkinson's disease, years later, do you become demented, and that is what all of these studies have really addressed, that issue, Parkinson's disease, yes, dementia later, what's the pathology. It's proliferation of the Lewy body process, and so I am pretty happy with arriving at that conclusion.

MR. LOEB: Arriving at the conclusion that there is PDD.

DR. AHLSKOG: Arriving at the conclusion that there is PDD, and it has a specific neuropathology. Now, I will qualify this and say that just like in Alzheimer's disease, where if you use the criterion, the criteria are stated in terms of probabilities, high probability, intermediate probability of diagnosing Alzheimer's disease, and the specificities of those criteria aren't all that great, you know, 60 percent, 50 percent depending upon, you know, exactly how you specify things.

So, there are going to be a few people in all of these groups that have something other than you think, and in our series, for example, of our 13 patients who clinically had PDD, one of them had PSP, and some of those things, you are just not going to get right in life, and that is true for all of these neurodegenerative diseases.

DR. KIEBURTZ: Dr. Litvan.

DR. LITVAN: Well, I fully agree. In fact, Parkinson's disease is a motor problem, but, in fact, the hallucinations and dementia has been described since the early 1800s, so it has been well known, it is much better characterized now. Certainly it occurs up to an 80 percent according to certain studies by Dag Aarsland.

So, it is an entity and it requires treatment, and I think that what has been presented does really go well with all the literature that we are aware of. So, I don't have any problems in distinguishing it as an entity.

I do agree that it would be nicer if we would have a clear cognitive profile, and there is

a criteria that is been developed by the Movement Disorder Society. There is a task force for that, but I don't think it is needed at the present time for this particular issue, because it is clear that the dementia occurs in Parkinson's, and it has many other characteristics that Alzheimer's doesn't have, not just the parkinsonism, but all the advance, non-motor features of Parkinson's disease.

DR. KIEBURTZ: So, on a completely different tack with Dr. Sacco and Dr. Olson and Dr. Koski, who are not movement disorder neurologists, to the best of my knowledge, this idea of being able to--the reason I bring that up is without this mind-set frequently in mind, seeing a patient who has developed dementia, do you think that is difficult for the practitioner to arrive at a conclusion that someone is now demented?

DR. OLSON: No

DR. KIEBURTZ: That is terse.

DR. OLSON: I would be happy to--no, I don't. First of all, you have the family, the patient's family that usually gives you a lot of

information. They want to tell you in great detail how the patient is screwing up, and what the problems are.

As you follow these patients, and we follow our patients for many, many years, of course, and you get to know them, and you start to see these things in them.

One of the things that I think is very characteristic actually of the patient with Parkinson's disease, which is very interesting, which has come out very much with the dementia of Parkinson's disease, is their slowness of response.

I remember my teacher, somebody by the name of Dr. Benjamin Boshes, who was an eminent neurologist in Chicago, and very interested in Parkinson's disease, taught us that when you ask questions of the patient, you have got to give them time, because they will eventually come out with the answer.

Well, that has been brought out there to a certain extent in this type of dementia, and it is different from the Alzheimer's patient in my

experience until they get very demented later on.

As far as the question of the memory deficit, again, that is something that has to be teased out a little more as far as the clinician is concerned in their office, and as you say, seeing these patients and moving on as also the executive function.

The behavioral disturbances are usually you become aware of. I hope that answers your question.

DR. KIEBURTZ: Yes, and I was actually even more broadly thinking, not necessarily in a Parkinson's disease patient, but just individuals you follow in practice arriving and deciding that someone has become demented.

DR. OLSON: Yes, definitely.

DR. SACCO: I would agree that most clinical practicing neurologists with observations that sometimes are either first time visits or multiple visits, and taking in all the information from families can come to a conclusion about the syndrome of dementia.

I think, as researchers, we get a little bit more embroiled into the types of dementia, the causes of the dementia, so I think of it as the clinician being able to decide yes, a clinical syndrome of dementia exists, but then can you break it down into the underlying cause, whether it's Alzheimer's, whether it's Parkinson's disease related dementia, or whether maybe even vascular dementia, that gets trickier for the common clinician.

So, I think that gets more difficult, but I think when faced with a Parkinson's disease patient with cognitive impairment, then, I think a clinician could make that distinction.

DR. KIEBURTZ: Dr. Koski, any thoughts?

DR. KOSKI: Not that would really extend with the exception that I think that we do generally do a Mini-Mental as part of a full neurologic examination. Very frequently it is incorporated with other aspects as you are trying to complete the examination.

I think that many times, although a family

is aware that there are some problems within the home situation, particularly with very mild patients, they are in a protected known environment, so then when you put them into the clinical examination, you know, as a neurologist, sometimes there is more stress on the patient, so they actually don't perform as well as they might actually in the home situation.

So, I think, yes, we can make that decision. I certainly agree that for the subcortical versus other forms of dementia, I think that is harder for the general practitioner.

DR. KIEBURTZ: Dr. Katz.

DR. KATZ: I just want to ask a question that I asked earlier, which you deferred, which is what would we expect to be the incidence of Alzheimer's disease in a cohort followed forward in time, non-Parkinson's patients?

The incidence in the few pathologic studies that have been presented, the incidence of Alzheimer's disease in patients with Parkinson's disease would then go on to get some sort of

dementia syndrome is very, very low, at least compared to Lewy body pathology.

So, I am just wondering, just given the prevalence or the incidence of both Alzheimer's and Parkinson's disease, what would you expect to see in a population followed forward in time of Parkinson's patients over X number of years, how many would just get Alzheimer's, and is that more or less what we are seeing in the pathologic studies, or is it much less than we expect, or what actually do we think about that?

DR. KIEBURTZ: I think I will see if there are some answers over there. I presume you are first asking the committee, and then we will check with the sponsor, anybody, okay? I mean it will very dependent on the age of the group you are following, of course, because of the age-specific incidence rates for Alzheimer's in various populations have been described in this population who are already diagnosed with Parkinson's disease, of course, will tend to be older, in the 60s and above, and the age-specific incidence rates for

individuals in the 60s, I would have to think about. We will see if Professor Emre has some thoughts.

DR. EMRE: I have the other hat, the Alzheimer's hat, so the frequency of Alzheimer's disease, about the age of 65, is around 5 percent, and it doubles every five years.

MR. LOEB: Will you say that again? I am sorry, would you repeat that?

DR. EMRE: About the age of 65, the frequency is about 5 percent of Alzheimer's disease, and it doubles every five years, so if you reach, say, 85, it is somewhere, 25 percent to 30 percent. It depends on the study. It varies a little bit from country to country, but about the age of 65, it is about 5 percent.

So, if you would follow patients with Parkinson's disease, about the age of 65, in general, you would expect 5 percent would develop coincident Alzheimer's disease assuming that pathologies of both disorders are mutually neutral, not doing anything.

Looking, in other words, if, for example, the prevalence of Alzheimer's disease is 5 percent about the age of 65, and of Parkinson's disease is 1 percent, that means 5 in 10,000 may, by chance, have coincident Alzheimer's and Parkinson's disease.

DR. KIEBURTZ: If you took a study like the Rogaland cohort that Aarsland reports, you would expect in the five-year period of observation, you would see about 5 percent of those individuals having AD, which I think is about the number they report actually.

DR. KATZ: As I recall, I think it was 6 percent in one study or something, but again, what the ages are exactly and how those match up, I don't know, but, yes, I just want to see if there is a sense that what you are seeing as far as Alzheimer's pathology is more or less what you would expect to see just by chance or just by the natural incidence of Alzheimer's.

DR. KIEBURTZ: Dr. Hughes.

DR. HUGHES: I guess a related question,

to me, is it's extremely persuasive if the rate of Alzheimer's type dementia in a Parkinson's disease population is as low as 5 or 7 percent, that we are dealing with a different disease.

So, I would be interested in knowing just where the low rate comes from, are those studies reasonably representative of patients with Parkinson's disease dementia, give the low rate of Alzheimer's type dementia?

DR. KIEBURTZ: Are these studies that were presented relatively representative of the studies?

DR. HUGHES: Mention was made earlier that the proportion of patients with Parkinson's disease dementia, well, Parkinson's disease that might have Alzheimer's type dementia is extremely low. I wrote down the number of 5 to 7 percent that I think came from somewhere.

I don't know the study or studies that led to that figure, and the question I have is are those studies representative of a broad population of patients with Parkinson's disease, and sort of a corollary to that is in the EXPRESS study

population, presumably, we would then also expect an extremely low rate of Alzheimer's type dementia in that study population.

DR. LEVERENZ: May I address that question?

DR. KIEBURTZ: Yeah, that would be great.

DR. LEVERENZ: Jim Leverenz, University of Washington, Seattle.

I think the Dag Aarsland study, which is a longitudinal study of Parkinson's, gets a little bit at that question, and the numbers from there were consistent with the other studies, which had a bit more of a selected sample.

I think those other studies were actually a little more specific to the EXPRESS, which is that you have very much selected patients who had Parkinson's preceding their dementia, so that is the one selection bias within that, but the Aarsland study would be consistent with that sample in a more population-based type study.

DR. KIEBURTZ: I think, too, that there aren't a lot of studies like this, so to say, you

know, the Aarsland study isn't one to present out of 10, it is one to present out of 1, I think. I mean there are longitudinal population-based cohorts looking at the incidence of Parkinson's disease and other dementias, but with the neuropathology, actually, it is fairly unique unless you can think of others.

DR. LEVERENZ: No, I think the pathology is relatively unique, definitively. You know, there is 5 to 7 coexistent Alzheimer's to a degree, as Dr. Emre mentioned, that you would expect.

DR. KIEBURTZ: Dr. Hurtig, anything you want to add to any of that?

DR. HURTIG: Howard Hurtig from the University of Pennsylvania, Philadelphia. I can only say that we have collected more data since our publication in the year 2000. We now have up to about 95 patients followed closely over years of a diagnosis of Parkinson's disease with and without dementia, and of those that we have autopsied that have dementia, the number of cases we are using the integrated criteria of sera-added Braak to make a

diagnosis of Alzheimer's where the probability is high, is about 10 percent. So, it's very closely aligned with what has been presented here.

I think in any series where you have maybe only 20 or 30 cases, you might wonder what else might be out there, but as our numbers accumulate, we are still using those strict criteria, around 10 percent, but that is still only about 40 brains with a diagnosis of dementia.

DR. KIEBURTZ: Thank you. I think another issue I think we should at least sort of have conversant on the table, we have, for example, the DSM criteria in the back of the slide kit here, and there are criteria for the diagnosis of Parkinson's disease and Alzheimer's disease, and individuals who specialize in those areas are probably quite accurate at making those diagnoses as verified by a postmortem pathology.

But I think we should probably be cognizant--that was my question of asking about the practitioner making a diagnosis of dementia, that many of these diagnoses are made in practice by

individuals who do not have specific expertise in either movement disorders or dementia.

The specificity and accuracy of their diagnosis is probably considerably lower. How low will some studies suggest getting it wrong on in four times, one in three times. There is a difference between there being good diagnostic criteria available and particularly applied in the research setting versus applied in the clinical setting.

Dr. Porter.

DR. PORTER: I will change the subject slightly back to the other issue. I know we are just discussing Question 1, but I would like--

DR. KIEBURTZ: We are just having a discussion, not about Question 1.

DR. PORTER: And I especially am not voting, but I would like to know if the answer to Question 1, if we have, in fact, criteria for clinical diagnosis, which is what the question asks for, is having Parkinson's disease an integral part of knowing that you have PDD, an acceptable process

for having a clinical diagnosis, because if you have to fall back on the cognitive issues, it is made pretty clear that that is pretty weak in the clinic.

So, I am just asking regarding Question 1, do widely accepted, valid, and reliable criteria exist for its clinical diagnosis, I think they do, but I think you have to say that you have Parkinson's disease first, and I think that we have to make sure that we sort of agree that that is what is meant by clinical diagnosis, otherwise, we are going to end up with semantic discussion here.

DR. KIEBURTZ: Question 1 aside, it may be useful to look at this, because the dementias associated with other medical conditions, for example, dementia associated with HIV disease, the dementia associated with Huntington's disease, these are also called out in the same DSM area, and the basic underpinning of the introductory area is you have got the other disease.

There is a reasonable pathophysiological explanation that that disease can lead to dementia,

so that is Step A. Then, secondarily, you are demented, and you meet criteria for dementia, which is largely functional, and you don't meet criteria for other things. That's the tricky part, that you don't have Alzheimer's.

The other primary identified dementias, which largely are the Alzheimer's type dementia and the vascular type dementia, and then you don't meet criteria for having a major depression, and that is something we have not talked about a lot here.

DR. PORTER: I agree with your approach completely. I just wanted to make sure that we talked about that, that we didn't stumble over that when we got to the question.

DR. KIEBURTZ: That is one thing, and I would be interested, Dr. Litvan, not to pick on you, the other comorbidity, which frequently develops and is actually thought to be part of the pathophysiology of Parkinson's disease, is depression, and to what extent is it important to--now, in the EXPRESS study, clearly, individuals who met criteria for major depression are excluded,

so I don't think that is a confounding issue in the interpretation of the study results there, but in practice, individuals with Parkinson's disease who present with or who have cognitive complaints, I think it would be important to establish in practice that they are not depressed.

I wonder what your thoughts are on that.

DR. LITVAN: Certainly, that is part of the assessment, and I think that when you make the diagnosis of dementia, you also assess whether they do have other neuropsychiatric problems, and depression is one of those, and it needs to be treated. Then, you see what the treatment reflects to see if there is complete improvement or not.

Obviously, the diagnosis of depression, as well, in Parkinson's disease is a little bit difficult, but I am not going to get there, but there are somatic problems that occur in Parkinson's disease and makes sometimes a diagnosis difficult. But I think it is just a differential diagnosis that needs to be acknowledged and treated, and it may overimpose with the diagnosis

of dementia.

MR. LOEB: I am probably getting ahead of ourselves here, but if, indeed, it is ultimately determined that Exelon should be indicated for the treatment of mild to moderate dementia in Parkinson's dementia disease, how would that change the nature of the debate in the country, or the way we look at these diseases, will the stories be written in such a fashion, will the people understand in such a fashion that Parkinson's is equal to Alzheimer's, that Alzheimer's is equal to Parkinson's, will that change the nature of discussion of these things in the U.S., and consequently, if that were to happen, what would be the consequences? I have a second question after that.

DR. KIEBURTZ: Well, you may get stunned silence from the rest of the committee, you will get it from me. It is a very interesting question I hadn't thought about.

DR. LITVAN: I think it's an excellent question and I think that it is being addressed

slowly but surely, because patients are starting to understand that that may be something that may occur in the future, and the only answer that you have is that you need to take one step at a time and see what is going on at that time, and not really dwell on what the future is. But, certainly it is a possibility that is higher, five times higher than in the general population, and it is something that you cannot hide.

I don't think that an indication will do more than just increase awareness of something that is the truth.

DR. KIEBURTZ: I think you raise a question could it be that there will be confusion amongst entities or that things will kind of be blurred and thought of as being all kind of the same thing, because the same treatments might work in different diseases, if I hear, and I think that is an important distinction to draw, not only for the general public, but probably for the general practitioner.

Dr. Koski.

DR. KOSKI: I would just like to ask another question, if I could. Basically, the clinical course in Parkinson's disease dementia versus Alzheimer's disease is basically different. Isn't that the case?

But I think it is a question of awareness and anticipation of problems for the individual.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: Sometimes the public often will equate dementia and Alzheimer's disease together, so just as we argue about criteria for the types of dementia that we recognize, or even beginning more to recognize in neurology, that there is some heterogeneity there, it will be up to us I think to educate the public, to not necessarily make the leap that dementia equals Alzheimer's disease, therefore, Parkinson's disease dementia equals Alzheimer's disease. It will be a matter of education for us to recognize that there is differences and then for the public to come along as we make it clear.

DR. KIEBURTZ: Could I ask Dr. Hughes a

question? Let me make this generic, so it doesn't look like it's getting at a question. Part of the idea about drawing inferences from a single experiment, the risks in that are reduced by having two experiments which show the same finding then hence drawing inferences from them.

If you are doing experiments in different settings, even though you are testing the same underlying principle, do you gain inferential stability by the experiments that are around the same mechanism, but are in a different setting? Am I making myself at all clear?

DR. HUGHES: It's a very complicated question. At one level and from a probabilistic level, you can think about getting two independent significant results with p values of 0.05 as being somewhat similar to getting a much more significant result, so a p value less than 0.05-squared or 0.0025 from a single study.

So, in terms of thinking about probabilities, this one study gives the same sort of level of evidence as two independent studies

with p values of about 0.05. It is not quite that, but it is pretty close.

So, I think the real question is, in my mind, in this situation, is are there particular issues to do with the population that you are studying or the people that are conducting the study, that would lead you to in some sense disbelieve these results to some extent and seek to want to replicate it using a different set of investigators, using a different set of patients, and so on.

That's unclear to me. On the face of it, this study seems to be well done. The issue about geographic variation, you know, I found the results there reasonably persuasive, that there isn't strong evidence of geographic variation. There doesn't seem to be, in response to my question, evidence that other products of experience, differences in efficacy in different populations.

So, it is not clear to me that a whole lot would necessarily be gained by trying to replicate this study. But, on the other hand, it does set a

precedent that you can push for a higher level of evidence in one single study, which probably has broader implications for policy, which are difficult to gauge.

DR. KIEBURTZ: Let me just come back to that last point just to understand. So, it's not so much about probability and inferences, but more some of the logistical reproducibility, is there some idiosyncratic characteristic of the study setting or the study investigators that makes it less--I guess those two things are actually intertwined in a way.

DR. HUGHES: Yes, they are intertwined, but I think that would be the main motivation for trying to want to replicate this particular study.

DR. KIEBURTZ: The other question, I think the sponsor made some allusion to guidance, but I think in other circumstances, maybe Dr. Katz wants to give a little background on that.

DR. KATZ: Yes. Dr. Struck talked about the evidence document, which lays out under what circumstances a single study could serve as

substantial evidence, whereas, at least two are usually required, but there are many, many examples. If a drug is approved for adults for a particular indication, typically, we ask for a single study in pediatric patients to get a pediatric claim.

It is very common in the world of epilepsy if a drug is originally approved to treat partial seizures, and the sponsor wants to get it approved to treat generalized seizures, typically, we would ask for one study in the new setting. In certain circumstances, you would ask for two studies if we believe anyway that they are completely unrelated from sort of a pathophysiologic point of view, but if we think the condition is likely related biologically to the original approval, it is very typical to ask for only one study.

The standard for success would be a p of 0.05. It wouldn't be anything higher than that, again in the typical case that I am talking about.

DR. KIEBURTZ: Dr. Temple.

DR. TEMPLE: We don't put it that way in

the document, but we are really behaving as if we have a strong prior and like closet Bayesians, and the simple, easy to understand way is one instead of two, which would not be a respectable prior in more rigorous terms, but it is what we have long done.

DR. KIEBURTZ: It is okay for closet Bayesians?

DR. TEMPLE: Yeah, it's okay for closet Bayesians. It gets too complicated if you try to figure it out, but at that level.

DR. KIEBURTZ: I am just trying to branch out a little. Like in cancer where maybe it's a different primary, but the mechanism is thought to be highly similar, does that ever happen?

DR. TEMPLE: It happens all the time. The most obvious is different stages of the same cancer, so the drug is approved for third line, it would be extremely unusual to do two studies in first line. It would almost always be one.

Then, you could have debates about this. You now go to a tumor of a sort of similar

pathologic spirit, maybe one is okay there. If you went over to sarcomas, maybe you think you need two. There is a lot of judgment in it, but you definitely gain growing assurance as you have more and more data in a variety of different tumors. That is typical. It is very hard to do two well-controlled studies in most tumors, and we don't usually ask for it.

On the other hand, you have got to distinguish that case from where you expect a very, very small p value, so we usually rely on a single study of adjuvant treatment, because they are very large, but the effect size, the design of the studies is such that you do tend to get very small p values. That is the different one study situation. That is where you really are getting a very powerful single study.

We also, of course, in oncology, you also get to look at the both the outcome you are most interested in, say, survival and response rate, so you have other things that make you believe the drug is active that all contribute to relying on a

single study.

DR. KIEBURTZ: Other questions from the committee?

Well, then, we will adjourn for lunch. we will reconvene at 1 o'clock sharp and have the open meeting, and then discuss and vote the questions.

(Whereupon, at 11:55 a.m., the proceedings were recessed, to be resumed at 1:00 p.m.)

A F T E R N O O N P R O C E E D I N G S

[12:55 p.m.]

DR. KIEBURTZ: I think everyone is here from the committee, so we will start with the open public hearing.

Open Public Hearing

DR. KIEBURTZ: I have an instructive statement for the meeting. It is called for particular matters meetings.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the Open Public Hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement. to advise the committee, if you do not have any such financial relationships. If you choose not to address the issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

I believe we have three speakers. Each of those speakers has five minutes to address the committee.

Bob DeBusk.

MR. DeBUSK: Good afternoon. I am Bob DeBusk, CEO of Lewy Body Dementia Association headquartered in Atlanta, Georgia. I thank you very much for giving us an opportunity to say a few words at today's committee proceedings.

The Lewy Body Dementia Association is a national 501(c)(3) organization dedicated to raising awareness of the Lewy body dementias (LBD),

assisting caregivers and families and encouraging scientific advancement towards a cure. We further believe it is our responsibility to advocate for Lewy body patients and their caregivers.

The Association's Board of Directors commends the Food and Drug Association for its consideration of cholinesterase inhibitors for the treatment of Parkinson's disease with dementia or PDD.

The Lewy body dementias, PDD being among them, are the second leading cause of degenerative dementia in the elderly in the United States, affecting over 1.5 million individuals and their families.

Those who suffer from dementias influenced by Lewy bodies struggle daily with an insidious disease whose memory and movement disorders closely mimic the combined symptoms of Parkinson's and Alzheimer's diseases.

Because Lewy body dementias are primarily age-related diseases, the LBD patient population is accelerating with the aging of the baby boomers -

the problem is rapidly getting worse.

The last decade has seen extraordinary progress in the research methodology, understanding, diagnosis, and management of the Lewy body dementias. For example, a decade ago, the Lewy body dementias were not even recognized as separate entities, being lumped with Alzheimer's and Parkinson's diseases.

It is well known among those who treat Lewy body dementias, as well as those who are afflicted by them, that cholinesterase inhibitors are effective in the treatment of LBD symptoms such as hallucinations, sleep disturbance, loss of cognitive skills, anxiety, delusions, apathy and attention disorders.

Yet, until now, there has been little effort to bring cholinesterase inhibitors to the marketplace and give it proper awareness and recognition as a drug that effectively treats the Lewy body dementias.

Those who care for loved ones having a Lewy body dementia often comment on how their

burden is lessened when cholinesterase inhibitors are used early in the treatment of the disease's cognitive and psychiatric features.

Others report on how the use of cholinesterase inhibitors have delayed the placement of their loved ones in a long term care facility. Thus, the use of effective drugs to manage these debilitating diseases not only helps the patient, it also helps to lessen the physical, emotional and financial complications too often experienced by those families who provide the patient's daily care.

The need for approval of the cholinesterase inhibitors is critical in managing psychoses in people with Lewy body dementias, because of disease-specific hypersensitivity to traditional antipsychotics. In addition, the recent FDA "Black Box" warnings with the use of atypical antipsychotics has limited treatments available to maintain people with Lewy body dementias safely in both home and institutions.

At this time the cholinesterase inhibitors

are currently the only safe option for treating and preventing the psychosis which is a trademark of Lewy body disease.

Again, we applaud the Food and Drug Administration's initiative in its consideration of cholinesterase inhibitors for the treatment of Parkinson's disease with dementia.

We further request that you utilize your seat of influence to encourage and support continued research into the pharmacological treatment and eventual cure of a disease that preys on some of our most vulnerable - our elderly mothers, fathers, sisters, brothers, husbands and wives.

Thank you for giving us this opportunity to speak for the tens of thousands who would be here to speak for themselves if they were not engaged in the most demanding role in their life - caregivers of loved ones with Parkinson's disease with dementia.

Respectfully submitted on behalf of the Lewy Body Dementia Association Board of Directors,

Angela Taylor, President.

Thank you.

DR. KIEBURTZ: Thank you, Mr. DeBusk.

Dr. Cohen is next here, so go ahead, Dr. Cohen.

DR. COHEN: My name is Perry Cohen. I am a patient advocate and a Parkinson patient advocate, and I work on issues with the FDA and with sponsors of new treatments on what we can do as patients to seek the development of new therapies.

I came here at my own expense. I have no financial relationship to the sponsor, and my motto has been "The missing ingredient in the development of new therapies is the voice of the patient."

I have one concern and then one sort of suggestion in relation to a bigger problem that I think this discussion today has addressed. My concern is what are the long-run side effects of taking medicine, the medicines being proposed here in combination with all the other dozens of PD medicines that we all take, I take about 40 pills a

day, and adding another to the mix just gets scarier and scarier.

A good example is the dopamine agonists which now, after about seven or eight years being on the market, are starting to be implicated for sleep attacks and compulsive gambling and other risky behaviors. A lot of people I know, including myself, have stopped taking some of these treatments because of the side effects that we didn't know about when they were first introduced.

That said, I think we have a problem in that we don't have much data on mental health issues and Parkinson's. We don't have much data on the population of Parkinson's either.

Some of the research that I have done with my past association with the Parkinson's Disease Foundation indicated that at almost half of the patients in the country don't even see a neurologist.

Only about half see a neurologist over a five-year period in the study that we did, and we don't know how many people have Parkinson's. We

think that there is 25 to 40 percent that may be undiagnosed.

So, when you get out into the country, there is not a lot known about Parkinson's, period, much less Parkinson's and mental health, which has only really come to the attention of even the specialists in the last several years, and there has been very little research done in mental health.

So, I think that a distinction that is being suggested here by the sponsor, categorizing PDD as a separate disease or a separate entity could be of really great value, and I would endorse doing that, however, it could be a distinction without a distinction if the treatments are all the same.

But my hope would be that by shining the light on this area, that we will get more research done in this area, there will be greater awareness in the community from the community physicians, greater awareness in the population, and, of course, the sponsor will promote their product in

this way, I would presume, so that that would be a positive benefit if we increase the research effort.

What I would like to challenge the sponsor and other of your competitors, who will no doubt come in and try to get the same designation for their products, because I know there are several that are being prescribed now by neurologists for Alzheimer's or Alzheimer's drugs that are being prescribed by neurologists for Parkinson's, that we set up a registry program similar to what I suspect the consortium for the Alzheimer's registry program have done.

I would like to have a response from the sponsor on whether they would promote research or help set up a research consortium to continue to monitor this treatment as more and more of the population gets exposed to it, and as more and more treatments become available.

Thank you.

DR. KIEBURTZ: Thank you, Dr. Cohen.

Dr. Lurie.

DR. LURIE: Good afternoon. My name is Peter Lurie. I am with Public Citizen's Health Research Group. We take no money from either government or industry, so I have no conflicts of interest to disclose.

I have provided to the members of the committee a copy of my testimony. I take it that you have that, so I will summarize.

We oppose the granting of this new indication to Exelon. The minimum criteria for approving a drug should be, first, the disease to be treated should be clearly defined and clinically evaluated as if it were distinct; the drug should have a clinically meaningful benefit, it should be demonstrated in well-designed and conducted studies, and the findings should be replicated.

I think those are reasonable criteria, not one of them has been met in this case.

First, there is no clear evidence that the dementia associated with Parkinson's disease is a distinct clinical entity. The EXPRESS study is said to have relied upon the diagnostic criteria

for dementia associated with Parkinson's disease from the DSM-IV, but the DSM-IV provides no basis whatsoever for making such a diagnosis.

With masterful circularity, it states, and I quote: "The essential feature of Dementia Due to Parkinson's Disease is the presence of dementia that is judged to be of direct pathological consequence of Parkinson's disease," going in circles.

A recent practice parameter from the American Academy of Neurology puts it bluntly: "DSM-IV criteria for dementia have not been validated in Parkinson's disease."

Now, DSM-IV does go on to describe some aspects of dementia, not one of which is unique to Parkinson's disease, but as noted by the FDA Medical Officer, patients in the EXPRESS trial "were enrolled based on their having dementia, but without the more distinctive cognitive deficits described in the DSM-IV."

Indeed, the Medical Officer even asked whether or not the patients in this trial were

different than the patients in the Alzheimer's Disease trial. It is noteworthy, too, that the clinical course of the placebo groups in both these trials and the previous Alzheimer's trials were very similar, raising further questions about the uniqueness of this entity.

I wasn't here this morning, but I am sure the sponsor pointed to supposedly characteristic pathological findings in this entity, but, in fact, there is tremendous overlap between the pathological findings in Alzheimer's, diffuse Lewy body disease, and those in the dementia associated with Parkinson's disease, and there is no study that even shows that the clinical features that are said to be more common in Parkinson's disease actually correlate with those pathological findings that are said to be more common.

In any event, the positive predictive value of either the clinical findings or the pathological findings have not been defined.

A recent issue of PLOS Medicine defined disease-mongering as, quote, "The selling of

sickness that widens the boundaries of illness and grows the markets for those who sell and deliver treatments." I think that is an apt description of what is going on here today.

A second point. The effects demonstrated in the EXPRESS trial are modest. There was about a three-point difference on the 70-point ADAS-cog scale commensurate with the improvement that one might observe over six months in a patient with Alzheimer's disease. It is a particularly modest benefit given some of the study limitations that I will now discuss.

First, according to the FDA, the ADAS-cog is, quote, "not particularly useful for evaluating executive function," even though that is one of the more prominent deficits in the dementia associated with Parkinson's disease.

Second, and I provide you with a reference, a survey was conducted of Canadian geriatricians and neurologists, and they asked them what would be the minimum difference on the Mini-Mental Status Examination that you would

consider clinically significant, and they identified a change in the Mini-Mental Status Exam about double what the FDA uses as its criteria for approval, or at least its recommendations in Alzheimer's patients.

Finally, even when the ADAS-cog has shown a statistical benefit in a study of a different Alzheimer's disease drug, the patients and caregivers did not observe such benefits, and that is reference 5 in my testimony.

There is an aphorism in statistics that says, "A difference, to be a difference, must make a difference." It is not at all clear that the statistical findings observed in this study have much clinical relevance at all.

The third point. The dropout rate is high and may explain rivastigmine's observed efficacy.

One of the problems with the study design, this is particularly important because this is a problem that applies not only to this study, but indeed to all of the studies that have been done in Alzheimer's dementia to this date.

In this particular study, the loss to follow-up rate was considerably higher than in the placebo arm, 27 percent versus 18 percent, and the difference was largely attributable to the adverse effects of the drug and the withdrawal of informed consent by more people in the rivastigmine group than in the placebo group.

If those suffering adverse effects or withdrawing consent were also less likely to have derived benefit from rivastigmine--and that is likely--then, the disproportionate loss of rivastigmine-treated patients likely creates a bias in favor of rivastigmine.

Again, this is a problem that has been pointed out, and again I have provided references to this effect in really essentially all of the previous Alzheimer's disease studies and may explain some or all of the findings in those studies, as well.

Now, it is true that in this study, there were a couple of efforts made to deal with missing data using intention to treat with last observation

carried forward, and also with retrieved dropouts, and neither of those meaningfully altered the findings.

But the fact is that those two adjustment methods are among the least sophisticated currently available. I am not going to get into these in any detail, but I will list them.

Other techniques include regression-based imputation, proper multiple imputation, and hot deck imputation. The FDA and the sponsor should explain why it is that these more sophisticated techniques were not used. Attrition bias is particularly important when you have modest treatment effects, as was the case over here.

Fourth, the sponsors failed to replicate its findings. To date, there have been five drugs that have been approved for Alzheimer's disease, and in each case, two randomized, placebo-controlled, double-blinded studies were provided.

As the FDA asserts, quote, "If dementia associated with Parkinson's disease is indeed a

condition that is distinct from Alzheimer's, then, it would seem appropriate to require that the results of the study be replicated."

Such replication again is important when the treatment effect is modest and subject to bias. There is no reason to stray from what has been the FDA's practice for dementia drugs up until this point.

Briefly, on safety, there are excesses in the incidence of nausea, vomiting, tremor, dizziness, diarrhea, and anorexia, which are substantial, and some of which could even be considered to be worsenings of Parkinson's disease.

So, let me conclude. We are left with a single trial of a product of debatable efficacy for a condition that may not exist as a unique entity. The quest for this new indication is itself mired in self-contradiction and should leave this committee with no choice but to reject the drug.

If rivastigmine is similarly effective in similarly designed trials for both Alzheimer's disease and the dementia associated with

Parkinson's disease, one might well conclude that the disease processes are not clinically distinguishable and that a separate indication for Parkinson's is not justified.

On the other hand, if hypothetically, a separate indication were warranted, why has the sponsor not submitted two trials, as was done for all of the Alzheimer's disease drugs?

The answers to these questions are quite simple, and they are not found in science, they are found in marketing, product differentiation and market segmentation.

Thank you.

DR. KIEBURTZ: Thank you, Dr. Lurie.

That will conclude the Open Public Hearing and now we will move to the committee's consideration and discussion of the questions that are posed, 1 through 6, on our agenda.

Questions for the Committee

DR. KIEBURTZ: We will move through them in order. As Dr. Katz alluded to at the beginning of the hearing, if these are the areas where the

FDA would like to hear a discussion about, but if people feel there are other pertinent areas, we will certainly entertain discussion around those.

If there are questions that seem to be particularly pertinent that arise during the content of our discussion, we can vote on those questions, too, if we can articulate them.

I will say this, when we go around to vote, the voting members of the committee, as we vote each question, we will go around the table in different directions, if you will just say your name and your vote, that will help for recordkeeping in the long run. If you don't do it, I will remind you, and if I don't do it, I will presume you will remind me.

MR. LOEB: When doing that, may one make a comment?

DR. KIEBURTZ: Yes. Hopefully, we will have exhausted most of the discussion in the contents before, but if you feel that that is necessary, certainly.

MR. LOEB: Could I raise something?

DR. KIEBURTZ: Yes.

MR. LOEB: I frankly don't know if this is in order, but I wonder if indeed we were to approve, if not No. 1, then what was said at the end here, that Exelon should be indicated for treatment of mild to moderate dementia in Parkinson's dementia disease, if indeed we were to vote to that question and approved it, what do we lose? What is at risk here? What is the negative to voting that, which seems to reflect, as I interpret it, the will of this group?

I am just trying to find out what is the down side to doing that? That is my question and comment.

DR. KIEBURTZ: What is the down side to--I am actually just thinking which question--

MR. LOEB: I was thinking essentially--

DR. KIEBURTZ: It is not really a question here.

MR. LOEB: As opposed to a question here that was the last paragraph before we broke for lunch. It seems to me that the evidence on behalf

of that seems to be pretty clear. You may disagree with me, but if it is, I am trying to ascertain why is there a deep concern about it, am I missing something here.

DR. KIEBURTZ: I would certainly be interested in other members of the committee, and perhaps Drs. Katz and Temple speaking about it, I would say generically, if there is no such entity, approving a treatment for it would not be appropriate. If there is such an entity, but the drug doesn't actually work in that entity, that would be inappropriate.

Why? Well, because then drugs would be used in people without any potential for benefit, that would potentially, as we just heard alluded to, give one of a class of drugs a competitive advantage which not be based in any real efficacy, but just give it a commercial advantage without any scientific basis, and people who have other problems which might be addressed by more effective treatments would be sort of derailed or sidetracked into a treatment that doesn't provide them benefit.

DR. PORTER: It also makes other new drugs harder to develop if you approve a drug for something that doesn't work, because then you have a hurdle that is artificial, that you would have to overcome, because you may not be able, in fact, to use a placebo, for example. It can have a lot of negative effect.

DR. KIEBURTZ: Dr. Temple.

DR. TEMPLE: So far at least, the existence of some drugs that are approved for Alzheimer's disease hasn't prevented the furtherance of placebo-controlled trials in that condition, and I don't think there is any doubt that an active controlled trial would be impossible to interpret in this setting.

I thought perhaps the question--but you have to tell me if I am right--was how much does it matter whether people with Parkinson's disease and dementia get treated because people think it's a lot like Alzheimer's disease that they have got as opposed to whether they think there is a really distinct dementia.

I was thinking of asking Dr. Lurie that. If they are either the same, in which case you just treat them with all the same drugs, or they are different and it's worth studying, but in the end, probably everybody is going to get treated.

But I think we would like to get it right as much as anything, and it does go to what kind of evidence you have to come forth with and what you say about it in labeling, and, you know, the whole field is better off if you can reach a conclusion that there either is or is not a distinct form of dementia.

It shapes the further studies, it shapes, you know, so it is better to get it right, even though as a practical matter, probably everybody is going to just be treated anyway.

DR. KIEBURTZ: Let's go Question 1, which reads: Is there a distinct form of dementia associated with Parkinson's disease--and I think these are all "and" statements, and parenthetically--and, in particular, a dementia that is distinct from Alzheimer's disease, so is

there a distinct form of dementia in PD that is furthermore distinct from AD, and--the second "and" clause--do widely accepted, valid, and reliable criteria exist for its clinical diagnosis?

So, we have had some discussion on this already. We have seen some data this morning, and there were several papers presented regarding individuals followed longitudinally with Parkinson's disease and who developed dementia and who did not, and in those individuals who developed dementia, neuropathological findings were established, which I guess that the neuropathologic underpinning was not that of Alzheimer's disease, but that doesn't necessarily point exactly to this question, which is a question of is there a distinct form of demential, is it different than Alzheimer's disease and can you diagnose it clinically.

Dr. Koski.

DR. KOSKI: For me, being obviously not an expert in this particular field in neurology, I must admit that I was very impressed with

pathological data. I think that the clinical data are really, really less clear, and that it's a spectrum of types of things, so you can see some of the same characteristics obviously in Alzheimer's disease and probably other forms of dementia, as well as the dementia associated with Parkinson's disease unless you are perhaps dealing with, first of all, an expert in this, and you are dealing with a patient perhaps early in the clinically course, but I think the pathology is pretty impressive.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: I would agree. This is a very complex question. It is really two questions in one I think that we are struggling with here. The first part of the question is I think easier, is there a distinct form of dementia associated with Parkinson's disease and is different from Alzheimer's. The second part--

DR. KIEBURTZ: Easier, and what is the answer to that?

DR. SACCO: I think yes.

DR. KIEBURTZ: I just wanted to be sure

that I understood your point.

DR. SACCO: I am having more trouble with widely accepted, valid, and reliable criteria for its clinical diagnosis. If you really dissect each of those, widely accepted, valid, and reliable, it is making it hard for us, so please help us.

DR. KIEBURTZ: Dr. Katz.

DR. KATZ: I am from the government, I am here to help.

[Laughter.]

DR. KATZ: What we are trying to get at with this question is whether or not we think that the average practitioner will be able to identify these people, and identify them as being different from some other people like people with Alzheimer's disease.

So, for example, obviously, there has been a lot of discussion today about the specific syndrome, if there is one, you know, the specific clinical features that make it distinct, and my sense is that everybody thinks that maybe on a population basis, there is something different, but

in an individual patient it would be difficult to do.

But remember the sponsor has asserted that you really don't need that, all you need in order to be able to make a diagnosis that conforms to the underlying pathology is somebody who has got Parkinson's disease, who at least two years later develops clinical dementia, sort of a generic diagnosis of dementia, which you have already I think agreed people can make, the average practitioner can make a diagnosis of dementia. That is the question you asked before.

Somebody should correct me if I am wrong, but my perception was that the criteria for a clinical diagnosis, at least according to the company and its experts, is diagnosis of Parkinson's disease followed by sort of a generic dementia. You don't necessarily have to conclude that the non-expert can tease out the executive dysfunction, all those things, in order to be able to say yes, there is a way to make this diagnosis clinically.

The company asserts that it can be done very easily clinically, and if you use just those simple, that two-step process, Parkinson's disease and generic dementia--I will call it that--you have a very good chance that you are identifying people with Lewy body disease, and not Alzheimer's.

So, you can define, you know, define clinical criteria any way you like. What we are trying to get at is can you identify these people clinically.

DR. KIEBURTZ: Let me just reframe that. Part of that--and to get to your question, Dr. Sacco, and then we will move around--I think the beginning part of the question might be a neuropathologically driven question, and the second part of the question may be a clinical diagnosis of dementia in the setting of PD. That is kind of how it has been framed up.

DR. KATZ: That is the thing. The company asserts that that is all you need in order to identify a population that does not have, for the most part, Alzheimer's disease, and we are trying

to get at can people do that, and I guess the question would be do you agree that that simple algorithm will get you there.

DR. KIEBURTZ: So, there is two questions embedded there. One, is that the right formulation, is that all you really need to do, and two, if that is all you need to do, can you do it.

Dr. Litvan.

DR. LITVAN: I believe that it is a clear nosological entity, Parkinson's disease and dementia as it was demonstrated here, and that clinical criteria will need to be developed to better diagnose it, but currently, we can go with what it is there, that is, diagnosing the dementia in someone that has Parkinson's and all the other features that are there.

So, in summary, I believe that a neurologist would be able to apply the simple criteria to make the diagnosis of Parkinson's disease and dementia, and be able to treat it.

MR. LOEB: Does that mean that the people with Parkinson's would have Alzheimer's dementia,

or the people with Alzheimer's would have Parkinson's?

DR. LITVAN: In general, I think that as we have seen, most of the people with Parkinson's will not have Alzheimer's, will have a dementia that has some features that may be difficult to differentiate from Alzheimer's clinically, but when you look at the brain, the pathology, it is different.

DR. KIEBURTZ: Dr. Olson, then, Dr. Ahlskog.

DR. OLSON: One of the points I wanted to make is that we often learn from our pathology. We then start to divide things and understand that there are different entities that perhaps we didn't recognize before.

I don't remember exactly when Lewy body dementia was first recognized as a separate entity, but 30 years ago we didn't know that there was something called Lewy body dementia, but now we do.

It certainly existed 30 years ago, but as we learn more and more, with our new histochemical

and other staining techniques, we are understanding so much more than we did before, and allows us to then more clearly define these entities and then think about the cause, treatment, et cetera, and study them better.

One of the points here, and again the second part of the question I am struggling with, too, is that as clinicians in the field, and not just Parkinson's experts, are educated about this entity, it may become much easier for them to recognize and to deal with.

I think that is clearly part of the process that needs to take place, so that people then can tease these different things out. We all now know about dementia with Lewy body disease and can differentiate it based on the criteria that are out there. I just use that as an example.

I think that type of education will help in this particular process.

DR. KIEBURTZ: Just to remind committee members, if you want to speak, make sure you catch Lieutenant Lyons' or my eye, and then we will just

make a list.

Dr. Ahlskog.

DR. AHLSKOG: I am going to expand on what Dr. Olson just said, and we are in a new era now where pathology has taught us a lot, and it hasn't been over 15 years or 10 years, it has been over 5 years, and that it has to do with all of these. It started out with genetic discoveries, the alpha-synuclein gene.

It turns out this is found in high concentrations in Lewy bodies, and it turns out that if you take this population of people who have two things, they have Parkinson's disease, then, there is an interval of time that elapses, and then they become demented.

We are not very good as clinicians in a busy clinic trying to sort out are their problems more executive or are they semantic dementias, is there an aphasia component, but we are pretty good as neurologists at saying that yes, this person is demented.

So, it is two steps, and I think are

getting hung up on this particular question. It is a little bit complex, "widely accepted, valid, and reliable criteria exist for the clinical diagnosis."

Well, you know, what conjures up in your mind is that the Queen Square Brain Bank criteria, you know, you need two from Category 1, three from Category 4. It is like going to Burger King, you know, and trying to figure out your order.

But this is two steps. It's do you have Parkinson's disease (a), and (b), there is an interval of time, and are you demented. So, that is all it is. If you accept those as criteria, it is really two steps and an interval, then, I would have to answer yes to that, as well.

So, I am happy to accept this particular question in the affirmative.

DR. KIEBURTZ: Is there anyone who feels or I would like to hear from someone who feels that once you have made the diagnosis of Parkinson's disease, and an interval passes, and person becomes demented, that prior to deciding that that person

has the dementia associated with Parkinson's disease as opposed to coexistent Alzheimer's disease, PSB, Huntington's disease, HIV dementia, or whatever, you need to do more detailed assessment of their cognitive performance in order to arrive at a diagnosis, an operating clinical diagnosis that warrants treatment.

DR. LITVAN: I do.

DR. KIEBURTZ: Go ahead. Tell me about that.

DR. LITVAN: I believe that whenever someone has a dementia, you need to kind of revise your diagnosis and be sure that you are on the right track.

Having said that, it means as well when you see your patient, if there is something that makes you think that there is no Parkinson's disease, because there is no good response to levodopa, because there is oculomotor disturbances, whatever, you are going to be revising your diagnosis.

The fact that dementia appears means that

it could be related to Parkinson's disease or it could be related to something else, so you need to be able to come down with a diagnosis of Parkinson's disease and dementia as ruling out all the other differential diagnoses, that is, you are going to be ruling out progressive supranuclear palsy, you are going to be able to rule out depression, you are going to be able to rule out there are no other disorders that could cause that, B-12 deficiency, whatever it is.

So, I don't think it is just to say it is dementia now, then, it is this entity. You have to really rule out treatable causes of dementia of other entities. So, that should be done.

DR. KIEBURTZ: Can I follow on that a little? So, all those things I kind of blurted out, and you reiterated, there are ways clinically in the laboratory to get a folate B-12, thyroid, so you do those things in someone who has incident dementia and assessment of mood.

But at some point, you are going to end up with two ruleouts. You are going to end up with

someone who is demented, who has got Parkinson's disease, who you have ruled out the other treatable and other secondary causes of dementia, but you won't be able to rule out Alzheimer's because Alzheimer's is a ruleout diagnosis, too.

So, in that circumstance, would you then be comfortable saying okay, then, this person has dementia of PD as opposed to AD because of all the neuropathology and other stuff?

DR. LITVAN: Yes, I would feel comfortable with that. I think that there is going to be a few features that eventually will help us understand this disease better and certainly if there are more visual-spatial disturbances, and if certainly there are more hallucinations, and certainly if there are more executive dysfunction, and less problems with forgetting, all that would make us think that this is truly more Parkinson's disease and dementia, and less likely Alzheimer's disease, but being certain 100 percent may be at times difficult, but that will not make any difference anyway here.

I think I would feel comfortable that this

is Parkinson's disease and dementia, the most likely cause being Lewy body disease rather than Alzheimer's disease just even by frequency.

DR. KIEBURTZ: Other questions?

Then, why don't we vote this Question No. 1. I will start with Dr. Porter. Oh, you are not voting, non-voting. Sorry.

Mr. Loeb. Just remember to say your last name.

MR. LOEB: Yes.

DR. KIEBURTZ: That was a yes for Mr. Loeb.

DR. LITVAN: Yes. Can we change this question to make it feel more reflecting that it is that we are voting on rather than what it really is stating?

DR. KIEBURTZ: Okay. That's fine. Let's go back. When I said is there any more discussion, that is the kind of thing I am looking for.

DR. LITVAN: If we could divide it in two parts and say: Is there a distinct form of dementia associated with Parkinson's disease--and

put it there--in particular, a dementia that is distinct from Alzheimer's disease as Question No. 1, I would say yes, certainly to that.

Are there widely accepted, valid, and reliable criteria for its clinical diagnosis, I don't feel comfortable answering that as a complete yes, because that is not the issue, but I mean if they don't exist in summary, but I do feel comfortable saying that this entity can be diagnosed by a neurologist following simple criteria that will be eventually further improved by a task force or whatever, I mean because that is, in fact, what is going to happen.

DR. KIEBURTZ: You mean the diagnostic criteria for Parkinson's disease dementia?

DR. LITVAN: That's right. So, what I am trying to say is that if we separate them, I would feel uncomfortable saying yes to widely accepted, valid, and reliable criteria, because it isn't existing, and nobody has validated or looked for its reliability.

DR. KIEBURTZ: I want to come back to

something we were talking about before, because one way to formulate this question might be do widely accepted, valid, and reliable criteria exist for the clinical diagnosis of dementia in the setting of Parkinson's disease.

DR. LITVAN: That, I feel comfortable.

DR. TEMPLE: No, no.

DR. KIEBURTZ: I didn't say that was the question, I said that is one formulation.

DR. KATZ: Well, that's true, I agree with that.

DR. KIEBURTZ: But that doesn't help.

DR. KATZ: We really want to know whether or not let's say the average neurologist, who will be seeing these patients, can identify these patients reliably. It doesn't say 100 percent specificity and sensitivity. It says accepted, valid, and reliable, can the non-expert easily identify these people.

So, whatever criteria you think exists--

DR. TEMPLE: Look, the committee has been discussing this. If it required that you be able

to tell from their loss of executive function or whatever it is that they have this one rather than that one, I gather everybody thinks that would be very difficult indeed, and the answer would be no.

What the company said, I would say at least 30 times, is you don't have to do that. If you have a person with Parkinson's disease and dementia that follows it by some period of time, your pathological data tell you that most of the time it is a Lewy body disease, not the other. That is another way to reach that conclusion.

So, it doesn't have to be because you know the difference between the syndromes. That would be nice, I guess, but another way is that you get it, you know, 90 percent right or 95 percent right by doing what they suggested as the way to do it.

I have to say this is a very critical question for whether those studies--the study that they did, only one, sorry--the study they did actually studied people with Parkinson's disease, because they didn't have a biopsy, and the clinical diagnosis is difficult, and they didn't fuss that

much about it.

The entry criteria were Parkinson's disease dementia, and the elapse of time, so if you don't believe something like that would pretty reliably predicts Lewy body disease, then, that is not a study of Parkinson's disease dementia.

So, it doesn't have to be because you can tell the difference from the type of dementia. It's okay, according to that question, if you can tell it in some other way by the concomitancy of the Parkinson's disease dementia, passage of time, and your evidence for that can only be, as far as I can tell, the pathological evidence, which most people seem to think is good. I mean I have no opinion about that.

DR. KIEBURTZ: So, the second formulation of the question as opposed to do widely accepted, valid, and reliable criteria for the clinical diagnosis of dementia in the setting of PD, which prompted them to say no, no, I think that is one formulation.

The other formulation is do widely

accepted, valid, and reliable criteria exist for the clinical diagnosis of Parkinson's disease dementia, which could be nothing more than the three things I just said, which is what Russell said before.

DR. KATZ: Right. I think people are getting hung up on this "widely accepted, valid, and reliable criteria," because the criteria, as presumably exists now, were not perfect, or maybe they are just too simple.

It's fine if the criteria is simple. Everybody has already said several times now, the company asserts you can do it simply, Parkinson's, a couple of years go by, and any kind of dementia, and you are going to be almost always right that that is Lewy body disease, it is not Alzheimer's. That could meet the definition from our purposes of widely accepted, valid, and reliable.

As Bob says, if you don't believe you can do it that way, you can't believe the results of this study have identified Parkinson's dementia patients, because there was no other way that the

company did it.

So, we are happy to change that. If people are getting distracted by what appears to be the complexity of the question, we can say do criteria exist so that these patients can be diagnosed by the non-expert. We are just trying to figure out if you think it can be done.

DR. LITVAN: I would feel more comfortable with the latter, because if you are talking about valid and reliable criteria, you are talking about it being immunological terminology, that is, accuracy, and there are not accuracy studies, so it is hard to vote for something that doesn't exist.

DR. KATZ: That's right, that's not what we mean.

DR. LITVAN: I would be more comfortable to change it to a terminology that really adapts to what it is there available and currently, what we are asking is, is it possible to diagnose this semantically and clinically, and I feel comfortable saying yes, but I don't feel comfortable saying anything about an accuracy study that doesn't

exist.

DR. AHLSKOG: Irene, wouldn't you accept those pathologic studies that really started out with the clinical end of things, and pretty much it's what was in the EXPRESS study. Parkinson's disease, interval, dementia, and inherent in the concept of dementia is that you rule out treatable causes, so that leaves us with those simple criteria that were pathologically validated.

DR. LITVAN: No, we don't know reliability. I mean there wasn't a study done.

DR. AHLSKOG: It would seem to me the gold standard would be Lewy body disease. I mean if you know the pathology, that is a pretty gold standard. I don't know how you can really go beyond that in this age.

I would be happy arguing that, because in retrospect, you know, we have really done that. We have done it, now, Aarsland has done it prospectively, Parkinson's disease became demented, and his findings were the same as these retrospective studies of Hurtig and Apaydin, and

Martello, and now Aarsland, Braak, so there are quite a few studies, and they are pretty consistent, all within the last five, six years or so in this new modern era of alpha-synuclein and immunohistochemistry, so that would be my argument.

DR. KIEBURTZ: I get the sense that we are getting something that is of more interest to us than the people we are advising if we get too much into this, but I understand what you mean by epidemiologic application of accuracy, which is to codify these criteria, and then go out and apply them to a population and get a sensitivity and specificity, that's how you would address the question of valid and reliability and the positive predictive value. They are not asking us if they have been tested in that way, or are you?

DR. TEMPLE: If you just look at what I understand the pathology claims to be, they are saying if you diagnose people as having Parkinson's disease dying with dementia, you are going to be something like 95 percent specific for Lewy body disease.

I don't know, that's not so bad compared to most of the things we do. If you believe that, I haven't read those papers, you guys obviously have, but that is not bad for a clinical diagnosis even though it is the most simple-minded diagnosis you can name, concomitancy of two conditions.

Dr. Mani,

DR. MANI: I just have a suggestion as to what language or how to rephrase this question in a way that might be acceptable to everyone. How about rephrasing it as follows, and I am referring only to the second component of the question, do operational criteria exist for this clinical diagnosis? That might make it easier.

DR. LITVAN: Yes.

DR. KIEBURTZ: That would be very easy.

DR. LITVAN: That would be very acceptable.

DR. KIEBURTZ: So, we are going to strike "widely accepted, valid, and reliable," and replace it with "operational" at your suggestion.

Then, I don't think we need to bifurcate

the question, because I was thinking we might want to do a 1(a) and 1(b). Let's just leave it as Question 1.

Mr. Loeb, do you want to reconsider your prior vote?

MR. LOEB: I would stay with my prior vote, is there a distinct form of dementia associated with Parkinson's disease, and, in particular, a dementia that is distinct from Alzheimer's disease, and then do we go from there to a new sentence, or do we say, "and do?"

DR. KIEBURTZ: Continue just in the same sentence, "and do operational criteria exist for its clinical diagnosis?"

MR. LOEB: Yes.

DR. KIEBURTZ: Thank you.

DR. LITVAN: Yes.

DR. KOSKI: Yes.

DR. OLSON: Yes.

DR. SACCO: Yes.

DR. HUGHES: Yes.

DR. AHLSKOG: Yes.

DR. KIEBURTZ: Yes.

We have got Question 1. We are making progress.

Question 2. Was the population enrolled in the EXPRESS study selected appropriately in the context of the proposed new indication, such that the effects of Exelon in that population could be considered distinct from those already established as occurring in patients with Alzheimer's disease?

DR. KATZ: Let me just sort preempt some confusion.

DR. KIEBURTZ: Yes, please.

DR. KATZ: I am not sure I will be successful.

DR. TEMPLE: Are you seeking ownership of the committee?

DR. KATZ: No, I am not, but I want to help before it becomes a problem.

Distinct from the effects of Exelon considered distinct, we didn't mean by that necessarily a different size of treatment effect on ADAS-cog or anything like that. We just wanted to

know whether this was an effect on the dementia of Parkinson's disease as opposed to any effect on Alzheimer's disease. That is what we meant.

DR. KIEBURTZ: Thank you.

Discussion on this? Dr. Porter.

DR. PORTER: Again, I am just trying for clarification. So, all you really want to know is was there an effect on Parkinson's disease dementia like you saw in Alzheimer's dementia more or less?

DR. KATZ: It is confusing to say like we saw, because that implies the same effect size, I don't know what that implies. All we are trying to say is that the drug has an effect, and, of course, a positive effect, on Parkinson's dementia, period, just period.

DR. PORTER: Okay. The drug has an effect on Parkinson's dementia, period, okay, that's good.

DR. KIEBURTZ: If you look at that question in context with Question 3, which otherwise selected appropriately, would get at things like were depression and vascular dementia, and other entities appropriately excluded.

I think Question 2 is really getting at do you think there is work in Parkinson's disease dementia as opposed to treating coexistent Alzheimer's disease in a group of people with Parkinson's disease.

DR. TEMPLE: Of course, it is also related to the first question that you just answered.

DR. KIEBURTZ: I mean if you answer yes to 1, you are almost--yes, the interdependency issue, okay.

Questions about this? Discussion about the question as Dr. Katz framed it?

In that case, we will vote the question starting with Dr. Ahlskog.

DR. AHLSKOG: Yes.

DR. HUGHES: Yes.

DR. SACCO: Yes.

DR. OLSON: Yes.

DR. KOSKI: Yes.

DR. LITVAN: Yes.

MR. LOEB: Yes.

DR. KIEBURTZ: Yes. Thank you.

So, Question 3 then arrives at this issue, was the population enrolled otherwise selected appropriately, and I think this morning we had some discussion about, and we saw the reviewer's notes, some particular concerns about exclusion criteria on other readily identifiable causes of dementia particularly possible vascular dementia.

Dr. Mani, may I ask you, some of the discussion we had today, is that helpful regarding vascular dementia in your mind?

DR. MANI: My concern was really--let me just clarify again what I was getting at. I think it is quite easy to do so. I am comparing the protocol I saw with the protocols that I am used to seeing in people with Alzheimer's, which I have been seeing for some years now.

Those protocols have a study schedule that very specifically states whether an imaging study was to be done or not as a procedure. In this particular instance, that was not stated in the study schedule, and that is the reason for the confusion or misunderstanding.

I would personally say that I am quite satisfied by the data that the sponsor has presented regarding whether a sufficient number of patients underwent imaging. I am quite satisfied by that.

Like you, I didn't have any access to the actual imaging reports, but in this particular situation, there may be no alternative except to trust the judgment of the clinician in each instance as to whether the diagnosis was appropriately made and vascular dementia and other entities were excluded, because as you and I will know, when you look at images, there is always room for interpretation between one radiologist and another. There are questions about correlations, there are questions about whether MRI is better than CT.

So, the bottom line is I think that my concerns have been satisfied.

DR. KIEBURTZ: Thank you. That is very helpful.

Further discussion on this question? Dr.

Litvan.

DR. LITVAN: Yes. I would have felt more comfortable if there wouldn't be patients treated with dopamine agonists, and I saw that at least 40 percent involved groups were treated with that, and I would have felt more comfortable that part of the cognitive impairment wouldn't have been related to that.

But I can accept what was done. The main issue I would like to be sure is clarified, that if dopamine agonists were changed throughout the course of the trial, or they were kept in the same way.

DR. KIEBURTZ: Thanks. I think you are asking a question of the sponsor particularly, so let me just clarify it, too, for the rest of the committee.

So, for movement disorder, doctors in the setting of someone who presents with cognitive complaints, you will frequently attempt to reduce downwards dopaminergic agents--well, everybody does this, not just movement disorder

doctors--dopaminergic agents in an attempt to eliminate what might be drug-induced delirium or other problems, and that you would do that with dopamine agonists, you would probably do that with MAOB inhibitors, you would do it with levodopa, amantadine, all these drugs you are going to try to push down. Some people, you have to leave them on some of that, because they become immobile and nonfunctional otherwise, and there is a balance between motor disability and cognitive disability.

So, just amplifying on that, and stop me if I amplified it inappropriately, but your question, I think this is directed at the sponsor, and maybe someone can reply to this, was there change in dopamine agonist prescriptions' use from baseline to 16 or 24 weeks.

I think the implicit notion is if a proportion of people were coming off dopamine agonists, that might partly explain their improving cognition, as well as the active intervention. So, you would like to see that by treatment arm. Thank you.

DR. TEKIN: The protocol clearly specified that the baseline levels of dopaminergic medications were to be kept constant throughout the trial, and the patients who did not fulfill this criteria were carefully collected during the study, and we have a number of protocol violators in which based on clinical judgment there was necessity to change the dopaminergic medication doses, but those protocol violators were limited to L-dopa dose changes.

I can provide to you the specific numbers for those patients. I believe a total of 40 patients. If you could provide me the exact slide for protocol violation change in dopaminergic medications.

DR. PORTER: These were in both arms of the study, thought, right?

DR. TEKIN: Right, distributed in placebo and Exelon arms.

[Slide.]

There were 39 patients in the Exelon group and 18 patients in the placebo group who increased

or started new antipsychotic therapies or dopaminergic medications. These include actually all psychotropic medications that was specified as protocol violation.

DR. KIEBURTZ: Actually, I think the question was reduction in dopaminergic medication.

DR. LITVAN: Right. The question is actually, now that you are bringing this up, there is two question. I think you did say before, but just to clarify again, it seems like the neuroleptics were decreased in the Exelon group, right?

DR. TEKIN: Correct.

DR. LITVAN: So, the question here is mainly has the dopaminergic agonists been decreased rather than increased.

DR. TEKIN: We should have increased doses, but I am not positive if we can provide you right away the decreased doses.

[Slide.]

This slide will provide you the information again for the dose increases, but I

think within our analysis, planned analysis, we did not look specifically into those decreases specifically for dopaminergic agonists.

These are the number of patients, breakdown of patients that were identified as protocol violators. The dopaminergic agonists were increased in three Exelon-treated patient and one placebo-treated patient.

But for your specific question as to those decreases of dopaminergic agonists, we will need to do some additional work for that.

DR. KIEBURTZ: It sound like, though, at least we know clearly that changing that was a protocol violation, so that did not happen with great frequency.

DR. LITVAN: You have them as protocol violators, those that were decreased in dose, as well, right?

DR. TEKIN: The protocol violation rule was based on new initiation and dose increases. We did not specify dose decreases. That is why I am not able to show you that data today, but that

shouldn't be difficult.

DR. KIEBURTZ: So, that wasn't right what I just said, it wasn't a protocol violation. You guys here, that is of interest to us, but we don't know what the answer is right now. Thank you for looking for that.

I think we need to go back to Question 3. Further discussion about this "otherwise selected appropriately," which in large part is were other treatable or diagnosable causes of primary dementia aside from Alzheimer's disease appropriately screened for in the inclusion of these subjects. That is what they are looking for.

Why don't we vote that. Mr. Loeb?

MR. LOEB: Can I pass on that?

DR. KIEBURTZ: You may always pass.

MR. LOEB: I will pass on that. We are talking about No. 3?

DR. KIEBURTZ: We are talking about No. 3.

MR. LOEB: I beg your pardon. I would say yes.

DR. KIEBURTZ: Very good.

Dr. Litvan.

DR. LITVAN: Actually, it's a hard one here, because I don't think we have all the data. Mostly, it's yes, but I can't--

DR. KIEBURTZ: You should vote based on the information you have, what you think is the best answer, and understanding that if you had different information, you might vote a different way. You have the information before you, and the discussion that has occurred, and you vote your best conscience.

DR. LITVAN: I would pass on this one.

DR. KIEBURTZ: Abstain.

DR. LITVAN: Abstain.

DR. KIEBURTZ: Abstain.

MR. LOEB: I hate to go back and forth, but you can see I tend to agree with the doctor. I guess I would have to abstain on that one. I don't have sufficient information.

DR. KIEBURTZ: That's fine.

DR. TEKIN: In the Exelon-treated groups, there were 4 patients, which was 1.1 percent with

decreased dopamine agonists, and in the placebo group, again, we had 4 patients, it was 2.2 percent, so limited to 8 patients total.

DR. LITVAN: So, I don't abstain. I say yes.

DR. KIEBURTZ: That's another just-in-time delivery today.

Dr. Koski.

DR. KOSKI: It allows me to say yes.

DR. OLSON: Yes.

DR. SACCO: Yes.

DR. HUGHES: Yes.

DR. AHLSKOG: Yes.

DR. KIEBURTZ: Yes.

MR. LOEB: Can I backtrack? You know these journalists, but I have deep respect for lots of people around this table, so I would say yes.

DR. KIEBURTZ: So, Mr. Loeb votes yes on Question 3. Thank you. It is always fine to revise your vote before the meeting adjourns, but not afterwards. Well, you can change your mind afterwards, but it just doesn't change the vote.

So, Question 4 is on the screen as you can see. Was the overall design of the study appropriate and were the primary efficacy measures used suitable for evaluating the efficacy and safety of rivastigmine in mild to moderate dementia associated with Parkinson's disease?

Again, it's a complex question, but the primary efficacy measures here, as we have discussed at some length, were the ADAS-cog, and you have the chance to have an explication of that in a little further detail, as well as we saw the actual response possibilities in histogram bars on the global impression of change. Those are the primary efficacy variables. Safety variables are more routine and are the standard measures of safety and tolerability.

I think this question gets to there is some cognitive dissonance. It was okay if Parkinson's disease dementia is different than Alzheimer's disease, you just told us that, but now we are using the measure we always use in Alzheimer's disease, is that appropriate.

So, is it an appropriate efficacy measure in this supposedly otherwise disease entity. The other part we heard is, well, the cholinergic hypothesis underlies, maybe some of the measures of ADAS-cog are oriented towards that, and we had data about specific items in the ADAS-cog presented, too.

Further discussion about thought of that as an outcome measure and whether that speaks to--Dr. Hughes?

DR. HUGHES: I guess I was struck by some of the differences in the way the dementia presents. For me at least, some of the secondary efficacy measures were important given those differences. So, I am not entirely comfortable. If we were going to do another trial in PDD, I am not sure I would advocate the use of the same primary efficacy measures. I just have this feeling that other measures maybe are more appropriate.

DR. LITVAN: I agree with that. I think, in fact, this trial shows that all the secondary

measures actually were quite significantly improved, supporting the value in this type of measures. So, the answer would be no, but on the other hand, we have all the information, so it really doesn't matter here, because almost everything, primary and secondary outcome measures were significantly improved.

But I think for the future, I think that is a major point made.

DR. KIEBURTZ: Dr. Porter.

DR. PORTER: I would just to point out something that hasn't been mentioned before, and that is, the Agency challenged the normality of the distribution of these patients, and did a non-parametric analysis, and it still came out positive on the major variables.

So, I think that we really have a lot of strength in the primary variables based on that.

DR. LITVAN: They may be less specific, though.

DR. PORTER: I am not saying that if you had it to do over, you wouldn't look at different

measures. You can always say that about any drug, absolutely. You always look back at a trial and say, gee, I wish I had done something differently, absolutely.

DR. KIEBURTZ: The question from me to the Agency, we heard in public testimony and in the primary outcome presented by the sponsor was the intention to retrieve dropouts, that is, taking observations in individuals who are off experimental treatment at the last visit irrespective of the lack of being on experimental treatment. The primary analysis by the Agency was using the perhaps more traditional last observation carried forward.

In the public testimony, I heard some comments about utility or possible use of more advanced imputation strategies including multiple imputation.

Did you do any other more what I guess would be considered more exploratory imputation models? No.

DR. TEMPLE: That is a subject of many

workshops and a lot of discussion. Everyone agrees that LOCF is sort of simple minded, but there isn't any full agreement on a particular better method.

We certainly have no problem with people using other methods, but we haven't begun to insist, but we are working on guidance that would push in that direction.

One of the methods it sounded like they used, but I don't know how many people that involved, was to use values for people who stopped taking the drug and continued on therapy. That is a maximally conservative approach in a symptomatic condition.

So, that is unusual. Usually, you don't have data like that on people, but that is a very conservative one. Whether less LOCF is conservative or not depends on why people left the study, but we have not been routinely doing our own. We agree that there are probably better approaches than the LOCF, and are sort of working on it.

DR. KIEBURTZ: Empirically, in this particular setting, the ITT plus RDO, that's

intention-to-treat plus retrieved dropout, which you just described as being the most conservative, was, in fact, the most conservative. The treatment effect was the smallest for that analysis.

DR. TEMPLE: Well, you would expect that. You take a symptomatic treatment away, and you expect people to drop back to where they were. We don't usually insist on that. It is very conservative, and people who are very, very enamored of ITT want that to be done, but we have not asked for that generally in symptomatic conditions.

DR. KIEBURTZ: Dr. Katz.

DR. KATZ: Also, just for what it's worth, the percentage of dropouts in this study is more or less what we see with the typical Alzheimer's study of similar duration.

DR. TEMPLE: Actually, the other question is there were two points at which things could have been measured, at least 16 weeks and 24 weeks. Sometimes it is helpful to see what the effect is over time and look at it at each time point when

the dropout rate is lower early, so I don't know if you did that.

DR. KIEBURTZ: I think we had graphs of all the primary--at least presented in here and in the briefing book--

DR. TEMPLE: We have graphs, but I didn't see p values attached to the 16-week time point, for example.

DR. KIEBURTZ: The 16-week for the primaries were both less than 0.05. That is my reading.

DR. TEMPLE: Was the dropout rate lower at that point? I mean that is another way to gain some assurance it is not all due to LOCF or something.

DR. KIEBURTZ: They were still in the midst of titration earlier than 16 weeks.

DR. TEKIN: If you could clarify the significance at week 16 for the primary outcome measure of ADAS-cog, I would like to project the data again.

[Slide.]

We have statistical significance at week 16, but the treatment difference, the magnitude of the treatment difference was relatively smaller.

DR. KIEBURTZ: I think what Dr. Temple would find useful is under those different time points, having a N stated, that is, the number of subjects. That will give us an idea of how many people have dropped out and not dropped out at that point. Is that your point? Yes.

DR. TEKIN: I would like to turn to the statistician, please.

DR. KIEBURTZ: Percent would be okay. We know what it was at the end.

DR. TEKIN: I am pretty confident that we have that information.

DR. KIEBURTZ: It look in our review here that there is about 30 more patients in the week 16, so that is a lower dropout rate--no, 30 out of 200. That's fine, thank you, I think we got the numbers we needed.

Any further discussion on Question 4?

I have forgotten which place I started

with, but I think I will start with Dr. Ahlskog.

DR. AHLSKOG: We are voting now?

DR. KIEBURTZ: Yes, unless there is further discussion, or since you are the first person voting, if there is something more you want to say?

DR. AHLSKOG: No, there is nothing more. I think we have discussed this as much as is necessary. I vote yes.

DR. KIEBURTZ: Dr. Hughes.

DR. HUGHES: I guess I would vote no because of the emphasis on primary efficacy measures.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: I am going to vote yes.

DR. OLSON: Yes.

DR. KOSKI: Yes.

DR. LITVAN: Yes.

MR. LOEB: Yes.

DR. KIEBURTZ: I am going to actually join my colleague, Dr. Hughes, and vote no. Just for clarification, just because I don't think ADAS-cog

is the best. To the issue of is it the appropriate primary outcome.

DR. LITVAN: I agree with that, but I thought that is now why we were voting, though, so can you please clarify this better.

DR. KIEBURTZ: I am not clarifying what we voted. I am just clarifying my vote.

DR. LITVAN: Then, I will change my vote, as well, because the reality is that I thought, well, what I was going to propose before voting was if we could change the sentence a little, just to reflect what we really believe, that is, that the measures may not be the best for primary measures, but they were secondary measures that were appropriate.

I think that that would reflect more what we all believe, that is, the sign was good, but probably it was kind of limited in selecting as primary efficacy measures, those that were chosen, but they were good secondary measures that overcome the limitations of the primary ones.

MR. LOEB: How about if we delete the word

"primary"?

DR. LITVAN: That would be okay.

DR. KATZ: I actually think we want to know--maybe we should sort of break this out--but I think we want to know whether or not the specific primary measures that we used, whether or not you think they were appropriate for this population.

I think that is something we would like to hear from the committee on. If you think they were not appropriate, it would be very useful for us to know whether or not you think the study still supports a claim for Parkinson's dementia, and if you do, why you think that.

In your case, you think it's because the secondary outcomes cover the relevant functions. We actually do want to know whether or not you think the primary efficacy measures, the ADAS-cog and the global, were appropriate for this situation.

If you don't, we would like to know whether or not you think the study really is supportive anyway, and if you do think it's

supportive of granting this claim, why.

DR. TEMPLE: I also want to know why you think it's appropriate to put people into the study based on sort of general measures of dementia, but not measure improvement that way, so we have got a lot of things we want to know.

DR. KIEBURTZ: Since it was in the middle of the comment that triggered all this, let me finish what I was going to say, which is I think that--I am answering the question appropriate--it is probably not optimal, it's not an optimal outcome measure, but unquestionably, the study demonstrates efficacy in the disease we are talking about, because it shows benefit on an insensitive measure.

The reason I want to make the comment is you can probably find treatment effects in the disease we are talking about more sensitively with other measures, and there is a problem with--I don't want the committee to get done and going forward thinking the only way you can develop drugs for dementia in Parkinson's disease is by using

ADAS-cog, because it is going to be a blunt instrument, and there is probably more sensitive and appropriate measures of cognitive--well, measures of treatment effects in patients with Parkinson's disease dementia.

That was my explanation for my "no," but not suggesting that it is not sufficient to support the claim, I think it is more than sufficient to support the claim.

DR. KATZ: Okay, but that is your explanation for your "no" vote. If that is what people who are voting no mean also, that is to say, these are acceptable, the ADAS-cog and the global are acceptable, they are just not optimum, we need to know that, too.

DR. KIEBURTZ: You have got to make the question ask what you want.

DR. KATZ: Again, that is what we thought appropriate meant. Appropriate doesn't mean the best, it means good enough to grant this claim. If there are other outcomes that you think are better, we certainly want to hear about that, too.

DR. TEMPLE We also listened to the discussion, but this is really whether you think the study showed what it needed to, to support a claim.

DR. LITVAN: But I think those are different questions.

DR. KIEBURTZ: Let's vote the question then.

DR. LITVAN: You divide them in different questions, so we can vote them appropriately?

DR. KIEBURTZ: Let's keep No. 4 being suitable.

DR. KATZ: Let's ask were the primary efficacy measures suitable. It doesn't mean the best. If you have a better idea of what is better, of course, we would like to hear that, too.

DR. KIEBURTZ: In which case I am the last one voting, everyone already voted, I will vote yes.

Does anyone want to change their vote on that in the way that is described? I changed my vote. That is why I am asking if anybody else

wants to change their vote. The only other "no" vote was--

DR. KATZ: Did you vote yes?

DR. KIEBURTZ: I voted yes. I would say they are suitable.

DR. HUGHES: Suitable.

DR. KIEBURTZ: So, now we are unanimous, and yes.

Now, let's open a discussion, because I want there to be some record of does the committee really think these are optimal or the best way to be going about looking for treatment effects in Parkinson's disease dementia. Could we have some discussion on that? Dr. Litvan, I know your answer is no.

DR. LITVAN: I fully agree that these are not the optimal measures, so I think that this is an important point, that I think should be made. These measures are suitable, but actually, the secondary measures like the neuropsychiatric inventory, the executive measures that they did or others that are available, should be better

measures in future trials.

In this case, it doesn't make a difference, because all of them are significantly and show efficacy anyway. All the measures show efficacy.

DR. KIEBURTZ: The pickle would be is if ADAS-cog was nonsignificant, and all these very important secondary measures, which we think are more sensitive to this clinical entity were positive, and we were sitting here with a 0.06 on ADAS-cog and 0.1's on the others, we would all be telling you, you should have--that's good. I don't want to see that happen.

DR. TEMPLE: If they were to pull out something like executive function--never mind whether I quite understand what that means--and make that the primary endpoint, would that make everybody happy?

DR. KIEBURTZ: Dr. Litvan, and I don't mean to squelch discussion, I think when you see how ADAS-cog, the Alzheimer's disease assessment scale, cognitive subscale, is created, it tried to

dip into those cognitive domains which are thought to characterize Alzheimer's disease.

One could imagine the PDAS-cog, that dips into those cognitive domains that are thought to be most reasonable and get standardized. It has just never been done. Partly in the public commentary, the light hasn't been shown on this so much, but there is probably merit to that is what I would say, and I don't think you would want to pull out symbol digit, or the Wisconsin Card Sort, or some very specific thing, but I also think the principle of marrying that with a global impression of change has been done is defensible, because it's hard to know whether these changes observed in cognitive test performance or standardized batteries of cognitive test performance mean much in the CIBIC-plus or the ADCS-CGIC are ways of getting at data in a standardized fashion.

DR. TEMPLE: So, the particular thing you would be interested in, obviously representing a fair amount of work by the expert community, would be a better targeted overall measure of cognitive

function in this condition.

DR. KIEBURTZ: The FAB, the frontal assessment battery, the RBANS, there are other kinds of batteries put together. They are a little more cumbersome, they are not quite as brief and clinically accessible as the ADAS-cog.

DR. LITVAN: Actually, the FAB takes three minutes to five minutes to be administered. It would be an easy one to be done, but in addition, the neuropsychiatric inventory that they did use is a much better measure, because it measures actually the behavioral problems that these patients have as a population, so it is a perfect measure.

DR. AHLSKOG: I have a feeling that if that had been the primary efficacy measure, we would be having the same kind of conversation, just changing words. For a primary measure, you don't want three different measures. Then, you run into all the issues of multiple comparisons, and so on.

So, you want, you know, one kind of hard-hitting thing that is (a) validated, and (b) comprehensive, and the ADAS-cog is fairly

comprehensive, and if you see these folks in the community, as you know as well as I do, it isn't just executive function, it isn't just frontal lobes. They have sort of pancognitive domains that are all affected, not exactly like Alzheimer's disease, but they are kind of affected across the board, a little more here, and a little more there in the other.

So, I guess I am happy with this because it's one of those things don't let perfect be the enemy of good.

DR. KIEBURTZ: I think it is without a doubt in other neurodegenerative disorders that are associated with cognitive impairment, Huntington's disease, other areas, you are going to get people targeting the cognitive problems because they are so disabling, and it is not unlikely that those will come forward with the ADAS-cog, because it is such a standard instrument, because it does assay realms of cognitive function, which are likely impaired in any dementing disorder, to different degrees, yes, but likely impaired.

But it immediately triggers this kind of question, which we have been struggling with all day, is there actually nosological separation, or are we just calling things different that really are the same, because we are using the same instrument to measure them, and that is going to be a tricky problem going forward to help separate that out.

DR. LITVAN: Actually, another measure that could have been a good one would be the Madison Measure Rating Scale, that has a lot of executive, as well as memory problems, and would have been a good one to measure a lot of the features here, and it would more a global type of measure.

DR. KIEBURTZ: But like do not let the enemy of good be better. It's good enough is what the vote was.

MR. LOEB: With all the backing and forthing, you vote yes, is that correct?

DR. KIEBURTZ: I believe the vote on Question 4 was unanimously yes, Dr. Hughes and I

both reverted to a yes when the appropriate was deemed to be actually read suitable.

DR. KATZ: The word "suitable" is already in the question.

MR. LOEB: I don't know how to define it, but I know it when I see it.

DR. KIEBURTZ: Yes, suitable, yes, something like that. The design was appropriate and the measures were suitable.

DR. KATZ: I thought long and hard about the choice of the words.

DR. KIEBURTZ: I didn't spend long and hard enough reading it was the problem.

Question No. 5. Do the results warrant replication for a claim for the treatment of dementia associated with PD to be granted? We have had some discussion about this.

Dr. Porter.

DR. PORTER: I would just like to reiterate what the sponsor said, which is that we are really looking at the same mechanism of action of this drug, that this is really an

anticholinergic drug, it does the same thing in Alzheimer's as it does in Parkinson's as best we know.

I think that another study would really be unwarranted here. I think that we would not learn anything new, I don't think that we don't already know. We already have highly successful primary outcome variables, and I think unless you want to look at new variables, which would, in fact, be a little bit unfair to the company, I think one study does it.

DR. KIEBURTZ: Dr. Hughes, do you want to amplify on anything you said earlier?

DR. HUGHES: Not really. As I said earlier, I think this study is fairly conclusive. I think it appears to be well done, and I echo Dr. Porter's comments that I don't see a whole lot to be gained from replicating this study, and arguably, there may be ethical issues in trying to replicate it.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: I think what convinces me that

one study may be enough here is, one, the wealth of experience with the drug in another disease entity where the mechanism of action may be similar, so I feel like safety, at least we know something about, and, two, the robust findings in all the secondary endpoints.

If there was some incongruity between primary and secondary outcomes, I would feel less certain. That is why I think I am more convinced by this one study.

DR. KIEBURTZ: Further discussion? Are you ready to vote this question?

Mr. Loeb.

MR. LOEB: No.

DR. KIEBURTZ: Dr. Litvan.

DR. LITVAN: No.

DR. KIEBURTZ: Dr. Koski.

DR. KOSKI: No.

DR. KIEBURTZ: Dr. Olson.

DR. OLSON: No.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: No.

DR. HUGHES: NO.

DR. AHLSKOG: No.

DR. KIEBURTZ: I am going to pass.

Question 6. Do the data presented in this application indicate that it is safe for use in this population at a range of 3 to 12?

Anyone want to comment on the general side effect profile observed of GI upset, nausea, vomiting, diarrhea?

DR. LITVAN: That is what you would expect from this kind of medications, so it is similar to what happens in Alzheimer's disease, and I don't think there is anything here from a safety point of view that seems to be different or concerning.

The fact that there could be more tremor, it is expected, as well, but it is not a major problem here. Most of the time, tremors are cosmetic issues, and if not, obviously, the patients were able to withdraw, and I think it is surprising, though, that there hasn't been more depression with a cholinergic agent, but there isn't, or any other complications from a vascular

point of view, but again there hasn't been any.

So, the issue is that it seems like a safe drug.

DR. KIEBURTZ: Dr. Ahlskog, maybe I will direct this sort of your way. Do people take comfort from the fact that the UPDRS scores did not look different even though tremor shows up as a side effect, does that help you in understanding that, or is that two different things?

DR. AHLSKOG: Looking at the data, too, it was broken down by item from Part 3 of the UPDRS, so tremor, I am not too concerned about. You know, a lot of folks with Parkinson's disease do just fine with tremor if bradykinesia is not a problem. So, I am satisfied with that.

My only safety concern I think was satisfied. I wanted to be assured that there wasn't going to be a cardiac rhythm problem, which is to say bradycardia, and I think that was addressed.

DR. KIEBURTZ: Any other discussion on this?

Let's vote the question, No. 6. Safe for use in this population?

DR. AHLSKOG: Yes.

DR. HUGHES: Yes.

DR. SACCO: Yes.

DR. OLSON: Yes.

DR. KOSKI: Yes.

DR. LITVAN: Yes.

MR. LOEB: Yes.

DR. KIEBURTZ: I will vote yes.

Since we are all here, is there further things that you would care for us to discuss, or items that generated in the discussion that you would like us to amplify on at this point?

Then, I would like the sponsors for their presentations, which were thorough, and appreciate your responsiveness to our questions to the FDA, for presenting the material to us in a clear fashion that we could review, to our public speakers for presenting your points of view, which takes some risk and courage to present in this forum, and we appreciate you bringing them forward

to us.

I think Dr. Katz has something to say.

DR. KATZ: I also just want to thank the committee. It has been an interesting day and you have certainly given us very clear answers, and I would like to thank the Agency staff, who did a lot of work, and in particular, Dr. Mani, who wrote up all the documents, did all the reviews, an extraordinary amount of work in preparation for this meeting.

DR. KIEBURTZ: Thanks to all the committee members for serving, and appreciate everyone's forthrightness, and the meeting is adjourned. Thank you.

[Whereupon, at 2:30, the proceedings were adjourned.]

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