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CENTER FOR DRUG EVALUATION AND RESEARCH

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE

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C O N T E N T S

C O N T E N T S (Continued)

P A R T I C I P A N T S

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Roy E. Twyman, M.D. (Industry Representative)

GUEST SPEAKERS

Ted M. Dawson, M.D., Ph.D.
Joel S. Perlmutter, M.D.

FDA PARTICIPANTS (Non-Voting)

Phillip Davis, M.D.
Russell G. Katz, M.D.
Mark Levenson, Ph.D.
CAPT Rafel D. Rieves, M.D.

P R O C E E D I N G S

Call to Order

DR. ANDERSON: Good morning. I am Britt Anderson. I have been given the opportunity of chairing today's session, and we will begin with a series of introductions around the table so we all sort of know who we are.

I am a neurologist. I am currently at the University of Waterloo. Why don't we begin at Dr. Twyman's corner of the table and we will just go around in a circle, if everyone could, please, sort of state your name and give a brief statement of your affiliation and purpose.

DR. TWYMAN: Good morning. My name is Roy Twyman. I am the industry rep. I am from Johnson & Johnson.

DR. ZIESSMAN: I am Harvey Ziessman, from John Hopkins University, Nuclear Medicine.

DR. HERSCOVITCH: I am Peter Herscovitch, head of the PET Scanning Department at the NIH, Bethesda, Maryland.

DR. FOUNTAIN: Nathan Fountain, at the University of Virginia, Department of Neurology and Director of the Epilepsy Program.

DR. VAN BELLE: Gerald van Belle, from the University of Washington, Department of Biostatistics.

DR. ROYAL: Henry Royal, nuclear medicine physician, Washington University, St. Louis.

DR. MATTREY: Robert Mattrey, radiologist, University of California San Diego.

DR. DECAMP: Wilson DeCamp, patient representative. I am also a retired chemistry reviewer from FDA.

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

LCDR NGO: Diem-Kieu H. Ngo, Designated Federal Official for today's meeting.

DR. TATUM: I am Jim Tatum. I am Associate Director of the NCI and I direct the Cancer Imaging Program.

DR. HOLMES: Greg Holmes, Department of Neurology, Dartmouth Medical School.

DR. RUDNICKI: Stacy Rudnicki, Department of Neurology, University of Arkansas.

DR. LEVENSON: Mark Levenson, FDA, Biostatistics.

DR. DAVIS: Phillip Davis, FDA clinical reviewer.

CAPT RIEVES: I am Dwaine Rieves, FDA, Director of the Division of Imaging and Hematology Products.

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

DR. ANDERSON: Thank you. For topics such as those being discussed at today's meeting there are often a variety of opinions, some of which are quite strongly held, and the goal of today's meeting will be a fair and open forum for discussion of these issues so that all individuals can express their views without interruption.

So, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act we ask that the advisory committee members please take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media may be anxious to speak with FDA about these proceedings, however, the FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topics during breaks or lunch. Thank you very much.

Conflict of Interest Statement

LCD NGO: I will be reading the meeting statement

into the record: The Food and Drug Administration is convening today's meeting of the Peripheral and Central Nervous System Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

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

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential conflicts when it is determined that the agency's need for a particular individual's

services outweighs his or her potential financial conflict of interest. Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular government employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussions of today's meeting, the members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/ writing; patents and royalties; and primary employment.

Today's agenda involves discussions of new drug application 22-454 for ioflupane I-123 injection, proposed trade name DaTSCAN, by GE Healthcare, proposed for detecting loss of functional nigrostriatal dopaminergic neurons by single photon emission computed tomography, SPECT, imaging in patients presenting with symptoms or signs of dopaminergic neurodegeneration. This topic is a particular

matter involving specific parties.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Roy Twyman is serving as the non-voting industry representative, acting on behalf of regulated industry. Dr. Twyman's role at this meeting is to represent industry in general and not any one particular company. Dr. Twyman is currently an employee of Johnson & Johnson.

With regard to FDA's guest speakers, the agency has determined that the information to be provided by these speakers is essential. The following interests are being made public to allow the audience to objectively evaluate any presentation and/or comments made by the speakers.

We would like to disclose that Dr. Dawson and Dr.

Perlmutter are serving as guest speakers. Dr. Perlmutter has acknowledged that he is an employee of Washington University School of Medicine.

Dr. Dawson has acknowledged that he is currently an employee of Johns Hopkins University School of Medicine, Department of Neurology. He is a researcher on contracts and grants from the National Institutes of Health, the National Institute of Neurological Disorders and Stroke, the National Institute on Drug Abuse, Simon's Foundation, Maryland Stem Cell Research Foundation, and the National Parkinson's Foundation. In addition, he is the Chair of the Scientific Advisory Board for the Bachmann Strauss Dystonia and Parkinson's Disease Foundation and a member of the board of directors. As guest speakers, Drs. Perlmutter and Dawson will not participate in committee deliberations, nor will they vote.

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

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

DR. ANDERSON: Thank you. I have been asked again to remind public observers that this meeting, while open for public observation, public attendees are not allowed to participate except at the request of the panel.

At this point we are going to proceed with our presentations and introductions, and CAPT Rieves is going to make a few introductory comments and introduce our guest presenters.

FDA Introductory Remarks

CAPT RIEVES: Good morning. I have a few prepared remarks, largely dealing with some of the regulatory background for today.

[Slide]

I welcome you to our discussion of the new drug application for DaTSCAN, which is the proposed trade name for ioflupane iodine-123 injection.

[Slide]

DaTSCAN is a radiopharmaceutical that was submitted under a new drug application in which the proposed

indication has been slightly modified since submission to state that the drug is indicated for visualization of the dopamine transporter, or DaT, distribution within the striatum by single photon emission computed tomography, or SPECT, imaging in patients presenting with symptoms or signs suggestive of dopaminergic neurodegeneration.

This proposal makes it clear that the drug is to be used in diagnostic imaging. Diagnostic imaging drug products, and radiopharmaceuticals in particular, have unique regulatory considerations compared to therapeutic drugs since the clinical study outcomes may consist of pictures rather than direct measures of clinical benefit.

[Slide]

Indeed, FDA has specific regulations pertaining to diagnostic radiopharmaceuticals and, most notably, to the evaluation of effectiveness. Specifically, the regulations state that effectiveness of a diagnostic radiopharmaceutical is assessed by evaluating its ability to provide useful clinical information related to its proposed indications for use.

[Slide]

Our regulations are largely summarized by two key

questions, one related to the indication and the other to the drug's usefulness. Specifically, does imaging with the radiopharmaceutical measure what it purports to measure? Secondly, is the measurement information clinically useful?

[Slide]

The risk to benefit considerations for diagnostic radiopharmaceuticals are also somewhat different from those usually applied to therapeutic products in that the radiopharmaceutical drug risks are usually evidenced in premarket studies, but the benefit is generally one associated with the interpretation of pictures and all pictures are surrogates for clinical benefit.

Our regulations note that the benefit or clinical usefulness may take several forms. For example, the usefulness may be self-evident, as is the case for detection of a broken bone or a cranial mass lesion. In these cases, clinical studies are often not essential to establish clinical usefulness.

However, if the usefulness is not self-evident, then usefulness must be established in clinical studies either by the establishment of performance characteristics where the pictures are compared to a truth standard to

describe sensitivity and specificity, or by verification that the pictures highly agree with the pictures obtained with an approved radiopharmaceutical.

Alternatively, our regulations state clinical usefulness may be established in another manner, such as by patient follow-up which for practical purposes equates to the use of clinical follow-up information to form a diagnostic truth standard.

[Slide]

The major challenges with the DaTSCAN application directly relate to the proposed indication and the usefulness data. We generally regard the proposed DaTSCAN indication as one along the lines of a biochemical type use, for example the detection of dopamine transporter protein, or DaT protein distribution in the striatum.

The company does not propose use of the drug to definitively establish any specific diagnosis such as Parkinson's disease. Multiple forms of data, animal, in vitro and human are available for review and we are interested today in your opinion as to whether DaTSCAN measures what it purports to measure.

Secondly, we are requesting a perspective on the

usefulness of the drug, particularly in light of the somewhat atypical features of the Phase 3 studies. For example, we are requested to use clinical diagnoses as markers for the biochemical feature, the defection of DaT protein.

[Slide]

I want to emphasize that we are not coming to this committee with a finalized, complete review of the NDA. Indeed, this discussion is a component of our review process where we are looking forward to your perspectives on the data as you understand it now, such that you can help us refine our final review focus.

[Slide]

Our agenda today is relatively full, particularly this morning. We are delighted to have two special presentations. Dr. Ted Dawson, from Johns Hopkins University, will provide an overview of neruodegeneration in Parkinson’s disease and then Dr. Joel Perlmutter, from Washington University, will discuss some imaging topics in the clinical diagnoses. Subsequently, the company and FDA will make presentations, all targeted to end before lunch. This afternoon is dedicated to the open public hearing and

our discussion.

Thank you for your help today and, Mr. Chairman, I return the podium to you.

DR. ANDERSON: At this point, if there are no questions or issues, we will proceed with Dr. Dawson's presentation.

Guest Speaker Presentations

Neurodegeneration in Parkinson's Disease

DR. DAWSON: Well, good morning. Thank you for the opportunity to give you an overview of neurodegeneration in Parkinson's disease.

[Slide]

I thought what I would do is give you a little historical perspective on Parkinson's disease and go through historically where we are today with understanding basic mechanisms of neurodegeneration in Parkinson's disease.

[Slide]

The first thing I thought I would mention is to just give you an overview of the impact and the extent of this disease. It is one of the most prevalent neurologic disorders. It affects about four million people worldwide. In North America the estimates are about 500,000 to a

million of people, and it is expected to double by 2040. Of the patients, about 50 percent are diagnosed after the age of 60 and the remainder are diagnosed before then. It affects all walks of life and ethic distributions.

[Slide]

It was first described by, or at least given credit to James Parkinson in 1817 in his essay called AThe Shaking Palsy@ although historians of neurology suggest that there were actually earlier descriptions, perhaps by Aristotle and even earlier in some ancient Indian texts where they actually used Indian herbs that contain high concentrations of levodopa to treat the symptoms. So, it has been around for quite some time.

[Slide]

Charcot, in the 19th century, really defined the symptoms of Parkinson's disease in which patients present with low frequency rest tremor, rigidity, stiffness of the limbs and trunks, bradykinesia, slowness of movement and as the disease progresses patients have problems with balance or postural instability.

[Slide]

In addition to these symptoms, there are a variety

of other symptoms which, in part, are direct manifestations of the motor manifestations such as small handwriting, freezing, decreased facial expression. Some patients have decreased voice. There is also a variety of other autonomic disturbances such as constipation and other autonomic problems.

More recently I would say it has been appreciated that patients also have a variety of cognitive disturbances such as anxiety, depression, sleep disturbances and, as the disease progresses, significant cognitive decline, initially manifesting as problems with executive dysfunction.

[Slide]

The disease progresses over about 20 years on average in patients and some progress faster, some progress a little slower. This is a slide that was modified from Stan Fong, in which patients, anywhere from the initial diagnosis to about 3 years have a honeymoon period where they can get by with minimal treatment of physical therapy.

Drug-on therapy is initiated and in about 3 to 8 years they develop what is called the motor complication period where they may have problems with wearing off, dyskinesia, dystonia. This is relatively well treated with

current medications, deep brain stimulation, then they develop a period which is called the resistant symptoms where the therapies that we have aren't all that effective. Then, later in the disease cognitive decline becomes a very significant part of the illness.

Again, the time frame is an average time frame. Some patients progress faster; some patients progress slower, probably dependent upon the etiology of their illness.

[Slide]

In Parkinson's disease, as we are all taught, motor symptoms are primarily due to degeneration of the nigrostriatal pathway in which dopamine neurons in the substantia nigra project to the striatum, and it is the degeneration of this pathway that leads to the motor manifestations, the rigidity, the stiffness, the slowness of movement in which these dopamine neurons degenerate in Parkinson's disease.

[Slide]

Again, Parkinson's disease is characterized pathologically by the loss of substantia nigra neurons. At least from my review of the literature, Brissaud was

probably the first person that noted this and he actually speculated that damage to the substantia nigra might lead to Parkinson's disease. We now know that this is one of the major pathologic features of Parkinson's disease.

[Slide]

Then, in 1912 Fritz Lewy described these eosinophilic inclusions that were scattered throughout the brain. These are pernicious[?] inclusions that occur in the brain. And, these are some representative examples that occur and it became the recognized pathologic hallmark of the disease.

[Slide]

It was really a culmination of several investigators, including Arvid Carlsson and Hornykiewicz in 1957 through 1965, that really led to the concept that it was degeneration of dopamine that probably accounted for the symptoms of Parkinson's disease. Arvid Carlsson, through work with reserpine in rabbits, had shown that loss of dopamine caused very similar parkinsonian symptoms in those rabbits and he ultimately won the Nobel Prize for his work.

Through a variety of subsequent scientific investigations the enzyme that is responsible for dopamine

synthesis was discovered. It is called tyrosine hydroxylase. Markers were developed for that.

Just shown here, you can see that in a normal patient you have very dense staining of dopamine neurons in the substantia nigra and in a patient with Parkinson's disease you have a dramatic drop off. Then, with a fluorodopa PET scan you can see that in the striatum there is an accompanying loss of dopamine in patients with Parkinson's disease.

[Slide]

So in summary on the features of Parkinson's disease, again, it is the most common neurodegenerative movement disorder. It is the second most common neurodegenerative disorder next to Alzheimer's disease. The symptoms, again, include akinesia, bradykinesia, slowness of movement, rigidity, tremor, postural instability and also cognitive impairment, depression, anxiety and other features.

It is due to the progressive degeneration of the nigrostriatal dopaminergic pathway. The neuropathology is characterized by the loss of tyrosine hydroxylase, positive dopaminergic neurons, also intracytoplasmic inclusions

termed Lewy bodies.

I would like to mention that with recent advances in the last decade or so it is generally accepted now that neuropathology in Parkinson's disease is more than just the loss of dopaminergic neurons. In fact, it is a widespread neurodegenerative disorder in which probablyB-or most investigators would agree that the loss of dopaminergic neurons is just the tip of the iceberg.

We have relatively good drug treatments which treat the symptoms, including deep brain stimulation to alleviate the symptoms. But, as I mentioned, we really don't know, or we don't have good therapy to treat the underlying causes of Parkinson's disease.

[Slide]

So, what causes Parkinson's disease? I have broken it broadly into three major categories. I think most investigators of Parkinson's disease would agree with these categories. One of the major risk factors for Parkinson's disease is age. Hence, on my first slide there is going to be an unexpected doubling of Parkinson's disease.

There is fairly strong evidence that genetics plays a very important role, either through monogenic forms

which I will talk about or through increasing the relative risk of getting Parkinson's disease. Then potential environmental causes also contribute ultimately to the degeneration of dopaminergic neurons and other neuronal cells.

I have just indicated down here, at the bottom, that just like the discovery of dopamine deficiency led to powerful new treatments to diminish the symptoms of Parkinson's disease, really understanding the cause of Parkinson's disease will lead to the next revolution in disease therapy.

[Slide]

I thought any talk on neurodegeneration of Parkinson's disease really has to mention the MPTP model. In the 1970s a cluster of cases of parkinsonism was identified that were indistinguishable from idiopathic Parkinson's disease. This was identified in narcotic users through the detective work of Bill Langston and other investigators such as Aaron Kopin at the NIH.

The causative agent was ultimately determined to be MPTP, and MPTP was a byproduct of synthesis of heroin by a narcotic distributor, an illegal narcotic distributor in

northern California. It was ultimately determined that MPTP poisons the mitochondria.

[Slide]

From the standpoint of a dopaminergic model of Parkinson's disease, it is actually a pretty good model. I have just listed here side by side the major symptoms of Parkinson's diseaseB-bradykinesia, rigidity, postural instability, tremor, loss of dopamine tyrosine hydroxylase, dopamine transporter, response to levodopa, development of Lewy bodies.

And, in certain models of MPTP intoxication you can see all these features. It was actually the discovery of MPTP which led to the discovery in idiopathic PD that there were decrements in mitochondrial complex I.

[Slide]

This just summarizes probably two decades of work, it is not complete, on how MPTP kills dopaminergic neurons. I have just listed here some of the therapies, in the black boxes, that have been tried to see whether they might slow the progression based upon the MPTP model. MPTP is converted by monoamine oxidase B to MPP plus. It has high affinity for the dopamine transporter.

It is concentrated in the mitochondria where it poisons complex I. It sets in motion a variety of death cascades that ultimately lead to death of dopaminergic neurons.

I won't go over each of the black boxes, other than to say that despite this wonderful model of dopaminergic degeneration, some of these drugs are still in clinical trials so we don't have the final word. But of the ones that have made it through to the end, we still don't have any proven neuroprotective therapies for Parkinson's disease.

I put at the top of this slide 20th century therapies for PD. If you remember, I mentioned that MPTP was discovered in the late 1970s. So, in the last decade there has really been a revolution in Parkinson's disease, which I call the post-genomic era, in which a variety of genes that cause Parkinson's disease have been identified.

[Slide]

I list a number of them here. The list is not complete. I will say that for the ones in red there is very strong and convincing genetic data that these genes cause Parkinson's disease. Alpha-synuclein and LRRK2 cause

autosomal dominant PD.

Parkin, pink-1 and DJ-1 and ATP13A2 cause autosomal recessive forms of Parkinson's disease. I list other genes, susceptibility genes, that increase one's relative risk for getting Parkinson's disease. The genetic data on some of these isn't as strong as the ones that are listed in red.

Mutations in alpha-synuclein in the promoters, polymorphisms and alpha-synuclein can determine one's relative risk for developing Parkinson's disease in that if you express high levels of alpha-synuclein you might have a higher risk of developing PD than somebody who expresses lower levels.

[Slide]

So, with the discovery of the genes we have really entered a new era of Parkinson's disease research in which we can model the disease much more accurately using genetic means. We can develop mouse models, animal models, study the neurobiology, try to correlate that with disease and phenotype, develop targets, develop new drugs and then ultimately test those back in humans. If we find something that we think works, then ultimately it will make its way to

a panel like this, hopefully, in the future.

We have also entered a new era in which we are able to make inducible pluripotent stem cells from skin of patients with Parkinson's disease. So, at the top of my figure we have this new loop. We just have to wait and see whether the promise of making stem cells from patients with Parkinson's disease is going to lead to new and better therapies for Parkinson's disease.

[Slide]

So, what has all this genetics taught us? I just have here an overview of what the potential genetics has taught us. I think it is important for people to realize that even though genetics is where the majority of research has focused right now by scientists who work in the lab, the majority of Parkinson's disease is still sporadic and we still have this major feature of mitochondrial dysfunction.

I think most investigators would probably agree that there are pathways which I call non-alpha-synuclein pathobiology and, on the right the alpha-synuclein pathophysiology in which these pathways may work in parallel and in series to ultimately cause death of dopaminergic neurons and other neuronal populations.

[Slide]

I thought in the last few minutes I would just highlight five of these genes and just give you a little overview and taste for where things are going with these genes.

So, alpha-synuclein causes autosomal dominant Parkinson's disease. There have been point mutations, duplications and triplications, and the duplications and triplications indicate that simple over-expression of a non-mutated protein can cause Parkinson's disease. Hence, that is why I mentioned that simple polymorphisms in alpha-synuclein which increase one's relative level of alpha-synuclein can determine one's relative risk for Parkinson's disease.

It can aggregate and fibrillize, and that is how it is thought to potentially cause Parkinson's disease. The reason there is such great interest in alpha-synuclein is that it is the major component of Lewy bodies. It is actually the building block of those proteins, those inclusions that were described by Fritz Lewy in 1912.

[Slide]

Alpha-synuclein inclusions are not only

characteristic for Parkinson's disease but a variety of other disorders such as dementia with Lewy body disease and multisystem atrophy, and so these have all been coined synucleinopathies. So, understanding how synuclein leads to neurodegeneration is of really major importance because not only can it impact on potential therapies for Parkinson's disease but these other disorders as well.

[Slide]

I also thought I should mention LRRK2. It is the most common known cause of Parkinson's disease. It probably accounts for about 1 to 7 percent of Parkinson's disease in patients of European origin and, depending upon your ethnicity, it can account for up to 20-40 percent of Parkinson's disease.

It is a very interesting protein. It is a large protein, which I show down here at the bottom of my slide. The take-home message is that it has kinase activity and abnormalities in kinase activity seem to be linked to its ability to cause degeneration of neurons, and the pharmaceutical industry has developed a lot of agents that are specific for kinases.

So, this is really one of the first mechanistic-

based targets that the PD community has had. So, I think we will be seeing a lot of exciting drug developments specifically targeted to LRRK2. Whether they will just treat patients with LRRK2 mutations or be also equally important in sporadic will take time to determine.

[Slide]

Parkin is the second most common cause of Parkinson's disease. As I mentioned earlier, it causes autosomal recessive Parkinson's disease. It is a protein that functions in the garbage disposal system of the cell in which it targets abnormal proteins for degradation by the proteasome which is in essence the garbage disposal of the cell.

Mutations in parkin are thought to gum up that system and lead to the accumulation of toxic proteins. So, strategies aimed at maintaining parkin in a functional state may have also potential therapeutic options.

[Slide]

I just thought I would mention briefly just the other two genes that have been identified. DJ-1 causes early onset of Parkinson's disease. It is relatively benign with long duration. There has been no autopsy material

described to date. It seems to function as a molecular chaperone.

Then, PINK-1 causes early to late onset Parkinson's disease and, again, causes relatively benign disease with a long duration. No autopsy studies are yet available and it is a mitochondrial kinase, again, opening up possibilities of potential drug targets.

[Slide]

My last slide just tries to put all these issues together. I have put in the center of this defects in mitochondrial complex I. That still seems to play a major role in sporadic PD. We hope that the discovery of these genes that we have identified, parkin, PINK-1, DJ-1, LRRK2 and alpha-synuclein, will allow us to develop new and better therapies that will ultimately allow us to not only target familial Parkinson's disease but sporadic Parkinson's disease.

I will end there and open it up to questions. Thank you.

DR. ANDERSON: Thank you, Dr. Dawson. At this point, I have been asked to ask if there are any clarifying questions for Dr. Dawson, and to emphasize that by

clarifying we mean to sort of inquire about a point of fact rather than introduce the issues more generally for discussion that are supposed to come this afternoon. So, are there any clarifying questions for Dr. Dawson?

[No response]

DR. ANDERSON: I have also been told that everyone has to read their name into the record so our tardy members at this point, if you will just state your name and your function on the committee and your expertise, please?

DR. GREEN: Mark Green. I am a clinical professor of neurology in neurology, anesthesiology and dentistry at Columbia University. I am director of headache medicine.

DR. FRANK: Dr. Samuel Frank. I am a movement disorder neurologist at Boston University. I am the consumer representative.

DR. ANDERSON: At this point, we will now proceed with Dr. Perlmutter's presentation.

Neuroimaging of Dopaminergic Neurons:

Evidence for Clinical Utility

[Slide]

DR. PERLMUTTER: Thank you very much and I appreciate the opportunity to come and talk here.

[Slide]

First I would just like to begin with my financial disclosures, although they were in part discussed. These are the places where I receive salary and grant support, and the sources, honoraria in the last two years, and my equity and consulting agreements with industry represent none.

[Slide]

So, let's turn to what the issue is on neuroimaging and use of these scanning agents for clinical diagnosis, particularly focusing on Parkinson's disease and parkinsonism.

First, is it useful? Are they useful for pre-symptomatic diagnosis? What is the evidence? Can it be helpful in differential diagnosis? Is it important or impactful for treatment decisions? Then, can it be useful for disease progression?

[Slide]

Now, we have heard from Dr. Dawson a bit about the pathology. I just want to state really what we are focusing in on in these imaging agents. So, as Dr. Dawson told us, there is loss of the dopaminergic cells in the nigra that project to the striatum, and it is the projection of these

nigrostriatal neurons that is lost in Parkinson's disease and in some other parkinsonian states that we are trying to image here.

[Slide]

There are basically three major strategies for looking at the presynaptic neuron. That is this neuron coming up from the nigra to the striatum. The first agent that was used was fluorodopa which basically reflects the decarboxylase activity which converts to dopamine. The reason that it reflects that is that it converts this neutral molecule to a charged molecule which gets trapped in the brain so you see uptake of radioactivity in areas where there is decarboxylase.

Other agents, and the ones we are talking about today, DaT compounds or DaT markers, are the dopamine transporter here that takes back dopamine from the synapse back into the presynaptic neuron, and there is a whole host of DaT markers.

Finally, more recently, there is the VMAT2 marker, and VMAT2 is the uptake protein that packages or basically takes dopamine and packages it into presynaptic vesicles in the presynaptic neuron.

Using any of these agents is an attempt to really get a handle on the integrity of the nigrostriatal neurons. That is the biology behind it.

[Slide]

Guess what, they all work in that sense. So, this is just an example from a monkey that was given MPTP, we heard about that, in one internal carotid artery, which knocks out the dopamine neurons on that side of the brain.

Here you see the before in two sides with either DTBZ for an L-dopa or a DaT marker, the left and right striatum, and here is afterwards, and you see loss of uptake. So, that is pretty straightforward.

[Slide]

So, let’s address the first issue. How good is this for detecting a defect in this pathway, here, compared to a specialist, a movement disorder specialist or a neurologist, in detecting functional abnormality?

This is actually fairly easy. The answer is it is very good. It really is very good. This is demonstrated. Even if you go to the monkey, it is very good for monkey neurologists because here you take monkeys and you give them various doses of MPTP, and the advantage of doing that is

you can actually go in and count the cells in these monkeys and look at it. Here is before L-dopa but the same is really true with any of the DaT markers or DTBZ. You can identify a defect in that pathway before you can observe any clinical manifestations of degeneration of the nigrostriatal system.

So, basically, you need a lot more degeneration to develop clinical manifestations that are detectable by a physician experienced in this area than you can with the scan. The scan is more sensitive. I don't think there is much question about that.

[Slide]

So, is that useful? That is the question? I can tell you it is extremely useful for research. So, right now and there have been other studies. This is a study done by one of my colleagues, Dr. Racette and myself where we looked at a large group of people with high risk of parkinsonism in this very large, extended Amish family, and by extended I mean 618 members, and there were a bunch of people that weren't quite sure if they were parkinsonian or not, and we wanted to do some genetic linkage analysis to see if we could find a gene in this group.

We took some of these people and we did fluorodopa, and it could have been DaTSCAN, just the same, and compared them to early, never medicated Parkinson's and normals, and we could identify people that had defects that confirmed it in this group that we could not be certain of otherwise. In this group it tells us, you know, that they are likely to have this defect and that could improve our genetic analysis. In fact, it improved the strength of the linkage analysis.

So, does that help for clinical work? I would say that would be extremely useful if we have a drug that will slow the progression, the degeneration, and avoid the development of symptoms and we prove that by identifying that defect in the proper population. In fact, there are studies right now going on, trying to find out who such populations may be, a big study that is being done looking at the people who have abnormal smell sense and then have other manifestations, finding high chance of them having a defect in the nigrostriatal system.

That doesn't prove Parkinson's disease but it does demonstrate that they have a defect in the nigrostriatal system. And, if we had a drug that would prevent the

progression, that could be useful. I am not convinced we have that drug right now but that is for the future.

[Slide]

What about diagnosis? How useful could this be in the differential diagnosis of people who have symptoms that appear to be like Parkinson's disease?

Well, I am going to first talk about what I think is really about the best study, and this was done by Dana Jennings, Ken Merrick and their colleagues. Here is the published stuff and I know they have much longer follow-up and probably have increased the numbers of these subjects but this is what I could find published.

They had 35 people referred to them from community neurologists that had a variety of manifestations with a question of parkinsonism, and these are some of the other conditions that they also had, essential tremor so shaking in both hands, drug-induced parkinsonism, perhaps psychogenic and then primary dystonia.

[Slide]

What they did, and this is now from their paper that they published in 2004, here are the diagnoses of the referring physicians, and what they distinguished was a

parkinsonian syndrome. That is not Parkinson's disease. They make it very clear. This is a parkinsonian syndrome so it could be any number of the parkinsonian conditions that could include progressive supranuclear palsy, multisystem atrophy, a host of other things that are degenerative, as opposed to essential tremor.

What they did, they had these people examined by two different movement disorder experts and they made their diagnoses at intake, and they did the SPECT scan of the DaT maker, in this case beta-CIT. They had two ways of analyzing the data, a visual way of looking at the image or quantifying it, and then they compared it to their gold standard which was truth in this case, which is quite reasonable.

They took this movement disorders expert who remained blinded to the results of the scan, repeated the exam 6 months later, and the diagnosis of that movement disorder blinded person made at 6 months was considered the gold standard. They compared the SPECT scan or the DaT marker scan to the gold standard.

What you see is that there is pretty close agreement. I mean, this is pretty good. The scan is almost

as good as the movement disorders specialist follow-up scan at 6 months. I mean, that is really the bottom line. It is pretty close.

Here you see one person who seems to have a normal scan. The movement disorders expert thinks that he still has degenerative Parkinson's. So, there is one misdiagnosis by the scan. Here would be another one where it would be considered to have a normal scan. The movement disorders expert thought that this was parkinsonism at 6 months.

[Slide]

Here they put together their sensitivity and specificity based upon these 35. Remember, in that 35 there are really only about 10 people that didn't have degenerative parkinsonism. And, in that group of people that didn't have degenerative parkinsonism the largest group was essential tremor.

By and large, most of the studies going forward have tried to see whether there can be a distinction between parkinsonism or parkinsonian syndrome versus essential tremor and how well does it distinguish. I am going to give you a few examples of that.

I also want to point out, by the way, that the

slides that I am showing you are a little different from what was handed out in your packet because I changed it around just a little bit. I found a mistake that I had made and I corrected that. So, I just want to point that out.

[Slide]

So, first let's look at an older study from 2005. This was retrospective and it is relatively small, with 13 subjects. They went back, and these are people with asymmetric essential tremor or asymmetric postural tremor. As a movement disorder neurologist I actually run a section of movement disorders at Washington University where we see more than 2,000 people with Parkinson's disease.

In this group you have people with asymmetry, and asymmetry is one of those clues of being Parkinson's disease. These are people that have a combination of either postural tremor, which is more characteristic of essential tremor but it is asymmetric. They found in these people, if they waited long enough and they had now tremor for more than 10 years and resting tremor for at least 2.5 years, that all of them subsequently developed a parkinsonian syndrome.

They went back and looked at 5 of those people who

had DaTSCANs with beta-CIT in that particular case, and they were suggestive of a defect. So, that was consistent. But, also, 5 of the people who were tested for dopaminergic response, in other words, give them a dose of DOPA and see if they get betterB-that also was a good test.

So, this was kind of interesting data. It is not really very controlled in any way. It is a retrospective review in the sense of just peeking at it.

[Slide]

Then there was a bigger study now looking at 61 people with various kinds of tremor. Here we have either rest tremor, mixed rest and postural tremor or postural tremor and, again, relatively asymmetric tremor. They put them into three groups and in each of these groups everybody who had a normal scan, in other words no evidence of nigrostriatal defect on the DaTSCAN, none of those people in follow-up, and this is follow-up for a little bit more than 2 years, had evidence of parkinsonism.

So, it seems to be that if the scan can be normal that would exclude parkinsonism in some of these people where it might be unclear. A little different from what we saw in the previous but smaller study.

However, if you look at the abnormal scans, in the abnormal 16, 12 of these went on to develop Parkinson's. In this group 60 percent did and 50 percent in these relatively small groups. So, within 2 years and a little bit longer this doesn't seem to necessarily equate with the abnormality on the DaTSCAN, although longer follow-up may give better concordance.

[Slide]

Another study, now a much bigger study looking at another SPECT agent, I believe this is the one in this application, looked at a large number of people and here they classified these people clinically. They classified them as either idiopathic Parkinson's disease, regular Parkinson's disease, one of the other parkinsonian syndromes, and that is where I am talking about with multisystem atrophy, progressive supranuclear palsy, vascular Parkinson's, essential tremor or a drug-induced Parkinson's.

You can see that the number here becomes very small. The number in each group is down here. The follow-up in this case was an average of 1.5 years.

Here what the scan revealed is a pretty clear

distinction between regular Parkinson's disease and the other parkinsonian syndromes as a group from essential tremor. That is a pretty good distinction here, not entirely but pretty good. But between the types of parkinsonisms there was absolutely no distinction at all.

How does that matter? Well, if you want to figure out what to do for these people that is a big issue and we are going to come back to that in a minute.

[Slide]

So, the question then becomes if there is an abnormal scan-Bthe last few slides would suggest that if there is an abnormal scan in somebody with essential tremor or Parkinson-like syndrome, that would suggest that they are going to have a parkinsonian syndrome rather than just essential tremor alone.

But what about if there is a normal scan? That first study I showed you of 61 people suggested that if it is a normal scan, well, they are pretty free.

Well, let's look at the value in this study where they looked at the negative predictive value. This was also retrospective so it is limited. They selected these 44 people with negative scans or normal DaTSCANs from 196

people referred that had scans. Of these 44, 36 were appropriately classified as non-degenerative, as one would anticipate. But 80 of these turned out to have degenerative Parkinson's of one kind or another.

So, now the question is does a negative scan mean that there is no parkinsonism? At least according to this study it would be suggestive that there is a risk that it may not. Although the bulk were correct, there is still an error rate here.

[Slide]

Furthermore, another study suggested that there may be an age dependence of that specificity. Here what they did, they had 177 people and they looked at these various groups, so Parkinson's disease; the other parkinsonian syndromes; diffuse Lewy body disease; vascular Parkinson's; this is mediation-induced Parkinson's; this is dystonia; essential tremor; psychogenic Parkinson's which in their case really were controls because in Helsinki they weren't permitted to scan normals at that point and this was essentially their control group.

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What they found is when they looked at the

specificity across all of the groups it was reasonably high, but if they compared it to people under 55 versus people over 55 the specificity dramatically dropped off with older subjects because the risk of these other conditions was higher.

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So, here we have an issue of how good and how much added value is there for doing one of these scans. The gold standard for all these studies so far has been follow-up by a movement disorders specialist or a neurologist. So, how much is the difference? How much is the cost?

Well, if the cost-Band there may be more current estimates of the cost of a DaTSCAN, but I put it here at $1,500. The real question from a clinical perspective is--well, there could be two questions, to be fair about it. One is what is the diagnosis for prognosis? That would be can you help somebody with a prognosis? The second question is how does it impact what we are going to do to help that person right away?

If a person has symptoms and you are not sure if it is a parkinsonian syndrome or not, and they have symptoms that are bothering them, then what I think you need to do is

give them medication to see if it is going to help. And, the question in my mind is does this scan help make that decision? In other words, seeing a normal scan, does it mean you don't need to give medicine? If you have an abnormal scan, do you need to give medicine? And, what is the cost difference there?

I would suggest a very liberal estimate of cost of carbidopa/levodopa for a month to test it is about that much. That is the SPECT scan. And, I think the cost benefit is marginal.

[Slide]

Now, that is not what everybody says or has published, to be fair about it. So, there is a nice study here by Antonini in movement disorders that goes through a fairly complex cost-benefit analysis demonstrating, from their perspective, the benefit of doing the scan. But I would suggest some of their assumptions are not consistent with what a lot of us do in practice.

For example, some of their assumptions include giving medication for 2 years before deciding whether it is going to work or not; and include also multiple visits to the doctor to try to sort this out; include hospitalization

in case there are side effects from medication, like psychosis or severe dyskinesia, which I think is highly unlikely in the first year or two of these people's disorder when you are trying to help determine something that occurs down the road.

So, I think a lot of the assumptions in those cost-benefit analyses are flawed, and I think that applies to both of these. Other people looking at that have published such concerns about those cost-benefit analyses. So, I would think the cost benefit is questionable and something to discuss.

[Slide]

All right, what about disease progression? Can it help with disease progression? So, if we take, on the basis of it, what we want to know from disease progression is the number of these nigrostriatal neurons and how many are surviving, does it measure that? That may not be the right question, but that is the basic assumption here.

I would think on the face of it this is true for fluorodopa, it is true for DaT markers, it is true for DTBZ, the big data is very helpful. You know, you get a normal subject; you get a severe; there is a big difference; and

mild people seem to be in between. So, it seems like there is this rank order distinction and I think that is pretty consistent.

[Slide]

However, there are some problems. This is an example of one study where the DaTSCAN was attempted to be used as a biomarker of disease progression. This is the L-dopa study where people without treatment for their Parkinson's disease, clinically diagnosed, were given three different doses of daily L-dopa or placebo, followed for 9 months, then taken off the medicines, washed out, and then they looked at their clinical effect or severity as measured by a clinical rating scale called the UPDRS. That is after presumed enough time to wash out the drug effects.

One caveat here is the number of people who washed out 1 week, and then 2 weeks gets to be relatively small, but there is no additional symptomatic change from 1 to 2 weeks. Certainly a change from taking drug to stopping the drug, but at that point it is really washed out. Lower on this scale means doing better; higher is worse.

What they found is that the people taking placebo seemed to be worse than those people taking drug. That is

not relevant yet. But then what was done is a subset of these subjects had DaTSCANs both at the beginning and at the end of the study.

Let me just go back. So, this would suggest that, if anything, the people taking L-dopa did better than the people taking placebo. DaTSCAN with beta-CIT in this particular caseB-this is the best case scenario, when you remove the people at the beginning of the study who had normal scans, thinking they were misdiagnoses, a reasonable thing, then you look at the change in the DaTSCAN over time and the people taking the highest dose of L-dopa had the greatest change as if they were progressing more. So, DaTSCAN is telling us it has progressed more; clinical measure says it has progressed less.

Which is right? Well, the truth is we don't know. You know, the clinical measures may be flawed for severity. The DaTSCAN may be flawed for severity. Let's look at it.

[Slide]

There is another example, just quickly, on this one. This is an example of where transplantation, in this case fetal transplantation, was done in people with severe Parkinson's and fluorodopa was used as an endpoint or

biomarker of disease progression.

They took people and made a hole in their head and put in fetal transplants on both sides or they took people, made a hole in their head and didn't put in fetal transplants so they did it blinded. They did that in Colorado and they evaluated them in New York. So, it was, indeed, a blinded evaluation.

You look at the fluorodopa uptake as a measure of these nigrostriatal neurons and you see before surgery and after surgery. This looks like there is an improvement. This is the putamen back here so there is an improvement where the transplants are done. Here is after sham surgery; no improvement. This would suggest that, gosh, this thing is showing us the benefit of the surgery.

[Slide]

However, people that had benefit were all under 60 and people who didn't have benefit were over 60 and their scans showed the same thing. So, the scan response in that case wasn't specific.

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In addition, a couple of patients had died in that study from other causes, and when they went and looked at

their brain and counted the number of residual neurons or grown neurons based upon tyrosine hydroxylase staining they could see that there was a benefit on one side or the other. This is just showing us the age dependence. Here is the staining. One side had a big change. The other side didn't have so much change. But the PET showed the same increase on both sides. So, again, the specificity it called into question.

[Slide]

So, how do we understand this? What is the real evidence that any of these markers reflect nigrostriatal neurons? That is the question.

Here is one study that was reported, and probably the first one, in monkeys where they gave them MPTP and did fluorodopa PET and then killed the animals and measured tyrosine hydroxylase immunostaining of the cells on both sides of the striatum. Okay? Very high R value; good correlation. But we would know from basic statistics that this is a totally invalid correlation because you don't have a good distribution of data here. You have a cluster here and a cluster there.

So, what I think we are really seeing is a rank

order distinction between affected and unaffected. So, I don't think that is really a valid assessment.

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There was, in fact, a much better study done with 17 monkeys. This was done at UCLA. They gave animals relatively low doses of MPTP so they only had a relatively mild lesion. The reason that was done is because when you do a more severe lesion the counting statistics are much worse and it is harder to make a good estimate of the numbers. So, this would be an optimal situation. Then they killed the animals and they took the brains out and they did actually a beautiful stereological counting study of tyrosine hydroxylase. In other words, they counted the dopaminergic cells in a proper fashion.

This study is frequently pointed to as giving evidence for the relationship of fluorodopa to number of cells because they have this p value, 0.05. But, in fact, that p value doesn't refer to the relationship between counts and fluorodopa. It just refers to these two different lines being different and, in fact, they found no relationship between cell counts and fluorodopa uptake.

[Slide]

What about the DaT marker? So, the best data that I could find looking at DaT marker and SPECT analysis, unfortunately, is from a rodent study. This is the best one that I could find. Here they took two groups of mice, one treated with 6-hydroxydopamine, which also goes in and destroys dopamine neurons, or MPTP. The results are basically the same.

Here is what they found, and this is very interesting. They used a fancy SPECT to do this. They found actually a very good correlation between the DaT marker uptake and striatal dopamine levels. That was a pretty high correlation.

However, if you look at the distinction when they compared to number of nigral neurons measured with tyrosine hydroxylase immunostaining, again, they report a good correlation but we see, just like before, that they made the same error. This is clustered data and there is no demonstrable correlation here. There is just a rank order difference between affected and non-affected, and if you look within the group there is no correlation within this.

So, what do we take from this? The best data of the DaT measure would suggest it does not reflect the number

of nigrostriatal neurons; may reflect DaT protein but not the number of nigrostriatal neurons; but it may reflect in a very reasonable way striatal dopamine. So, it depends on what you want to know.

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So in summary, what is its clinical utility from my perspective? Pre-symptomatic diagnosis, no question. I think these scans are more sensitive than our examination of a person. Does that have clinical utility today? I don't think so, not until we have something that can slow disease progression.

Differential diagnosis, I think the appropriate clinical question is does somebody respond to DOPA if they have an unclear syndrome? And, I don't think the data is sufficiently compelling that this would alter how I would treat somebody. So treatment decisions, I find it not necessary.

For disease progression I think it is still unclear, and I think that needs to be sorted out and that is a matter of research. Thank you very much.

Clarifying Questions

DR. ANDERSON: At this point, do we have any

clarifying questions for our presenter? Yes, Dr. Tatum?

DR. TATUM: I have one question. You talk about the biomarker part, and I understand what you are saying, what about for the purposes for the development of new drugs or new therapies where it would be for patient selection, enrichment, stratification?

DR. PERLMUTTER: Yes, that is a very good point. Let me address two points here. First the issue about patient selection for a study, I think if we are trying to do a study in early Parkinson's where the chance of misdiagnosis is greater and there is pressure to enroll people in a study, this is probably a way of enriching the population and making it more homogeneous.

Then, on the other end, it would mean that the application of the drug, whichever is proven, would require that scan to be an appropriate person for that. So, I think that is possible.

For determining disease progression in a study, I think that remains unclear. But for patient selection in research I think that is very potentially very usable.

DR. ANDERSON: Yes, Dr. Mattrey?

DR. MATTREY: Clarification for me, not being a

neurologist, you described that study where dopamine was given. I forget exactly how the scenario went where you had the 600 mg, etc. Is there any evidence that externally given dopamine interferes with the process that could impact the imaging findings?

DR. PERLMUTTER: The effects of an intervention on the markers is a very major concern for everybody doing these kinds of studies. So, I think probably the best data is it probably doesn't make that much difference on these DaT markers but different kinds of therapeutic interventions may make a difference and may lose the specificity, and it very much depends upon the intervention.

The challenge in these kinds of studies is that frequently they are pilot studies with a small N to try to determine whether there is an effect on the imaging. Then when you ramp up for a big study and the N is much higher you may, in fact, detect a change and now it is unclear and sometimes it turns out that there was an effect. But in this case I think there is reasonable data to suggest that it is probably not a factor.

DR. ANDERSON: Dr. Royal?

DR. ROYAL: The monkey study that you showed where

these scans were abnormal before the monkeys became symptomatic, there was some quantification of the scan results. How important is quantification in order to measure DaT markers?

DR. PERLMUTTER: That was addressed actually by Dana Jennings and Ken Merrick in their original study. They had a visual analysis and a quantitative analysis, and I think their quantitative analysis was a little better than their visual analysis but the visual analysis wasn't bad.

DR. ANDERSON: Dr. Kieburtz?

DR. KIEBURTZ: On the last slide when you said differential diagnosis, I just want to make sure I understand, you mean as opposed to a pharmacologic challenge when you say Anot needed?@ Because the prior discussion seemed to be as opposed to an L-dopa challenge.

DR. PERLMUTTER: So, the question is just to clarify what I was trying to say.

DR. KIEBURTZ: Yes.

DR. PERLMUTTER: What I was trying to say is that if I am trying to decide what to do with a patient and if it is unclear to me if this is a little essential tremor or there are some parkinsonian features and I am trying to

figure it out, and this is bothering this person and they are having some disability, then would I get a SPECT scan for a DaT marker to help me decide what to do or would I say it doesn't matter what the SPECT scan is going to do I am going to give this person medication and see if they get better. That is my point because that is really the key point, and there were enough false negatives in some of these other studies that it would not prevent me from giving them the medication anyway, and I think giving the medication is more directly addressing the question and I think it is a lot cheaper.

DR. ANDERSON: Dr. Katz?

DR. KATZ: Are there parkinsonian syndromes that don't respond to L-dopa so that your test dose of L-dopa might not be able to help you make the diagnosis?

DR. PERLMUTTER: So, one of the key things I think most everybody agrees on is that when I use the term parkinsonism that includes Parkinson's disease. Predominantly what Ted Dawson was talking about is a DOPA-responsive condition. There are other parkinsonisms, progressive, supranuclear palsy, multisystem atrophy, etc. that, in fact, may have modest response to DOPA initially

but in general it is not sustained and it is not nearly as good.

I think everybody agrees that these DaTSCANs or any of these scans do not distinguish those conditions, don't distinguish Parkinson's disease from these less responsive DOPA conditions. Does that answer your question?

DR. KATZ: But could the DaTSCAN or some other scan help to differentiate those parkinsonian symptoms that don't respond to L-dopa treatment from other clinical symptoms that might be confused with those parkinsonian symptoms but they, themselves, are not parkinsonian? In other words, can it distinguish diagnoses where the treatment with L-dopa might not?

DR. PERLMUTTER: Let me see if I get this correct. So, for example, if there is essential tremor, which is not really a parkinsonian condition but if it is asymmetric it might kind of look like that, and the DaTSCAN would be normal whereas there could be PSP or progressive supranuclear palsy, a degenerative scan which may show an abnormal scan also is not responsive to L-dopa in that case.

Now, the point is that idiopathic Parkinson's L-dopa response is much more common than those others, and

those other conditions sometimes have modest response so I am not sure that that would make a difference in what you really do for the person. Again, I would still try L-dopa because you can't be certain about those.

DR. ANDERSON: So, this completes the invited presentations and at this point we are going to move to the industry presentation component of the meeting which will be broken into two parts by a break, but at this point we will move to Dr. Brooks to begin his introduction.

Industry Presentation

Introduction

DR. BROOKS: Good morning, everyone. Dr. Anderson and members of the PCNS, Dr. Katz, Dr. Rieves and those of the FDA, advisory committee and guests.

My name is David Brooks. I am a neurologist. I work at Imperial College in London. I run a busy movement disorder clinic there and I also work part-time for GE Healthcare. So, that is my conflict.

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I would like to thank the committee on behalf of GE Healthcare for giving us a forum to present the benefit/risk profile of ioflupane, also known as DatSCAN,

which is a novel imaging agent which we propose for use in visualization of dopamine transporter distribution in the striata in patients.

At the moment there are no approved products of this nature available in the USA though this product is widely available and used in Europe. But I believe, perhaps in contrast to the last speaker, that when we have finished our presentation you will see that this could be a very useful adjunct to clinical diagnosis and management of patients by providing a rationale for either withdrawing or using dopaminergic agents in movement disorders and certain dementia syndromes.

So, we are going to share with you relevant data from key preclinical and clinical studies to provide objective evidence for such a claim.

So, the indication that we are looking for is different from the one that you will see in the briefing package. We had a dialogue with the FDA and we decided that we would move for the indication that DaTSCAN is indicated for visualization of dopamine transporter distribution within the striata using single photon computed emission tomography, known more generally as SPECT, in patients who

are presenting with symptoms or signs that might be suggestive of a dopaminergic deficiency disorder, and this could include a number of parkinsonian syndromes.

We are not proposing that this is a diagnostic agent and can discriminate between these parkinsonian syndromes. We are simply looking to see if there is a dopamine deficiency state or not.

In Alzheimer's disease the dopamine system is intact, but in the second most common dementia, which is dementia with Lewy bodies, the Lewy bodies that you see in Parkinson's disease and that was so beautifully shown by Ted Dawson, there is a dopamine deficit and so one is, in principle, able to discriminate these two types of dementia using a DaT transporter marker like DaTSCAN.

Since we are looking for a detection claim here as opposed to a diagnostic claim, the regulatory requirements are rather different, as I am sure you realize.

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So, the key points that we are going to emphasize during the presentations that follow are that, first, by binding to DaT protein, DaTSCAN enables robust and reliable visualization of DaT transporter distribution within the

striatum and it is very sensitive to detecting abnormalities of that distribution.

It has been used in over 200,000 subjects so far and it is extremely safe and well tolerated in our experience. And, we would propose that visualizing DaT distribution is useful as a diagnostic adjunct. As I say, we are not claiming it is a diagnostic agent but we are claiming it can be very helpful in providing a rationale for whether dopaminergic strategies should be used or not used in patient groups, particularly those with movement disorders and dementias.

[Slide]

So, the presentation will go as follows: I am going to say some words about the DaT transporter biology and, indeed, how ioflupane, which is another name for DaTSCAN, binds to the dopamine transporter. Then I am going to introduce my colleague, Dr. Sherwin, who will talk about the clinical development program to date which has taken place around DaTSCAN and he will demonstrate the efficacy and safety of this agent in clinical trials.

We will then take a short, 15-minute break and Donald Grosset, who is a neurologist who works in Glasgow,

in Scotland and has a big movement disorder service and is very experienced in the use of DaTSCAN, will explain how he uses it in his clinical practice and whether he finds it valuable to have access to this agent in practice.

That presentation will be followed by Mark Stacy, who is a movement disorder specialist at Duke University Medical Center, and he will discuss the rationale for making DaTSCAN available to movement disorder and dementia specialists in the USA. Finally, I will wrap up with some concluding statements.

[Slide]

So, DaTSCAN is an intravenous radiopharmaceutical and it is designed for use with SPECT imaging. It has iodine-123 as the radioisotope attached to it. Iodine-123 is a gamma emitter and it has a half-life of around 13 hours. It very sensitively detects and images DaT transporters in the striata of the brain.

It has been in use and approved in Europe now for about 10 years, and it is currently in use in 32 countries in Europe. As I said, over 200,000 patients have been exposed to this agent without any safety issues that we are aware of.

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It is provided in a vial as a ready-to-inject solution and it is only available on prescription, and that would be our intention in the USA.

So, ioflupane is a small organic molecule. It has a cocaine-like structure and so, in principle, it could have the stimulatory and addictive properties of cocaine but the dose that we inject is less than 1 mcg in practice and it is sub-pharmacological. To date, we have observed no stimulatory properties of this agent. In fact, you would probably have to inject several thousand vials to get a stimulatory effect from the drug.

It lasts for 13 hours so that it can be widely distributed from one center, and the dose we recommend injecting is between 3-5 mCi, and we recommend that because it gives good signal to noise in the images but the radiation dosimetry around 4 mCi is well within the recommended range by radiation licensing authorities.

[Slide]

How does DaTSCAN or ioflupane actually work? Well, this is a cartoon of the presynaptic dopamine terminal in the upper part of the image. Then we have a postsynaptic

striatal neuron with dopamine receptors D1 and D2 sites in the bottom part of the cartoon.

What you can see is that the dopamine neuron contain vesicles, these blue spheres, and it contains dopamine, the little red spheres, within the vesicles. And, dopamine is released into the synaptic cleft where it acts on the postsynaptic receptors, and then dopamine is inactivated by being taken back up into the presynaptic terminal by dopamine transporters, which are shown here as green cylinders in the cartoon.

You can see that ioflupane and, indeed, cocaine derivatives, bind to these transporters. They are not at the same site as the site that takes up and re-processes dopamine into the neuron.

[Slide]

Here we see two autoradiograms of a mouse and, indeed, Joel Perlmutter alluded to this study in his presentation. On the left side you see an autoradiogram that is stained with an antibody to the DaT transporter and you can see the DaT binding in the striatum bilaterally as the dark grey area in that autoradiogram.

In the right image the mouse is being treated for

5 days with MPTP, a dopamine toxin, and you see that all DaT transporter binding has been eliminated in that mouse.

[Slide]

One can image these mice now, which is a lot cheaper than monkeys, using high resolution SPECT systems. Here you see 2 SPECT images, 1 in an intact mouse and 1 in a mouse that has been treated for 5 days with MPTP. The ellipse contains the striata which shows DaT binding very strongly in the intact mouse which correlated with the subsequent autoradiogram. In the second image MPTP has destroyed all the specific DaT binding but you can see non-specific uptake of ioflupane into the orbits. You see there, in the Harderian glands that the DaTSCAN is evident and it is not affected by MPTP poisoning.

So, in this study, again as I think Joel showed, there was strong correlation between in vivo ioflupane binding in these mice before sacrifice and then after sacrifice you can see the that level of DaT binding revealed by immunoreactivity correlated well with the previous in vivo ioflupane binding, confirming that ioflupane is binding to the DaT transporter in vivo in these animals.

[Slide]

So, ioflupane binds DaT. It has very high affinity. It is sub-nanomolar and since DaT is concentrated primarily in the striatum, though found at low levels in other brain areas, it is primarily the striatal signal one sees with SPECT scans with DaTSCAN and one, in fact, can show if one takes autoradiographs of human brain slices that, again, DaTSCAN is selectively bound in the striata. It is inhibited by competitors to the DaT transporter like mazindol and methylphenidate. It does bind to other monoamine transporters but it has lower affinity than the DaT transporter.

[Slide]

Here for example, we have on the right image a brain atlas, a transaxial slice at the level of the basal ganglia, and you can see that the caudate and putamen have been colored blue in this atlas to make them prominent.

On the left-hand side one can see an autoradiograph of a human postmortem slice at the level of the basal ganglia and here they have used iodine-123-labeled DaTSCAN or ioflupane and you can see that the signal is very much concentrated in the caudate and the putamen. This gives the signal a sort of cashew nut or semicolon-like

appearance when one sees in vivo scans with DaTSCAN.

[Slide]

This would be a typical normal study. Here you see the so-called cashew nut-like appearance. The heads of the caudate are shown at the top of the image on the left and one sees the anterior and posterior dorsal putamen as the tail to the heads of the caudate. This is a typical symmetrical image of a normal subject or, indeed, dystonic or essential tremor patient where there is no dopaminergic deficit.

[Slide]

In contrast, if one looks at a patient who has a deficit of their dopaminergic function--it could be one of the parkinsonian syndromes, it could be dementia with Lewy bodies--then one sees a classic pattern of abnormality. The putamens are very much targeted by these pathologies. The heads of the caudate are relatively spared and often the signal is asymmetrically involved. If one sees the pattern on the right, then one can be confident that one is dealing with a degenerative disorder involving the dopamine system and there would be, therefore, a rationale for considering either dopaminergic agents if it is a parkinsonian case or

withholding them if it is dementia with Lewy bodies, which we will discuss later.

[Slide]

There is abundant evidence that DaT transporters are involved in degenerative disorders. In Lewy body dementia, the second most common dementia, one finds up to a 50 percent loss of nigrostriatal neurons in autopsy series and a corresponding loss of DaT transporter binding in the striatum.

In the parkinsonian disorders which would include Parkinson's disease, supranuclear palsy, multisystem atrophy and others, one sees again around a 60, often 70 percent loss of nigrostriatal neurons at end stage and, again, a similar loss of striatal transporters, primarily in the putamen area.

Indeed, there have been studies correlating cell counts in the nigra with loss of DaT transporters in the striatum. We would argue, in fact, that it doesn't really matter what the nigral cell counts are. I mean, a big issue was made of it but what is really critical in determining a patient's status clinically is how the terminals are performing in the striatum and not how many cell bodies you

have in your nigra.

But that aside, there was a study by Piggott showing very nicely in parkinsonian autopsy specimens that there was a significant correlation between loss of DaT binding with loss of 123-ioflupane and nigral cell counts in the nigra.

[Slide]

That concludes my presentation on the biology of the DaT transporter and its interaction with DaTSCAN or ioflupane and I would now like to ask my colleague, Dr. Sherwin, to come and review the clinical development program and the efficacy and safety of DaTSCAN in patient studies.

Clinical Development Program

DR. SHERWIN: Thank you, Dr. Brooks.

[Slide]

First I will present an overview of the DaTSCAN clinical development program. Then I will present some results from the Phase 1 and 2 studies, and finally I will give details on four key studies which support efficacy.

The program began in 1996 with a study in parkinsonian patients. In 2000 DaTSCAN met its first regulatory milestone, receiving approval for use in

parkinsonian patients in Europe. DaTSCAN was then studied in patients with DLB, dementia with Lewy bodies. In 2006 it was approved for use in DLB patients. In March of this year GE Healthcare filed a new drug application to obtain approval of DaTSCAN in the United States for a detection indication.

The European approvals were for diagnostic claims linked to parkinsonian syndromes and DLB. We changed to a detection indication for the US because it better reflects what that scan actually does.

Between the approval in Europe and initiating the US filing process, we developed our US manufacturing capacity for iodine-123. The US NDA includes extensive data on the safety and efficacy of DaTSCAN.

[Slide]

The Phase 1 and 2 studies, shown in green, provided information on safety, biodistribution, dosimetry and the appropriate time to begin imaging after injection.

The first Phase 3 study, in blue, supported approval of DaTSCAN in parkinsonian patients in 2000. The second Phase 3 study was conducted as a post-approval commitment in support of the European approval.

The first DLB study, in red, supported approval for DLB in 2006. The second DLB study, notable for its duration, is an ongoing study initiated by Dr. Zuzana Walker of University College, London.

Dr. Walker is here today and is available to answer questions. She obtained DaTSCAN images in 80 subjects between 1996 to 1999 and is following them until death when autopsy results are obtained.

[Slide]

Of the clinical studies submitted to the FDA for review, the first was the Phase 1 study of dosimetry and biodistribution. The study was a Phase 1 study, FP-1, in 12 healthy human volunteers, 6 women and 6 men. They received DaTSCAN and were imaged at 8 time points between 10 minutes and 48 hours after injection. Brain activity was 7 percent of the injected dose at 10 minutes; 3 percent at 5 hours; and 1.6 percent at 48 hours.

Striatal activity was approximately 30 percent of the whole brain activity. By 48 hours 60 percent of the dose had been excreted in the urine, and it was estimated that 14 percent was eliminated in feces. For an average 70 kg individual the effective radiation dose is 4 mSv. To put

this number into perspective, it is about the dose of radiation one would receive during a chest CT examination and is well within the range of common nuclear medicine procedures.

[Slide]

The next study looked at the time window for imaging in patients with Parkinson's disease as well as healthy subjects. This Phase 2 study, FP-2, demonstrated the time course of striatal activity. The upper curve is in healthy controls and the lower curve is in patients with Parkinson's disease.

There are two prominent findings here. The first is the stability of striatal activity in both groups between 3 and 6 hours after injection. This is the region enclosed by the box.

The other is the large difference in striatal activity between healthy controls and patients with Parkinson's disease. The reduced activity in the Parkinson's patients indicates reduced binding of DaTSCAN and is consistent with the known loss of nigrostriatal neurons and DaT which both occur in Parkinson's disease.

[Slide]

There are four studies in the NDA that support the efficacy of DaTSCAN in detecting abnormal DaT distribution. The first study is the Walker study which focused on dementia patients. The strength of this study is the use of autopsy as the truth standard to assess the efficacy of DaTSCAN.

The other study in dementia patients, 301, was sponsored by GE Healthcare. It used expert clinical diagnosis based on consensus criteria previously correlated with autopsy.

The last two studies were GE studies conducted in subjects with symptoms of movement disorders. Both used as the standard of truth expert clinical diagnoses based on consensus criteria that had been previously correlated with autopsy.

[Slide]

Each of these four studies had the same basic design. Each subject was given an intravenous injection of DaTSCAN and underwent SPECT imaging starting between 3 and 6 hours after injection. On the left is a picture of a subject in a SPECT scanner to give you an idea of what the imaging process looks like.

Imaging data were collected over 30 to 45 minutes and then processed by computer. The imagerist then reviewed each image and categorized it as normal or abnormal. Normal images, such as the one shown on the upper half of the slide, indicated normal DaT distribution in both striata. The abnormal images, such as the one in the lower half of the slide, indicated abnormal DaT distribution in one or both striata.

In both cases the image categorization was compared to a standard of truth. The standard of truth is an independent test intended to give the true state of the patient. In the studies I will discuss the standard of truth was either autopsy or expert clinical diagnosis.

When both the standard of truth and the DaTSCAN image assessment indicated abnormal DaT distribution then the DaTSCAN image was classified as a true positive. Alternatively, DaTSCAN images could have been categorized as a true negative, a false positive or a false negative depending on the outcome of comparison to the standard of truth. The numbers of each image classification were then used to calculate sensitivity and specificity as a performance characteristic using the standard formulas for

sensitivity and specificity.

[Slide]

The important points here are that sensitivity is primarily determined by the number of false positives, that is, under diagnosis. And, specificity is primarily influenced by the number of false positives or over-diagnosis.

[Slide]

Now I will digress for a moment to present DLB because DLB is not only the more challenging diagnosis but is not as well known as Parkinson's disease. DLB was first described in 1984 when pathologists noted cortical Lewy bodies in patients with dementia at autopsy. Retrospective examination of case notes reviewed a clinical picture distinct from Alzheimer's disease. Consensus diagnostic criteria for this novel clinical entity were developed and first published in 1996.

Many patients diagnosed clinically with Alzheimer's disease are found at autopsy to actually have DLB. It affects 5 percent of non-institutionalized adults over the age of 85 and approximately 20 percent of all dementia patients.

The clinical diagnosis of DLB requires the presence of at least two of the core features shown here, namely, fluctuating cognition and levels of consciousness, recurrent visual hallucinations and spontaneous parkinsonism.

One important reason to recognize DLB is that DLB patients respond differently to neuroleptic drugs which are frequently administered for symptoms such as hallucinations. Administration of neuroleptics to DLB patients may result in a severe drug reaction in about half the patients. This reaction has been reported to be associated with increased mortality. Recognition of DLB is, thus, important in order to make appropriate management decisions. The ongoing Walker study is using definitive standard of truth for DLB, autopsy.

[Slide]

The objective of the Walker study is to investigate the striatal dopaminergic system of patients clinically diagnosed with DLB. Starting in 1996, 80 subjects were imaged with DaTSCAN and are being followed until death. Results are periodically published as data accumulate.

The primary endpoint is the image interpretation as positive or negative based on the consensus of 3 readers who are blinded. The standard of truth is autopsy conducted by an independent group at the University of New Castle who are blinded to DaTSCAN results. As of July of this year, GE has full data including autopsy results for 27 subjects.

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Of the 80 enrolled subjects, 27 have autopsy data available. The initial clinical diagnoses of the 80 enrolled subjects were 27 DLB, 19 Parkinson's, 17 Alzheimer's, 1 corticobasal degeneration and 16 healthy controls. Of the 27 autopsy subjects, there were clinical diagnoses at baseline of 14 DLB, 4 Parkinson's, 7 Alzheimer's, 1 corticobasal degeneration and 1 healthy control.

For each of the 27 we have a clinical diagnosis, a visual interpretation of the DaTSCAN image and an autopsy diagnosis. This enables us to compare both DaTSCAN and clinical diagnosis to autopsy to determine their accuracy. The autopsy results support the accuracy of DaTSCAN.

[Slide]

Of the 27 autopsied subjects, there were 13

subjects with autopsy diagnoses consistent with nigrostriatal pathology and loss of DaT; 9 with DLB; 3 with Parkinson's disease. One was a healthy control subject who had autopsy findings of Alzheimer's but who also had a striatal infarct.

Of these 13, 11 had DaTSCAN images that were read as abnormal, giving an agreement rate of 85 percent. This represents the sensitivity or true positive rate for DaTSCAN images.

The remaining 14 subjects were found to have non-nigrostriatal pathology that was not consistent with extensive loss of DaT. Ten had Alzheimer's disease; 2 had frontotemporal dementia; 1 had corticobasal degeneration and 1 had no specific diagnosis. Twelve of these 14 subjects had DaTSCAN images that were read as normal, giving an agreement rate of 86 percent. This represents the specificity of a true negative rate of the DaTSCAN images.

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This is a graphical representation of the results. The left graph shows sensitivity for DaTSCAN as the left bar and clinical diagnosis as the right bar. Both had sensitivity of 85 percent.

The right graph shows specificity for DaTSCAN as the left bar and clinical diagnosis as the right bar. DaTSCAN had a specificity of 86 percent and baseline clinical diagnosis had a specificity of 50 percent.

Now, specificity is mainly determined by the number of false positives and 100 minus the specificity gives the false positive rate. The specificity results indicate that the clinical diagnosis had a 50 percent false-positive rate, suggesting that the physician over-called the diagnosis of DLB in those cases. On the other hand, DaTSCAN had false positives in only 14 percent of subjects.

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So, in the Walker study a DaTSCAN visualized abnormal DaT distribution was in 85 percent of subjects who had autopsy findings consistent with reduced DaT distribution. It also visualized normal DaT distribution in 86 percent of the subjects who did not have autopsy evidence of reduced DaT distribution. These data support the proposed indication.

The results of this study provide compelling evidence of the accuracy of DaTSCAN because of the use of autopsy as the standard of truth. Nevertheless, the other

three DaTSCAN studies also provide strong evidence of the efficacy of DaTSCAN.

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In these studies expert clinical diagnosis was the standard of truth for DaTSCAN imaging rather than autopsy findings. Clinical diagnosis is an imperfect standard. It doesn't have 100 percent sensitivity and specificity. In fact, that is the reason we are trying to get approval of DaTSCAN to provide an additional useful tool for evaluating patients.

Although expert clinical diagnosis is imperfect, autopsy studies show it is often correct in diagnosing PD and DLB but may be weaker at excluding those conditions. The sensitivity and specificity results of our studies represent another means, beyond direct demonstration of binding in nonclinical studies or human autopsy results, for estimating how well DaTSCAN performs. In addition, these studies provide information on the consistency of image evaluation across readers, as well as intra-reader reproducibility.

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In order to submit the results to FDA it was

necessary to generate study reports to US standards from the European studies. First we submitted the data in electronic format in accordance with FDA preference. This allows independent analysis of the data.

The original data were converted to the SDTM format. SDTM stands for study data tabulation model and it is an industry standard. Then we reran analyses, tables and figures using the SDTM formatted data which allowed verification of the original study conclusions. For clarity and preciseness, we wrote new study reports to reflect the updated analyses rather than amending the original reports. However, we provided all of the original study reports to FDA for their reference.

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In the new reports we restated study objectives from diagnostic accuracy to accuracy of detection of striatal dopaminergic deficits, our term for abnormal DaT distribution. This better reflects what DaTSCAN actually does as a diagnostic adjunct.

Although the objectives were restated, there were no changes to the fundamental study designs. Patients received DaTSCAN and were imaged. Images were assessed as

normal or abnormal. Image assessments were compared to a standard of truth and sensitivity and specificity were determined. Images were not reread for the US reports. The original image interpretations were used.

The reports focused on more robust conservative analyses, namely sensitivity and specificity, based on blinded reads from the intent-to-diagnose population rather than unblinded image reads from the per-protocol population.

Finally, we tried to include all subjects in the analyses even if they had been excluded from the European study reports to try to maximize the number of evaluable images to support a detection claim. Specifically, the healthy volunteers in study 003 had been excluded from analyses of specificity in the European reports but were included in the analyses of specificity in the US study reports.

So, as I present each study I will present side by side comparisons of the US and European report results so that you can judge for yourself what impact these changes have had on the results.

[Slide]

Like the Walker study, GE study 301 also assessed

DaTSCAN in subjects with dementia. This was an open-label, non-randomized, multicenter, single dose Phase 3 clinical study to assess striatal uptake of DaTSCAN in subjects with dementia.

The study was conducted between November, 2003 and June, 2006. The objective was to estimate sensitivity and specificity. As in the Walker study, the primary endpoint was image assessment as positive or negative for dopaminergic deficit.

This assessment was made independently by each of 3 blinded readers. Prospectively defined null hypotheses were, number one, that the sensitivity of DaTSCAN was 65 percent or less and, two, that the specificity was 73 percent or less. The threshold for significance was 0.025 for each hypothesis.

The standard of truth was expert clinical diagnosis based on consensus criteria previously correlated with autopsy. The expert clinical diagnosis was a consensus opinion of a panel of 3 dementia experts who reviewed each subject's baseline clinical information. The panel was blinded to the DaTSCAN results and 326 subjects with dementia were enrolled at 40 European centers.

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Evaluable subjects were defined as those for whom both a visual image assessment and a standard of truth diagnosis were available. As I said before, this allows classification as true positive, false positive, true negative and false negative, etc.

Sensitivity was determined for each of the 3 blinded readers, as well as the average of the 3 results. In this study the sensitivity ranged from 75 percent to 80 percent and averaged 78 percent. As evidenced by the p values shown, the null hypothesis was rejected for 2 of the 3 blinded readers.

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For specificity evaluable subjects were defined the same way as for sensitivity. Specificity ranged from 88 percent to 91 percent and averaged 90 percent. As evident from the p values, the null hypothesis was rejected by each of the 3 blinded readers. These results are similar to those of the Walker study which had sensitivity and specificity of 85 percent and 86 percent respectively.

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So, in this study DaTSCAN visualized abnormal and

normal DaT distribution with high concordance with the standard of truth, 78 percent sensitivity, 90 percent specificity. There is very good agreement between readers, with kappa scores ranging from 0.82 to 0.92, with 1.0 being a perfect score. There is also very good within reader agreement, ranging from 0.92 to 1.0, again 1.0 being a perfect score.

[Slide]

The next study is 003 which looked at patients with movement disorders. Study 003 was a multicenter Phase 3 study conducted in 1997 and 1998 at six European centers. The objective was to determine sensitivity and specificity.

The primary endpoint was assessment of the DaTSCAN image as positive or negative. This assessment was to be made by the unblinded on-site personnel. However, I will present results using a secondary endpoint, the blinded image assessment by 5 readers. The reason is that this assessment is considered to be more robust.

The majority opinion of the readers was also recorded. For example, if at least 3 of the 5 readers called a subject's image as abnormal, then that result was recorded as the majority opinion. There is no formal

hypothesis testing in this study. The standard of truth was the expert clinical diagnosis made at study entry using published consensus criteria. One hundred and eighty-nine patients, of whom 160 had a parkinsonian syndrome and 29 had essential tremor, as well as 35 healthy volunteers, were enrolled.

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Evaluable subjects were defined as previously reported. There was consistently high sensitivity across all the blinded readers and it ranged from 92 percent to 97 percent. The majority value is 95 percent. These results suggest that DaTSCAN accurately detected abnormal DaT distribution in patients with a parkinsonian syndrome.

[Slide]

For specificity evaluability was defined as before, and specificity ranged from 81 percent to 97 percent, with a majority value of 94 percent. Again, these results suggest that the DaTSCAN accurately detected normal DaT distribution in subjects who did not have a parkinsonian syndrome.

[Slide]

So, DaTSCAN visualized abnormal DaT distribution

in 92 to 97 percent of subjects who had a parkinsonian syndrome according to the standard of truth, and it visualized normal DaT distribution in 81 to 97 percent of patients who did not have a parkinsonian syndrome. There was very good agreement between readers, with kappa scores ranging from 0.83 to 0.92.

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The final study was also in subjects with movement disorders. Study 304 was a multicenter Phase 3 study conducted between 1999 and 2005 at 10 European sites. The objective was sensitivity and specificity of DaTSCAN imaging.

The primary endpoint was the assessment of images as positive or negative. The assessment was to be made by both on-site and blinded readers, however, only the blinded results are reported here because they are believed to be more robust.

In this study DaTSCAN imaging was conducted at baseline, 18 months and 36 months. I will be presenting only the baseline DaTSCAN results but later Dr. Grosset will discuss the results from 18 months and 36 months. There was no formal hypothesis testing in this study, and 179 subjects

with symptoms of early parkinsonism and 3 healthy volunteers were enrolled.

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Evaluable patients were defined as before. Sensitivity was nearly identical across the 3 blinded readers, ranging from 77 percent to 79 percent, with an average of 78 percent. So, as predicted, DaTSCAN images detected dopaminergic deficits in patients with parkinsonian syndromes with good sensitivity.

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For specificity, it was identical across the 3 readers at 97 percent. As predicted, DaTSCAN images did not show deficits in subjects without a parkinsonian syndrome.

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The conclusions of the study again are that DaTSCAN was able to visualize abnormal DaT distribution as well as normal DaT distribution with very high sensitivity and specificity. The agreement between readers is very good at 0.98 to 1.0, with 1.0 being a perfect result.

One of the strengths of this study is the combined use of movement disorder experts, standardized diagnostic criteria that had been previously compared to autopsy, and a

36-month duration of follow-up. All the study conclusions based on the study reports generated for the US submission were consistent with the conclusions based on the European study reports.

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Earlier I described the preparation of the US study reports and some of the changes that existed between those reports and the European reports. As I mentioned, I will give a side by side comparison of those results.

So, a summary comparison of the US and European CSRs supports the consistency of the study conclusions. First, for study 301, the dementia study, the US results are very similar to the original European results and there is no difference in the conclusions. The null hypotheses were rejected for 2 of 3 readers for sensitivity in both reports and for 3 of 3 readers for specificity, again in both reports.

[Slide]

For study 003, for the primary endpoint the on-site blinded read results were also very similar. For the majority assessment the two sets of results were identical.

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For 003, by blinded reader again you can see nearly identical--in fact, identical results between the US and European reports.

[Slide]

For the remaining two of the five blinded readers, again, identical results for the two reports.

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For study 304 the two reports agreed exactly for these analyses.

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Now I will summarize the safety data for DaTSCAN. The safety data reported here are based on 942 subjects from eight completed GE clinical trials conducted in Europe. With the post-marketing experience there have been an estimated total of 216,000 patients exposed to DaTSCAN as of June of this year.

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The safety profile for DaTSCAN is very favorable. Among the 942 subjects 5 deaths were observed. However, no death was considered related to DaTSCAN. The events leading to death were bronchial carcinoma in 1 case; pneumonia in 1 case; fracture of the femur in 2 cases; and septicemia in 1

case.

Overall, 36 subjects had one or more serious adverse event. However, no serious adverse event was considered by the investigator to be related to DaTSCAN. Including non-serious adverse events there were 588 events reported in 231 or 25 percent of subjects. Seventy-three or 12 percent of these events were considered at least possibly related to DaTSCAN by the investigator.

There were no gender or age-related differences in adverse event frequency or severity that were of clinical concern. There were no clinically significant findings or trends in laboratory data, vital signs, ECG or EEG.

The radiation exposure from DaTSCAN imaging is similar to 1 year of background radiation in the United States and is similar to other diagnostic imaging procedures. For comparison, a chest computed tomography examination, or CT examination, has a similar dose of radiation.

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The post-marketing experience has shown that hypersensitivity and injection site pain have been reported and have been added to the proposed US label. However,

there have been no changes to the risk/benefit profile requiring any major changes to approved labeling anywhere DaTSCAN is approved.

There has been only 1 serious averse event reported and it was not attributed to DaTSCAN. Overall, the safety profile is benign, as would be expected for a diagnostic agent.

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From the clinical program we would conclude that DaTSCAN visualization of DaT distribution was very consistent with autopsy findings as well as expert clinical diagnosis. The sensitivity was 75 to 97 percent for abnormal distribution. Specificity ranged from 81 percent to 97 percent for normal distribution.

There is very good inter- and intra-reader agreement. The results were corroborated by autopsy in the Walker study. The safety profile is acceptable in light of the proposed use of DaTSCAN as a diagnostic imaging agent. Therefore, the benefits outweigh the risks.

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After the break Dr. Donald Grosset will discuss the benefit/risk profile of DaTSCAN in movement disorders.

DR. ANDERSON: Thank you. We are going to take a 15-minute break. I am asked to advise the panel members to, please, not discuss the issues amongst yourselves during the break but to retain your comments for the open sessions. We will resume at 10:15.

[Brief recess]

DR. ANDERSON: I am asked to tell public observers at the meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel. Now we are ready to resume.

DR. BROOKS: Thank you. The next speaker on behalf of GE Healthcare is Donald Grosset, who is a neurologist practicing in Glasgow, Scotland with a large movement disorder practice and extensive experience with DaTSCAN, and he will address the clinical utility of DaT imaging.

Clinical Utility of DaT Imaging

DR. GROSSET: Thank you. Good morning.

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I am Director of the Movement Disorder Clinic in Glasgow, in the west of Scotland, and this is a position I have held for 14 years. I have extensive research and

clinical experience with DaTSCAN, being principal investigator for two of the clinical trials on DaTSCAN which Dr. Sherwin has presented. I have co-authored ten papers on DaTSCAN and the clinical experience is in our west of Scotland service during the past 9 years since it was licensed in Europe.

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There are patients who present a real diagnostic challenge in the movement disorder clinic. These are, firstly, patients at initial presentation where there are features that are ambiguous for having a Parkinson's disease disorder, or a similar degenerative parkinsonism, or have a benign tremor and parkinsonism disorder.

If the presentation is one which needs immediate management, then we now have the option to go ahead with the DaTSCAN to help differentiate these clinically ambiguous cases. If we do not yet need to make an active management decision for these patients we can adopt a wait and see approach.

Later during the diagnostic process potentially we have patients who have been diagnosed as Parkinson's disease. They have been started on anti-Parkinson

medication and they have developed features which are atypical for what we expect for Parkinson's.

When we are thinking of that atypical nature, we are thinking of patients with a more benign disorder, a more benign tremor parkinsonism disorder and, therefore, we are looking at cases who have less rapid progression than expected for Parkinson's disease, and we are looking also at patients who have gone on to anti-Parkinson treatment but where the response is uncertain.

That treatment response can be difficult to assess, and I am going to present evidence indicating that patients can enter a treatment pathway and maintain inappropriate anti-Parkinson treatment, sometimes for a period of several years, which is clearly adverse to them since they are exposed to the adverse effects and would not develop benefit.

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One of the first things that we are interested in clinically is that we can undertake the DaTSCAN test early at that initial presentation. In other words, we want the scan to be sensitive to the presence of early degeneration of the striatal dopaminergic system.

Study 304 had the advantage of having baseline scans performed early during the clinical course, and the scans were repeated at 18 months and 36 months. So, we could categorize the patients as having a baseline normal scan. Remember, this is the independent, blinded review of the scan, independent of clinical data. The baseline scan could be categorized as normal and we would hope to see that that remained normal throughout follow-up and crucially, as well, we would hope that an abnormal scan would predict abnormal scans when repeated at 18 and 36 months.

We would also expect that there would be no change. If we did a measurement over time, there would be no change in that measurement for the normal scans over time. But the patient with Parkinson's, which we know progresses at a rate of around 7 percent per year, we would have a measurable change over time when we look at these repeat scans.

Now, this study also allowed us to look at a subset of patients who clinically fulfill criteria of Parkinson's, are clinically diagnosed as Parkinson's, but, surprisingly, have normal DaTSCAN. These have been referred to by the acronym SWEDD. So, these are subjects without

evidence of dopaminergic deficit.

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So, here we have these patients who were all entered into this trial as having diagnostic uncertainty between having parkinsonism and tremor disorders. We have the uptake in the DaTSCAN in the putamen brain area on the Y axis, referred to as the age-corrected uptake, and the left-hand group is the 37 cases whose baseline scan was categorized as normal.

Over time there was no change in either the status of those scans which were, again, normal at 18 and 36 months and there was no measurable difference in the age-corrected uptake percentage.

In the right-hand group of 3 we have the baseline, 18 and 36 month scans for cases initially categorized as abnormal. These are an average reading of 50 percent of normal uptake. These showed a slope of progression over time at 18 and then again 36 months.

So, clearly, we are seeing patients who are baseline normal, remaining normal, no measurable difference, baseline abnormal, deteriorating further over time.

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Then the group that had a clinical diagnosis of Parkinson's disease but a baseline normal scan. This clinical diagnosis is the 3-year, blinded video review of these patients' clinical appearance. So, this is an independent assessment conducted by 2 clinicians, not knowing the scan result, and describing these patients as having a clinical appearance of Parkinson's disease.

So, these 13 patients, SWEDDs, are a subset of the 37 normals seen in the left-hand panel. Again, over time we are seeing those patients, who were categorized initially as normal, having no measurable change when the scan is repeated at 18 and at 36 months.

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Another opportunity to analyze DaTSCAN and look at sensitivity in early disease is this well-known presentation of Parkinson's called hemi-Parkinson's. Many patients present initially with unilateral symptoms affecting one side of the body, arm and/or leg. We know that that disease progresses to bilateral involvement within a year or two, and certainly within three years, in all cases.

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In this setting then we can look at the DaTSCAN

uptake. This was study 003 which Dr. Sherwin presented. We can compare, in the left-hand group, and we are now looking at putamen uptakes expressed as a ratio, we can look at the symptomatic hemisphere. So, this is the side that is causing the patient's signs and symptoms, the symptomatic hemisphere for these 21 patients, a subset in study 003, with this early hemi-Parkinson's.

These cases have a differentiation from healthy age-matched volunteers, the right-hand panel. But in the middle we see the results for the as yet clinically unaffected side of the body referable to the pre-symptomatic hemisphere in the brain. These, again, were abnormal readings, very similar to those in the symptomatic hemisphere.

So, this, again, supports the idea that the DaTSCAN is sensitive to early disease in showing abnormalities even when there is not yet clinical manifestation.

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However, we had 1 outlying observation, a single patient whose symptomatic and pre-symptomatic hemisphere reading is within the normal range. This patient was

clearly of interest to us and we monitored the patient through extensive follow-up and have reached an alternative diagnosis of dystonic tremor.

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Subsequent to that a series of these cases who are misdiagnosed as Parkinson's and who have normal DaTSCAN was reported from London by Schneider, all with dystonic tremor, having a mix of features of Parkinson's, typical parkinsonian features including rest tremor and other markers, but also having markers of dystonia which could be in the neck or arm.

The diagnosis had been made of Parkinson's by various clinicians, including general neurologists in 4 cases and even by a movement disorder expert in 2 cases.

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So, what this has helped tell us is that dystonic tremor is a good mimic at times of Parkinson's disease. These patients can fulfill the clinical diagnostic criteria. DaTSCAN turns up to be normal. Schneider has done a series of 10 where we find 1 in our earlier work.

Here we have a scenario where DaTSCAN has allowed us to understand a condition that mimics Parkinson's disease

but which does not merit anti-Parkinson treatment.

[Slide]

There are other diagnoses which can be a potential explanation for these subjects without dopamine deficiency on their scanB-the essential tremor case, the drug-induced Parkinson's case and in the presence of dementia the Alzheimer's disease case, contrasting to Lewy body dementia.

The crucial issue here is the group of disorders on the left of striatal dopaminergic deficiency, which is detectable with DaTSCAN, and the group on the right have no dopaminergic deficiency. And, the group on the left should be tried on levodopa or a dopamine agonist, sometimes both in later disease, and the group on the right do not receive benefit from that treatment and preferably should avoid it.

[Slide]

If we look on a community basis at the accuracy of Parkinson's diagnosis and again think of what number of patients is there who are inappropriately taking anti-Parkinson medication, this study, by Schrag from North London, analyzed 131 patients. It applied the usual strict clinical diagnostic criteria. It included 1-year follow-up, and it rejected a prevailing diagnosis of Parkinson's

disease in 15 percent of cases.

Not all of these patients should have anti-Parkinson medication withdrawn because the alternative diagnosis may also benefit from anti-Parkinson treatment. Therefore, taking all those patients who should not be on anti-Parkinson treatment, it is 5.3 percent of the study group.

[Slide]

We looked observationally in our own clinic at patients who had been referred for routine clinical evaluation with DaTSCAN and whose scans had tested normal. This is 150 consecutive cases who were then followed up for an average of 2.5 years.

What we looked at here on an observational basis was the association of having a normal DaTSCAN with a follow-up diagnosis and with the treatment decisions. The final diagnosis was 97 percent for non-Parkinson syndrome. Anti-Parkinson treatment had been used in 24 percent of patients.

Most of these had been withdrawn without evidence of deterioration, leaving the final proportion taking anti-Parkinson therapy now reduced to 7.3 percent. What this

study did not prove was that the DaTSCAN had led to the diagnostic or treatment decision.

[Slide]

We went on and conducted a study in the community, looking at 610 patients who had a diagnosis of Parkinson's disease and were on anti-Parkinson medication. On this occasion we deliberately sought out features initially from the clinical case record and subsequently by clinical evaluation to challenge the diagnosis of Parkinson's disease. These are the features that I mentioned before, an uncertain or atypical response to treatment; a low escalation of anti-Parkinson medication dose; and other similar observations.

We made a decision within this study that we would not conduct DaTSCAN on a routine basis. We would only conduct DaTSCAN where we felt this was clinically going to help us in our differential diagnosis. This meant that of the 50 patients that we thought were atypical for Parkinson's disease, we reached that conclusion but went ahead with a DaTSCAN in 25. In the remaining 25 we elected not to do a DaTSCAN because we were clinically more confident.

When we did the DaTSCAN in 25, in fact, 11 of these turned out abnormal. So, our clinical opinion that this was atypical for Parkinson's disease was not reflected in the DaTSCAN.

We then took patients who had normal DaTSCAN and clinical assessment, along with 25 cases who had a clinical assessment alone, and offered these patients withdrawal of anti-Parkinson treatment under supervision. And, 33 did so and stopped treatment without deterioration.

Two, unfortunately, when they stopped their treatment deteriorated. These two cases had only been assessed clinically. We had not judged it necessary to do a DaTSCAN. When they did, unfortunately, get this deterioration we performed DaTSCAN and found that these were both abnormal.

[Slide]

So, this is a real-life example of the implementation of DaTSCAN aiding diagnostic evaluation, re-evaluation in this case of patients with a prevailing diagnosis of Parkinson's disease and taking anti-Parkinson medication. DaTSCAN was applied selectively as an adjunct to support clinical assessment.

It was a help in identifying the misdiagnosis cases. It did help prevent inappropriate withdrawal of treatment in patients with abnormal DaTSCAN, and the clinical interpretation alone was helped by DaTSCAN in 11 cases with abnormal baseline DaTSCAN and we could have benefitted further in these 2 other cases that were incorrectly clinically re-diagnosed as not having Parkinson's disease.

[Slide]

The clinical application of DaTSCAN then is in patients with diagnostic uncertainty between Parkinson's disease and similar degenerative syndromes against tremor and parkinsonian disorders either at initial presentation when the features are ambiguous and we cannot reach a clear clinical interpretation, or if the patient goes on treatment and has an atypical therapeutic response or an atypical progression rate.

Examples within that where it would be difficult to reach a good diagnostic conclusion without DaTSCAN include cases who have drug-induced Parkinson's where stopping the potentially offending drug could be difficult. This is the antipsychotic medication for patients with

schizophrenia, for example, and the epileptic patient taking sodium valproate which can cause a drug-induced parkinsonian disorder; also where a trial of anti-Parkinson therapy would be predicted to be more problematic, such as the more elderly patient potentially with cognitive deficit.

[Slide]

When then is DaTSCAN inappropriate? It is not a screening tool and not a stand-alone diagnostic tool for screening patients with movement disorders. It is not required when the patient has clinically definite Parkinson's. If there is a good therapy response and if there are later complications which really typify Parkinson's disease we do not require a DaTSCAN to reinforce that.

It is not appropriate to differentiate Parkinson's from the other dopaminergic degeneration disorders, and it is not used either to grade disease severity or monitor disease progression as both of these are more appropriately performed clinically.

[Slide]

I will now pass to Dr. Stacy.

DR. BROOKS: Thank you very much, Donald. The

final speaker is Dr. Mark Stacy, from Duke University Medical Center, and he is going to talk about the rationale for having DaTSCAN available in the USA.

Medical Need and Rationale for DaTSCAN in the USA

DR. STACY: Thank you, David.

[Slide]

Good morning. My name is Mark Stacy. I am a neurologist from Duke University and specialize in the practice of Parkinson's disease and movement disorders. My research and clinical practice has concentrated on the diagnosis and treatment of Parkinson's disease and I have published extensively in these areas. I have also been privileged to care for thousands of people with Parkinson's disease at Baylor College of Medicine, the University of Missouri, the Muhammad Ali Parkinson Research Center and at Duke University.

[Slide]

I have ten years personal experience with DaT imaging in the United States and contacts with clinical trials conducted in the North American-based Parkinson's study group. Three major multicenter therapeutic trials undertaken by the Parkinson's study group are published,

ELLDOPA, PRECEPT and the CALM-PD trials.

This histogram illustrates the baseline status of the nearly 800 patients enrolled in the PRECEPT trial using an agent similar to DaTSCAN. The full impact of the 85 subjects without dopaminergic deficit in this trial is not known. Furthermore, the follow-up of these SWEDD patients has never demonstrated progression to dopaminergic deficit.

All three trials enrolled subjects diagnosed by expert clinicians using standard clinical criteria, and all of these patients would have been expected to have a striatal dopaminergic deficit. However, DaT imaging showed that a significant proportion had no deficits and, therefore, no need for dopaminergic therapy. These studies illustrate that important diagnostic errors are not rare and they are even made by experts in controlled circumstances.

[Slide]

To provide additional perspective on erroneous diagnoses in the movement disorders community in this country I would like to review a recent clinical report from Columbia University. Dr. Lewis and his colleagues interviewed and evaluated 71 consecutive patients in their clinic for essential tremor and they found a misdiagnosis in

26 of these subjects. They found Parkinson's disease in 11; dystonia in 6; a dual diagnosis of dystonia and Parkinson's disease in 5; and other diagnoses in 4 other patients.

Interestingly, all except 2 of these patients had been seen by a neurologist prior to this referral. Perhaps most alarmingly, the tremor had been present in these patients for an average of more than 11 years. Again, accurate diagnosis is fundamental to patient care and it is not a rare occurrence in practice of movement disorders.

[Slide]

Accuracy of diagnosis often results in concerns in patients seeking a second opinion. Patients may seek a second opinion for medical management. They seek a second opinion for possible surgical intervention, and they may seek a second opinion for just confirmation of diagnosis. If the initial diagnosis of Parkinson's disease is correct or benign essential tremor is correct we probably would not make a number of changes in medications.

But before we would send someone to surgery we would want to see if there was a typical progression in Parkinson's disease, if they had severe dyskinesia or other motor complications, and then I think it is a reasonable

referral.

In many cases the diagnosis is incorrect and in that case we look at response to therapy. We consider an alternative diagnosis. We consider stopping medication, and we may assess response to a new therapy.

[Slide]

The consequences of misdiagnosis can lead to false reassurance or falsely alarming prognoses. If you have benign essential tremor and are told that you have Parkinson's disease you may make plans in your life that are not necessary.

Inappropriate therapy may prevent patients from receiving appropriate therapy so the patient referred to me with a diagnosis of Parkinson's disease who has had benign essential tremor for 8 years and a very poor response to anti-Parkinson therapy is both comforted and annoyed with change to a therapy that is more appropriate. Inappropriate therapy also exposes a patient to potential complications of medications either through dopamine replacement medicines or neuroleptic medicines.

I have listed these side effects here. The one I would like to emphasize is impulse control disorders, mainly

because it is an interest in my research. Impulse control disorders, when originally reported, were felt to be approximately 1 percent of our Parkinson's population.

It is now felt to be in excess of 15 percent of patients receiving anti-Parkinson's medicines. It is also now reported in restless leg syndrome and increasingly reports of pramipexole and other dopamines being used for patients in an off-label setting of fibromyalgia. It is now reported to be occurring in this population.

Impulse control disorders in my practice have produced devastating consequences, and I think it is important to give every patient an opportunity to avoid taking these medicines if they are inappropriate. Similarly, I think it is important to give patients who have the diagnosis of diffuse Lewy body disease every chance to avoid being put on medications that would increase their Parkinson's symptoms such as neuroleptic therapy.

[Slide]

If we compare the European Union practice and the practice in Parkinson's disease in the United States, I would contend that the diagnostic evaluation is the same; treatment options are the same; patient management

approaches with referral groups and tertiary centers are the same. The only real difference is assessing functional dopaminergic status with DaTSCAN. As mentioned many times before, DaTSCAN has been available in Europe for the last decade and has been shown to be safe.

[Slide]

So, if I had to think about when I would use DaTSCAN in my practice, I can think of two areas where it would be very helpful to me. One is that patient whom I have considered to have Parkinson's disease and put them on appropriate dopaminergic therapy and they have not responded to that therapy. In those cases a DaTSCAN would help me to determine how I would further counsel that patient. So, if I had a patient that did not respond to a levodopa challenge I would look at a scan. If the scan showed a dopamine deficiency I would consider whether that patient did have Parkinson's disease and my challenge was not appropriately long enough or with appropriately high dosage.

We do know from the levodopa trial, the L-dopa trial, that patients seen at the 3-week follow-up, receiving 150 mg and 300 mg per day, did not show a change from placebo. So, at least a 3-week challenge from levodopa is

not sufficient in that series. It was sufficient at 9 weeks. We just don't have the data between 3 and 9 weeks.

If I had a patient where I wanted to consider multiple system atrophy I would reassess for autonomic findings. From PSP I would reassess for extraocular motility findings. For corticobasal ganglionic degeneration I would look for apraxia or increasing asymmetry. For diffuse Lewy body disease I would assess for cognitive difficulties.

If the scan was normal, again, perhaps the patient had essential tremor and dystonic tremor and I would reconsider these diagnoses. If they had a drug-induced parkinsonism or they still had a Parkinson's finding I would look hard for those combination therapies of a tricyclic and an antipsychotic. I would look for antiemetics. I would look for other medicines with parkinsonism.

The other area I would consider a scan is for a patient who has very minimal symptoms of Parkinson's disease, and a patient that would be really inappropriate for levodopa or a dopamine agonist challenge. We have agents that we use very readily in our Parkinson's practice that may or may not be neuroprotective but there are data to

suggest this, and who are we to say to a patient who wants to try every opportunity to get better or to resist the decline in therapy that I want to take one of these drugs? I would not expect a clinical response from these drugs and so it may be appropriate to order a DaTSCAN before initiating that therapy.

Finally, as a clinical researcher, my activities in clinical research, particularly in my proof of concept ideas, would benefit from institutional availability of a DaTSCAN. European clinical research, for instance Dr. Schrag's data, could only occur because she had the scan available and we don't have this available in any fashion in the United States.

As a practicing physician, I believe that the DaTSCAN data are safe, and I believe this is a useful adjunctive tool for evaluation of my patients.

Thank you.

Concluding Statements

DR. BROOKS: Thank you very much. It is my privilege now to finish with a few concluding remarks. They will be very brief.

[Slide]

I hope that we have convinced you that DaTSCAN allows very sensitive visualization of both normal and abnormal patterns of DaT distribution in the striata. As you saw from the trial data, the kappa values are in the 0.9 range, both inter- and intra-reader. So, it is remarkably easy to visualize the distribution and to determine whether it is normal or abnormal, but training is provided to all centers which wish to use this agent.

Although we do not regard DaTSCAN as a diagnostic agent, we feel that it is a novel diagnostic adjunct and it can help in areas of uncertainty, particularly the SWEDD cases you heard about and whether or not it is rationale to use dopaminergic medication in these patients if they don't appear to be responding to drugs in the way you would wish. It also helps you decide whether to withhold drugs in certain dementia disorders.

There seems little doubt that DaTSCAN is extremely safe. We have had over 200,000 patients exposed to it now without difficulties. And, it is extremely well tolerated. You have an injection; you come back 3 hours later for your 30-minute scan. There appear to be very little problems with the use of the DaTSCAN. So, I would argue that the

benefit/risk profile of DaTSCAN is extremely positive.

[Slide]

So, we are very happy to take questions on this presentation and we have a list of people here, both external consultants and members of GE Healthcare, who would be happy to take your questions.

Clarifying Questions

DR. ANDERSON: At this point the questions are supposed to have a clarifying nature. We will start with Dr. Katz.

DR. KATZ: Yes, maybe somebody said this and I missed it but there has been a lot of talk about normal and abnormal scans. So, maybe my question is for the company. Do you have a bright line definition of what constitutes an abnormal scan? And, would that definition only identify people who have relatively advanced disease?

DR. BROOKS: Dr. Jacobson would like to take this question.

DR. JACOBSON: I am Arnold Jacobson, a nuclear medicine physician with GE Healthcare. The essence of the assessment is that the patterns are very clear once the scan becomes abnormal. And, because patients, when they are

becoming symptomatic, already have the fairly significant loss of the nigrostriatal neurons, that is one of the reasons that it is fairly straightforward to detect the abnormalities. Because you are not dealing with pre-symptomatic patients usually you already have a significant loss.

[Slide]

In the trials themselves the scans were categorized in terms of normal, which you see here on the left for healthy volunteers and a pattern of first asymmetric loss of putamen, posterior putamen on one side and then typically a pattern, so-called class 2, with bilateral signal loss where you tend to see mostly only caudate uptake and then, obviously, the most severe where you start to look at virtually all of the uptake in the striata.

So, the data from the trials is very clear in the vast majority, as was pointed out by Dr. Brooks, in terms of the kappa values. Most readers have very little difficulty distinguishing normal from abnormal.

DR. KATZ: Just for clarification, so if you are thinking about writing labeling and talking about abnormal

scans that, you know, this is a diagnostic aid or adjunct for certain parkinsonian symptoms or nigrostriatal degeneration syndromes, what would you say? What would somebody look for?

DR. JACOBSON: Well, I think the very earliest evidence is the asymmetry in terms of the asymmetry between the striata, particularly in relationship to the symptoms. That is why the technical aspects of the imaging are very important in order to be able to accurately assess symmetry versus asymmetry.

There are certain quality control measures and acquisition measures that need to be done properly. But the intention is to include effectively indications or demonstrations of what patterns of abnormality you would expect to see in earliest disease as an aid to a new user of the product.

DR. ANDERSON: I think Dr. Twyman was next. Do you still have a question, Dr. Twyman?

DR. TWYMAN: My question is exactly what Dr. Katz had. Just a further clarification, is there an age difference in this pattern, I guess, that needs to be taken into consideration?

DR. BROOKS: The natural effect of aging is to uniformly affect DaT binding by about 5 percent reduction per decade. So, one does see with age a slight decrease in the amplitude of the signal, but you do not get the asymmetrical loss of putamen relative to caudate function that one sees in the parkinsonian syndromes. So, in fact, visually it is very difficult to detect an age effect but quantitatively one can pick up a slight decrease with time. It is very easy to distinguish someone who is elderly but normal from someone with a parkinsonian syndrome just on the pattern of loss.

DR. ANDERSON: I think Dr. van Belle was next.

DR. VAN BELLE: I think we are all fishing in the same pond. I have the same kind of question. Maybe you could go to slide C-58. There is an age-corrected uptake and I have two questions. One is the uptake is expressed as a percentage. So, my question is what is the denominator. Secondly, how much of an age effect is there? I think you have answered that in part but I would like to have a little bit more detail. Thank you.

DR. BROOKS: Dr. Grosset, do you want to take this? [Slide]

DR. GROSSET: Yes, if we can look at this slide,

the reason that this data is presented as age-corrected uptake is that this is the combined results across multiple centers across Europe, and this is the best way to combine the data from different scanning techniques.

The effect of age correction is modest but it is regarded as the best thing to do to get the most accurate representation. As Dr. Brooks has said, the age change is minimal but one can apply a correction factor and that is represented here.

More usually, in our own center we would not conduct any age correction and we would conduct a visual interpretation, and also our nuclear medicine colleagues who report this will make a measurement of uptake ratio as a supplement. But the primary assessment is based on visual assessment.

DR. VAN BELLE: So, what is the denominator in this case? Because it is expressed as a ratio, what is the ratio based on?

DR. GROSSET: The ratio is based on occipital uptake which is deemed to be non-specific. So, this is the ratio of specific to non-specific uptake.

DR. ANDERSON: I think Dr. Ziessman was next.

DR. ZIESSMAN: Could you clarify, please, in the clinical trials that were discussed was quantification done as well as subjective interpretation of the studies? And, if quantification was done was attenuation correction performed as well?

DR. BROOKS: Would you like to take that, Dr. Sherwin?

DR. SHERWIN: Yes, in the clinical trials we did do quantification. Whether or not attenuation correction was done or not, I don't know the answer to that. Dr. Jacobson says no. No attenuation correction was done.

DR. ANDERSON: Dr. Herscovitch?

DR. HERSCOVITCH: Several speakers have commented on the lack of total reliability of the clinical diagnosis and you have highlighted the high kappas and reliability of your readers, but your readers were, of course, experts in academic centers and nuclear medicine physicians. Do you have any data on, once this method, should it be propagated in the community of nuclear medicine physicians, how well will the community nuclear medicine physicians do with regard to the reliability of their readings?

DR. BROOKS: We have training programs to make sure

that there are workbooks, examples of images and, in fact, people have held sort of weekend courses on how to read these scans to train people. We haven't formally, as I understand it, collected data to see afterwards whether they are performing as well as expert nuclear medics. We have no reason to think that they cannot do as well, but we haven't conducted a trial to determine that. Donald, do you have any data in this area? It is our intention to perform formal training at all sites that wish to use this modality.

DR. HERSCOVITCH: A second question, on slide C-88 it said the role of DaTSCAN in the USA would be to improve patient selection for therapy trials, both for movement disorders and dementia. In fact, is that not possible through the IND mechanism? Is it just not possible at all to do clinical trials with this agent unless it is approved with an NDA?

DR. BROOKS: As far as I am aware it is not GE's purpose to use the agent in that way. That was Dr. Stacy's individual suggestion, that it could be used in that way. Would you like to comment, Paul, on the use of this agent for selecting people for trials?

DR. SHERWIN: That is not part of the indication

that we are seeking so that would be up to the individual physicians. It is our understanding that, you know, they would not be prohibited from doing that if DaTSCAN were approved.

DR. HERSCOVITCH: But I guess the question was the other way around. Why could it not be available under IND the way, for example, amyloid imaging agents are? I believe one perhaps even is licensed by your company? It is made available under an IND for clinical trials of anti-dementia drugs. There is no legal reason or technical reason why this agent couldn't be used to improve patient selection for therapy trials under an IND, is there?

DR. SHERWIN: That is a regulatory question that I am not qualified to address.

DR. RIEVES: Dr. Herscovitch is correct, there is no regulatory objection to that option.

DR. ANDERSON: Dr. Kieburtz?

DR. KIEBURTZ: Just two questions of clarification in 301 and 304. I will start with 304. There are about 180 subjects in it but 100 were evaluable. That is because people were lost? It is only the people who had the 36-month repeat evaluation?

DR. BROOKS: Right.

DR. KIEBURTZ: In 301 there are about 320 people of which about 220 were evaluable. That loss is due to excluding the possible DLBs?

DR. BROOKS: That is my understanding but perhaps Dr. Walker, who is part of that trial, could comment.

DR. WALKER: In the primary analysis the possible cases were excluded at baseline. However, they were evaluated at 1-year follow-up. That was not presented.

DR. KIEBURTZ: But the bulk of that loss of those subjects is the possible DLBs?

DR. WALKER: Yes.

DR. BROOKS: Did you want to comment on 304, Paul?

DR. SHERWIN: For 304 about 53 percent of the entering subjects were evaluable at the 36-month follow-up. This was anticipated, you know, that there would be a lot of dropouts over a 3-year follow-up.

For 301 the possible were not included in the primary endpoint. They were included in secondary analyses but that does explain, as Dr. Walker said, the difference in the numbers.

DR. ANDERSON: Dr. Tatum?

DR. TATUM: I want to pick up on two or three things. First, I want to take on the question that Dr. Herscovitch put on the floor. Technically it is correct; logistically it is a nightmare. For somebody who has to do this frequently, as I do with oncology drugs, trying to combine something that is not approved and available in a trial where you have broad selection criteria to find something, it is very problematic. So, I think it is very helpful to have something widely available if you are going to do this kind of study, although technically I know it can be done.

My other question is for Dr. Brooks. What do we know about the DaT transporter kinetics? Is this something that is very stable? Does it recycle? Does it get internalized? What is the rate of that, if it is? And it relates to what is the binding site of the tracer on that receptor. You said it wasn’t going to the channel. It was different from that. It is probably allosteric so it is probably not affecting function but I don’t know that. Do we know where it is binding? What is the avidity of it?

DR. BROOKS: Dr. Pickett, would you like to take that?

DR. PICKETT: Yes, I am Roger Pickett, from GE Healthcare in the UK.

The dopamine transporter has a protein that crosses the membrane in 12 domains. The domain for the uptake of dopamine is separate from the binding domain for the inhibitors. Does that answer the question?

DR. TATUM: Not totally.

DR. PICKETT: I am sorry, I can't comment on recycling.

DR. TATUM: Okay. So, I think it is an interesting question. If it is binding to the receptor and the receptor is internalized you would actually end up potentially with tracer residualization within the cell and you are no longer looking at the receptor density. I don't think it is important to the overall indication you are looking at but I am wondering what is really going on here. I was kind of struck by the kinetics curves of uptake and maybe there is some of that going on.

DR. PICKETT: The tracer isn't internalized. It is readily displaceable.

DR. TATUM: It is displaceable? You can displace it from its binding site on the receptor afterwards?

DR. PICKETT: Yes.

DR. ANDERSON: Dr. Holmes?

DR. HOLMES: Maybe you could just clarify for me. You are saying there is no relationship between severity of the disorder and the scans? Is that correct? You had three different types of abnormalities I believe that you could see.

DR. BROOKS: Right.

DR. HOLMES: Was there any relationship between what you were seeing and the patients' clinical symptoms?

DR. BROOKS: Yes, indeed. This was not assessed directly in the trial data we presented but there have been investigator-initiated trials showing that there is a clear correlation between bradykinesia and rigidity and the uptake of DaTSCAN on the DaT sites in the putamen.

Having said that, the correlation is not perfect. It can also be influenced to some extent by treatment, for reasons that were discussed earlier in the presentations. So, we do see a significant correlation and, as a rule, the more severe the DaTSCAN the more severe the patient.

DR. ANDERSON: Dr. Rudnicki?

DR. RUDNICKI: A question about the autopsy series

that you have. It was stated that there was a 50 percent clinical specificity with the initial diagnosis. I was curious, as these people were followed over time and I suspect at least in some circumstances the clinical diagnosis changed, what happened to that number.

DR. BROOKS: Dr. Walker, do you want to comment?

DR. WALKER: Yes, that is correct. The data presented is for the initial diagnosis. With time it became clear that some of the patients had alternative diagnoses. But we don't present the numbers because later on we knew the results of the scan so we were not anymore blind to the result of the scans. So, it would include the diagnosis and include taking into account the result of the scan.

DR. BROOKS: I think though the trial highlights the difficulty in making the diagnosis of DLB. There is a high error in the clinical standard of truth in practice with modern consensus criteria still.

DR. ANDERSON: Dr. Katz?

DR. KATZ: A question for Dr. Grosset on slide C-69 which describes the community study in 610. Maybe you said this, how do you know that the 11 patients who had abnormal scans that continued treatmentB-I assume those are the ones

in whom you continued treatmentB-it was the appropriate thing to do? In other words, how do you know those scans were correct?

DR. GROSSET: We don't. We elected to accept the result of that scan in this case. It is possible that those DaTSCANs or some of those DaTSCANs were incorrect. The purpose of this study was to determine if there is a cohort of patients who are on anti-Parkinson treatment and do not have Parkinson's disease. And, we really do not wish to withdraw anti-Parkinson treatment from patients who may have Parkinson's disease.

As you saw, we did this in 2 cases on a clinical basis alone and these patients deteriorated fairly significantly and then we had to restart them back on treatment, which is fine; they didn't come to any ill effect, but it is an undesirable outcome. So, we accepted in that case that we would not proceed with withdrawal on a trial basis in people who had abnormal DaTSCANs.

DR. ANDERSON: Dr. Mattrey?

DR. MATTREY: A question regarding the autopsy gold standard. Obviously, when a patient came to autopsy the DaTSCAN was available. Was the brain evaluated? I assume

it is obvious histopathologically if there are no dopaminergic neurons left. But did you actually stain for the DaT protein?

DR. BROOKS: My understanding is not but Dr. Walker will clarify.

DR. WALKER: No. No, we didn't. For the DaT protein we would have to look at the frozen brain and we didn't. This was a histopathological examination. So, evaluation was of the substantia nigra, of the number of cells and also looking at the number of cells in the striatum.

DR. MATTREY: Thank you.

DR. ANDERSON: Dr. Frank, please?

DR. FRANK: Looking at the gender distribution in the data, it is about 2/3 men, which is fairly classic. Is there data on minority populations or on genetic forms of Parkinson's or Alzheimer's to suggest that DaTSCAN imaging may be different in those populations?

DR. BROOKS: We did not include large numbers of ethnic minorities in these trials and they were not formally genotyped either. So, we don't have data addressing that situation. There is some limited data in Japanese subjects

showing the uptake of DaTSCAN is very similar to that seen in Caucasians but that really is the only data set we have at present. Having said that, we have no particular reason to think it would differ across races.

DR. ANDERSON: Dr. Green?

DR. GREEN: In many of the studies presented earlier, other than the Walker study, it was stated that the standard of truth was expert consensus which was previously compared to autopsy data, but I have no sense as to documentation as to how often that occurred and what that correlation was.

DR. BROOKS: I believe that the expert consensus criteria have been validated at one time against autopsy data. I don't know if you want to clarify that, Dr. Sherwin. They were using autopsy validated consensus criteria.

DR. GREEN: No, I understand that but that is not specific enough to give me any sense as to the extent of that kind of correlation.

DR. SHERWIN: These were published studies which have reported sensitivity and specificity values against autopsy. Slide on, please.

[Slide]

This is a summary of the criteria that were used for parkinsonian syndrome and Parkinson's disease in study 003. There is autopsy correlation of those criteria. They were the UK Parkinson's Disease Society brain bank criteria. Here is 1992 correlation. They showed a positive predictive value of 82 percent for the progressive supranuclear palsy in 003. That has been found to have a sensitivity of 50 percent and specificity of 100 percent. However, for those patients they also had to meet the brain bank criteria in that study.

Findley and Koller criteria for ET that were used in study 003 have been found to have positive predictive value between 94 and 100 percent based on a study shown there by Lewis and Rashput. For DLB the sensitivity is 83 percent; specificity 95 percent based on McKeith and co-workers who published in 2000.

DR. ANDERSON: I have a question, a clarifying question. In the initial part of the presentation you say, well, we are going to compare DaTSCAN to consensus clinical expert diagnosis, a way of sort of validating that it does what we say it does.

Then, when we want to say what its clinical utility is we are going to bring up those experts who are part of the same group that developed the consensus criteria to say how poor they are at diagnosing it. Therefore, the DaTSCAN should sort of supercede, or augment, or serve as an adjunct to their diagnosis.

So, how do you rationalize the use of sort of the same group of expert opinion as both validating DaTSCAN's action and demonstrating sort of the need for something better than clinical opinion?

DR. BROOKS: Will the experts comment who produced the criteria and did the images?

DR. SHERWIN: There have been data published on sort of garden variety clinical diagnoses that that has been correlated with autopsy and found to be deficient. I think the Hughes article showed that in about 25 of 7 cases there was an error rate. However, the same group later published an article showing that movement disorder specialists had a very, very small error rate. I don't recall the exact number but it was above 90 percent. I think it was about 98 percent. Dr. Grosset is nodding his head.

So, the comparison is sort of that the general

neurologists diagnosing Parkinson's disease may have a higher error rate than movement disorder specialists who see Parkinson's disease patients every day for a living. That is the distinction that we are making.

DR. BROOKS: I think we accept that there is a problem here. It was essentially the best we could do under the situation. It would be great to have everyone completely independent in this situation.

DR. ANDERSON: Dr. Herscovitch again, please.

DR. HERSCOVITCH: Just to follow up on your question, Mr. Chairman, concerning the expert clinical raters that were involved in some of these studies, I may have misinterpreted this but in the write-up it said that for study 304 the 2 clinical expert readers who determined the standard of truth only had a kappa value of 0.37 at 18 months and 0.968, I guess, at the next evaluation.

So, how reliable were they as a standard of truth if they didn't have a particularly high kappa value with regard to their agreement of what the truth was? Perhaps I have misinterpreted the write-up. It is just one sentence.

DR. BROOKS: Paul?

DR. SHERWIN: Well, there is a distinction between

the kappa values for the images, which were very high, and the kappa values for the movement disorder specialists in 304 who performed as the standard of truth. So, you are saying the kappa values at 18 months were about 0.3-something and at 36 months they were 0.68, which had improved over time.

It illustrates the point that over time it is easier for people to make the diagnosis because the symptoms become more apparent. However, your question is how valid is that as a standard of truth. You know, it is the best that we could do with those specialists. They were movement disorder specialists. They evaluated videotaped neurological examinations and that has been shown to be a valid method by Lewis, at Columbia.

So, I think it highlights to us the ease of diagnosis of these abnormal DaT distributions by DaTSCAN because of the high image agreement rate, and I think it highlights the difficulty in clinical diagnosis.

DR. HERSCOVITCH: I am not disagreeing with that but, again, given that degree of disagreement, how does that lead to confidence in using the expert clinical assessment of the standard of truth with regard to determining the

performance characteristics of DaT imaging? That was basically my point.

DR. SHERWIN: Thank you. I did not quite get that. That kappa was for the movement disorder specialists providing separate diagnoses. Then they came together and gave a consensus diagnosis and that was used as the standard of truth. So, the kappa score doesn't really reflect what was actually used as the final standard of truth which was based on the consensus of those 2 movement disorder specialists who adjudicated between themselves in cases where they disagreed.

DR. ANDERSON: At this point we will have one more question and then we will move to the FDA's presentation. We can come back to revisit some of these issues later if we need to. Dr. Twyman?

DR. TWYMAN: Yes, on the same line on the standard of truth, looking at the autopsy data from Dr. Walker's study which appears to be very important, on slide C-28 I am trying to reconcile the 50 percent number for the specificity for the clinical diagnosis. If that is really the accurate specificity of the clinical diagnosis the standard of truth used in the clinical trials must be pretty

poor overall.

So, can you help me actually with what the actual numbers are for the true negatives and the true positives and the false positives that drove that 50 percent clinical diagnosis specificity?

DR. BROOKS: Zuzana, the exact number of true negatives and true positives?

DR. WALKER: There were 2 false negatives and there were 2 false positives.

DR. ANDERSON: Could you just spell that out in more detail? The true negatives were what, they really were what and they were called what?

[Slide]

DR. WALKER: One of the cases that was clinically diagnosed as dementia with Lewy bodies and was also diagnosed at autopsy as dementia with Lewy bodies and also Alzheimer's disease had a normal scan. So, that was 1 false negative.

The second false negative was a patient which again had dementia with Lewy bodies at clinical diagnosis and then at autopsy there was a diagnosis of dementia with Lewy bodies. There was a very long lag between the scan and

autopsy. It was one of the last cases. So, there was a 7-year difference, and although the autopsy clearly states that the patient has dementia with Lewy bodies the stage is only intermediate. So, the patient, even at autopsy 6.5 years later, had a very mild illness. So, it is possible that at the times when the patient was scanned that the scan was not sufficiently abnormal to be rated visually as abnormal.

We also performed quantitative measures as part of the research project and the patients in reality did have abnormal results for one side which were only jut below the cutoff of what we felt would be abnormal.

There were also 2 cases where the diagnosis was Alzheimer’s disease and the scan was abnormal. In that case the patient was at autopsy found to have Alzheimer’s disease with cerebrovascular disease and they had an infarct. One of the cases was found to have at autopsy frontotemporal dementia and in reality the autopsy did state that there was loss of nigrostriatal projection. There was a loss of cells in the substania nigra. So, the DaTSCAN mirrors autopsy but it was not due to Lewy body pathology but to frontotemporal dementia pathology.

DR. ANDERSON: We are going to try to squeeze in one more.

DR. KIEBURTZ: I was just going to say to answer your question that I think Table 16 in the FDA briefing document will show you the two-by-two tables you are looking for.

DR. ANDERSON: Now we are going to proceed with the FDA presentations.

FDA Presentation

NDA Overview

DR. DAVIS: Good morning.

[Slide]

My name is Phillip Davis and I will summarize the major aspects of FDA's preliminary review findings.

[Slide]

As previously mentioned, we are bringing DaTSCAN to the committee in order to help us complete our review of the application. Specifically, we are seeking perspectives on two key questions, do data verify that DaTSCAN measures what it purports to measure? And, is the DaTSCAN information clinically useful?

[Slide]

The following slides will address four major areas, beginning with the applicant's marketing proposal. Next I will provide a regulatory background and context for the application, followed by an overview of the efficacy and safety data. Then Dr. Mark Levenson, our lead statistician, will provide more detailed information on the major clinical studies.

[Slide]

So, what does the drug purport to do? As previously mentioned, the most recent proposed indication for DaTSCAN relates to visualization of the DaT protein distribution in the striatum by SPECT imaging.

[Slide]

The specific DaTSCAN proposal notes the drug is administered intravenously at a dose of 3-5 mCi, with imaging performed 3-6 hours later. The image interpretation is based upon the appearance of DaTSCAN uptake in the striatum.

[Slide]

The proposed package insert notes the image is interpreted based upon striatal activity shown in transaxial images. This slide shows the duplicated package insert

images. A normal image, as shown at the top of the slide, is proposed to be characterized by symmetric, comma-shaped uptake within the striatum. Abnormal images, exemplified by the images at the bottom of the slide, are described as taking various forms of decreased uptake in the putamen and/or caudate.

[Slide]

Radionuclide products have specific regulations pertaining to efficacy based mainly upon the proposed indication. The regulations provide four major indication categories which are structural delineation, for example, visualization of knee cartilage with contrasted MRI; or functional, physiological or biochemical information assessment, for example, assessment of abnormal glucose metabolism with F18 FDG; or disease or pathology detection, such as detection of a liver mass with contrasted CT; or specific diagnostic or patient management information, such as the detection of metastatic cancer with iodine-123 MIBG.

The nature of the proposed indication determines the type of effectiveness data necessary to support the product's efficacy. In general, we view the proposed DaTSCAN indication as consistent with a biochemical

assessment type indication.

[Slide]

The regulations note that effectiveness data for radionuclides must address two aspects. First, the data must verify that the imaging test measures what it purports to measure. That is, the data must establish its accuracy. Accuracy is generally established based upon the determination of the radionuclide's sensitivity and specificity when compared to a standard of truth or when compared to a reliable reference test. Alternatively, the regulations note the accuracy and usefulness can also be established in another manner, such as by verification based upon patient follow-up.

Secondly, the effectiveness data must establish that the radionuclide provides useful clinical information. The FDA guidances state usefulness may be obvious, such as visualization of a broken bone or detection of a brain mass, such that clinical studies are not needed to establish usefulness. Otherwise, the clinical usefulness must be established in clinical studies. In most prior imaging drug approvals usefulness has been implicit with the establishment of acceptable sensitivity and specificity.

[Slide]

To illustrate the FDA approval of a radionuclide with a biochemical assessment indication which is similar to the proposed DaTSCAN indication, I cite the indication for F18 FDG. The label notes F18 FDG is indicated in PET imaging for assessment of abnormal glucose metabolism to assist in the evaluation of malignancy.

The effectiveness data supporting this claim was based upon a well-accepted mechanism of action, particularly from in vitro data, and published reports of a broad range of sensitivity and specificity using pathology as a truth standard.

The product label also notes that no adverse reactions have been associated with the product. The lack of safety concerns in the context of a well-accepted mechanism of action and reasonable evidence of some clinical usefulness supported the product's approval.

[Slide]

To place the potential DaTSCAN indication for visualization of dopamine transporter protein distribution within the striatum into a regulatory context, we regard this proposal as consistent with the regulatory options for

a functional, physiological or biochemical assessment indication.

However, our challenge in the NDA review returns to two key questions: Do the data verify that DaTSCAN measures what it purports to measure? And, is the DaTSCAN information clinically useful?

[Slide]

The DaTSCAN regulatory history is outlined here. In January, 2008 the FDA held a meeting with the company to introduce the product. We were informed that the product had been approved in Europe in 2000, and we were presented with an outline for a Phase 3b clinical study that was to be conducted during the time of an upcoming NDA application.

In August of last year we had a pre-NDA meeting where FDA informed the applicant that the extent of deficiencies within the completed Phase 3 studies appeared insufficient to support their use as confirmatory evidence of effectiveness. We recommended the company conduct at least one new Phase 3 study that used a prespecified clinically meaningful primary endpoint.

In March of this year we received the NDA which contains only data from the European development program.

Notably, these studies were designed and conducted without FDA review. FDA did provide comments regarding the Phase 3b study proposed in January of last year, but this study has not begun.

[Slide]

Like most new drug applications, the DaTSCAN safety and efficacy data can be divided into two major categories, the clinical and nonclinical studies. However DaTSCAN represents a form of molecular imaging, a product category that we anticipate will rely relatively heavily upon supportive nonclinical data to help establish the mechanism of action of the imaging probe.

The major DaTSCAN nonclinical data consists of various in vitro and in vivo animal studies that assess the binding of DaTSCAN to the dopamine transporter protein, as well as certain in vivo animal imaging studies that also include tissue analyses, as well as safety toxicology studies.

The supportive clinical studies consist of certain publications that describe the DaTSCAN active moiety's binding to human brain, and particularly in imaging autopsy study referred to as the Walker study. The Phase 3 studies

are proposed to provide the main confirmatory efficacy evidence.

[Slide]

The preliminary FDA nonclinical data observations support the contention that DaTSCAN binds relatively selectively to the dopamine transporter protein. For example, animal models show correlations between imaging results and the loss of the DaT protein. Additionally, imaging of non-human primates confirms localization of the DaTSCAN effective moiety to the striatum.

[Slide]

The supportive clinical data are notable for certain in vitro observations. In studies of recombinant human transporter protein the active moiety of DaTSCAN had a 3- to 4-fold selectivity for the DaT protein over the serotonin transporter, and 100- to 300Cfold selectivity for the DaT protein over the norepinephrine transporter.

The NDA also include published data that using autoradiography of human brains also verifies that the DaTSCAN active moiety binds to the striatum.

[Slide]

The major supportive study is an interim report

from what may be referred to as the Walker study. This study was initiated in 1996 at a single center in the UK. It uses an exploratory observational design in which a variety of subjects, but particularly those with dementia with Lewy bodies or Alzheimer's disease, undergo DaTSCAN imaging. Thereafter, patients who die may undergo autopsy to establish a definitive diagnosis of either DLB or other form of dementia.

In the interim report on-site clinical diagnoses and on-site blinded DaTSCAN imaging results were compared to the autopsy truth standard of either DLB or Alzheimer's disease.

[Slide]

At the time of the NDA submission 22 patients had undergone imaging and also autopsy. In this relatively small number of subjects DaTSCAN and the clinical diagnoses generally had similar sensitivities of 78 percent. However, the DaTSCAN specificity of 85 percent numerically exceeded the 46 percent value assigned to clinical diagnoses.

The low specificity for clinical diagnosis suggests that it may be particularly unreliable if it is used as a truth standard to differentiate DLB from

Alzheimer's disease or, as the sponsor proposes, for the distinction between striatal dopaminergic deficit and no deficit.

This is an important concept since one of the Phase 3 studies, study 301, used the clinical diagnosis as a standard of truth. It should be noted that the criteria for pathology and clinical diagnosis of DLB were based on the 1996 consensus criteria, not the revised 2005 consensus criteria for DLB.

As restated at the bottom of the slide, the Walker study suggested that the clinical diagnoses were incorrect in nearly half the cases while the DaTSCAN results were incorrect in approximately 1/5 of the cases when both were compared to neuropathology as the standard of truth.

[Slide]

Data from three Phase 3 European studies were submitted within the marketing application. Two of these studies, which were referred to as 304 and 003, examined movement disorder imaging outcomes. The third study, 301, examined imaging outcomes from patients with dementia. All studies enrolled predominantly Caucasian subjects and compared imaging outcomes to clinical diagnoses.

[Slide]

The study results were presented in the NDA with certain reporting modifications. Specifically, the previously finalized European study reports were rewritten and supplied in a version that focused upon the assessment of sensitivity and specificity where the truth standard was a clinical diagnosis made either at baseline or over a follow-up period. In the revised US study reports the clinical diagnosis truth standard was conceptualized as one corresponding either with presence or absence of striatal dopaminergic deficit.

For example, a clinical diagnosis of essential tremor was defined as no deficit, while a diagnosis of Parkinson's disease, dementia with Lewy bodies, multiple system atrophy or progressive supranuclear palsy was represented as a striatal dopaminergic deficit.

In general these modifications maintained the major analytical features of the original study reports. However, the study designs used many features that we regard as atypical for confirmatory clinical studies.

[Slide]

This slide illustrates some of the challenges with

the Phase 3 studies. In general, we anticipate at least three key features for a confirmatory imaging study. These include a prespecified primary endpoint hypothesis that has clinical meaningfulness, as well as a statistical analysis plan, a reliable standard of truth and fully blinded, independent image reads.

As shown on the table, none of the Phase 3 studies contain all these key features. Study 304, as shown in the first column, was a study that largely examined patients with early movement disorder signs or symptoms. It used a truth standard that consisted of clinical diagnosis following 3 years of follow-up, along with fully blinded independent image reads. However, the study lacked a fully developed, prespecified primary endpoint hypothesis.

Study 301, in the second column, was a study that largely examined patients with dementia. Study 301 did include a prespecified primary endpoint hypothesis and fully blinded independent image reads. However, the reliability of the truth standard is questionable since it was based upon a diagnosis of DLB or non-DLB dementia established at baseline. The study did, however, also contain clinical diagnoses after 12 months of follow-up.

Study 003 had multiple limitations in that it lacked a prespecified hypothesis. The truth standard was based upon on-site diagnosis and the image reads were performed by site investigators, both in an unblinded manner as well as an unverifiable blinded manner. Hence, we regard study 003 as particularly deficient in design features and useful predominantly for supportive, descriptive information.

[Slide]

In addition to the overall study design challenges, the 2 confirmatory studies underwent protocol modifications. Study 304, the study that enrolled predominantly subjects with early signs and symptoms of parkinsonism, had a protocol that underwent 10 amendments. The original protocol, finalized in 1998, called for the site image reads and site clinical diagnoses with the truth standard. By 2005 the protocol had been amended such that major study features had changed the plan for blinded, independent image reads and the consensus panel diagnosis after 36 months of follow-up as the standard of truth. The final primary endpoint was a descriptive summary of various performance characteristics.

[Slide]

Study 003 is a study that enrolled patients with established movement disorder diagnoses and had a protocol that was finalized in 1997. The protocol was modified four times that year but the major design features were maintained to consist of site image reads and site clinical diagnoses as the truth standard.

The study also included blinded image reads by a panel that included some of the site investigators. The study's primary endpoints were descriptive summaries of the performance characteristics based on the site DaTSCAN interpretations.

[Slide]

Study 301, which enrolled patients with various forms of dementia, used a protocol that underwent four modifications. However, these modifications did not change the fundamental design plan which consisted of independent, blinded image reads and a comparative truth standard of consensus panel diagnoses formed at baseline and after 12 months of follow-up.

The prespecified primary end of the study was defined as an establishment of DaTSCAN sensitivity of

greater than 65 percent and specificity greater than 73 percent when baseline image reads were compared to the baseline clinical diagnoses.

[Slide]

As previously described, the sponsor has reported generally favorable performance characteristics from the Phase 3 studies. However, these reports have multiple limitations and the data will be summarized in more detail by Dr. Mark Levenson following my overview of the safety findings.

[Slide]

The major DaTSCAN safety considerations may be summarized in terms of the adverse reactions, the potential for thyroid accumulation of radioactive iodine, and radiation exposure concerns.

[Slide]

The post-marketing experience vastly exceeds the DaTSCAN exposure in clinical studies. Overall, the sponsor estimates at the time of the NDA submission that over 168,000 subjects had been exposed and, to that date, no serious adverse reactions or deaths had occurred related to the study drug administration.

[Slide]

Within the eight clinical studies composing the safety database DaTSCAN was administered to 942 subjects. Twenty-five percent of these subjects experienced at least 1 adverse event, only 4 percent experienced events that were assessed by the study investigator as potentially related to DaTSCAN administration. Four percent of the subjects experienced at least 1 serious adverse event and 5 subjects died. However, none of the serious adverse events or deaths were related to DaTSCAN administration. As shown at the bottom of the slide, headache was the most common adverse event related to DaTSCAN administration and it occurred in approximately 1 percent of the population.

[Slide]

Other safety concerns pertain to the potential for thyroid accumulation of the radioactive iodine and the overall radiation safety. Administration of an iodine uptake blocking agent was used in the clinical studies, and the draft labeling also includes a similar proposal.

Iodine-123 decays with emission of gamma rays and the effective dose following administration of 5 mCi of the product is estimated approximately 4 mSv, which is within

the NRC guidelines for annual exposure to occupational workers and within the range of current nuclear medicine procedures.

Overall, our review finds that the product is associated with minimal safety concerns. To continue our discussion of Phase 3 study data, Dr. Mark Levenson, our lead statistician, will provide further comments. Thank you.

Statistical Review of Efficacy

DR. LEVENSON: Good morning.

[Slide]

My name is Mark Levenson. I am the primary statistical reviewer for DaTSCAN. Today I will discuss the preliminary statistical review of the Phase 3 studies of DaTSCAN.

[Slide]

First I will discuss the statistical design aspects of the Phase 3 studies. Then I will present some key results and finally I will discuss the level of evidence the studies provide for efficacy.

[Slide]

There were three Phase 3 studies. Study 003 was a

study of movement disorder patients. Study 304 was a study of early movement disorder patients. Study 301 was a study of dementia patients. All three studies were conducted in Europe without a US investigative new drug application.

As you have heard, there were changes from the original European protocols and clinical study reports for the US submission. Unless otherwise noted, I will be referring to the original European protocols and reports.

[Slide]

The primary objective of each of the three studies addressed the diagnostic value of DaTSCAN to distinguish diseases such as Parkinson's disease from essential tremor. The US indication under review concerned the visualization of the DaT protein within the striatum. The sponsor uses the studies as supportive of the proposed indication by equating clinical disease diagnoses with the presence or absence of the DaT protein. Thus, clinical disease diagnosis was used as the standard of truth for the DaT protein distribution.

[Slide]

This table summarizes key statistical design aspects for the three studies. Study 003 and 304 each

addressed movement disorders. Patients in study 003 had established clinical disease diagnoses, whereas patients in study 304 had early signs of parkinsonism. Study 003 included patients with diagnoses of Parkinson's disease, multiple system atrophy, progressive supranuclear palsy and essential tremor.

The primary diagnostic distinction was between Parkinson's syndrome diseases and essential tremor. The primary diagnostic distinction in 304 was between probable or possible Parkinson's disease and non-Parkinson's disease.

Study 301 addressed dementia. The study included patients with dementia with Lewy bodies, Alzheimer's disease and vascular dementia. The primary diagnostic distinction in 301 was between probable DLB and non-DLB. Note that this distinction does not include possible DLB.

The primary standard of truth for study 003 was local diagnoses at baseline. The standard of truth for 304 and 301 was based on central review. For study 304 the review was based on evaluation at 36 months. For study 301 the review was based on baseline evaluation. As discussed by Dr. Davis, the Walker study calls into question the validity of the clinical diagnoses of DLB at baseline.

[Slide]

The primary image read for study 003 was a local unblinded site read. However, in addition to the local read, 5 of the 5 investigators blindly read all images. The primary image reads for study 304 and 301 were 3 central blinded readers. The primary endpoints for all 3 studies included sensitivity and specificity. Study 304 also included other accuracy measures, including positive predictive value, negative predictive value and accuracy.

The primary statistical analysis for both study 003 and 304 were 95 percent confidence intervals. It is important to note that there were no prespecified statistical tests or thresholds for these studies. Study 301 had prespecified statistical tests. Sensitivity was tested against a value of 0.65 and specificity was tested against a value of 0.73.

[Slide]

Now we will present some key results of the study.

[Slide]

First, the disposition and demographic summaries.

[Slide]

Study 003 enrolled 250 patients, and 224 of these

patients received DaTSCAN. All of these patients had standard of truth evaluations. Of these 224 patients, 220 had evaluable images. The efficacy set on this table is defined as those patients with a standard of truth evaluation and an evaluable image.

There were 220 patients in the efficacy set for study 003. The primary efficacy set included those patients who were part of the primary diagnostic distinction. Thirty-six healthy volunteers in the study were not part of the primary efficacy set.

For study 304 I highlight that only 102 of the 179 had a standard of truth evaluation. The main factor responsible for this difference is the 3-year follow-up required for the standard of truth evaluation. Later on we will compare that patient set and the efficacy set for this study.

For study 301 I highlight the difference between the efficacy set and the primary efficacy set. The main factor responsible for this difference was that patients with possible DLB were not included in the primary efficacy set. Overall, for all three studies the vast majority of dosed patients had evaluable images.

[Slide]

Here are some demographic summaries for the three studies. In each study the majority of patients were male. The median age for the 2 movement disorder studies was 64 and 63. The median age for the dementia study was higher, at 75. Note that almost all patients in these studies were Caucasian.

[Slide]

As I have noted, because of the 3-year follow-up in study 304, a large number of patients were not in the efficacy set. This table and the next compares baseline factors for the dosed patient set and the efficacy set. This table shows that the demographics were similar for the two patient sets.

[Slide]

This table gives the local baseline diagnoses for the dosed patient set and the efficacy set for study 304. Based on these baseline factors, there were no observed differences between the dosed patient set and the efficacy set.

[Slide]

For study 301, as I have noted, a large number of

patients in the efficacy set were not in the primary efficacy set. Of the 313 patients in the efficacy set, 56 patients had possible DLB and 26 patients had no diagnoses. These 82 patients were not included in the primary efficacy set. A secondary analysis considered the possible DLB patients.

[Slide]

Now I will discuss the sensitivity and specificity of the blinded readers for the three studies. Unless otherwise noted, these results were based on the primary efficacy sets and the primary diagnostic distinctions. All confidence intervals are 2-sided 95 percent exact intervals.

[Slide]

Here are the results for the 5 blinded readers in study 003. Recall that the study consisted of patients with existing diagnoses and the blinded readers from this study were chosen from the study investigators. The point estimates for sensitivities ranged from 93 to 97 percent and the lower limits of the respective confidence intervals ranged from 87 to 93 percent. The point estimates for specificities ranged from 74 to 96 percent and the lower limits of the confidence intervals ranged from 54 to 81

percent. As stated before, there were no prespecified thresholds or statistical tests for this study.

[Slide]

Here are the results for the 3 blinded readers in study 304. The point estimates for sensitivities were all approximately 78 percent and the lower limits of the confidence intervals were all approximately 66 percent. The point estimates for specificity were all 97 percent and the lower limits of the confidence intervals were all 83 percent.

It is interesting to compare these results to those of study 003. In this study the sensitivities were notably lower. Perhaps this is because the study involved patients with early signs of parkinsonism and not patients we existing diagnoses as in study 003.

[Slide]

Here are the results from the 3 blinded readers in study 301 for the primary diagnostic distinction of probable DLB versus non-DLB. The point estimates for sensitivities ranged from 75 to 80 percent. The point estimates for specificities ranged from 89 to 91 percent. The study had prespecified thresholds of 65 and 73 percent for sensitivity

and specificity based on the lower limits of the 95 percent confidence intervals. For 2 of the 3 readers the thresholds were exceeded. For 1 reader the sensitivity threshold was missed by a very small amount.

[Slide]

This table shows the effect of including the possible DLB patients in the analysis in study 301. The sensitivities and the specificities on the left are those from the primary analysis shown on the previous slide. The sensitivities and the specificities on the right are those with a diagnostic distinction of probable or possible DLB versus non-DLB. The inclusion of the possible DLB notably lowers the sensitivities. This comparison demonstrates a balance between the validity of the standard of truth and the clinical relevancy of the population. I will return to this idea later.

[Slide]

This table compares the sensitivities and specificities based on the baseline standard of truth, which were the primary ones, and the 12-month standard of truth diagnoses. The results based on the two time points were similar. Extending the diagnosis time point to 12 months

did not result in notable changes. It is possible that 12 months of follow-up is not sufficient for DLB diagnosis.

[Slide]

Now I will discuss the study results and the level of evidence they provide for efficacy.

[Slide]

First some summary of the studies. Only one study, 301, had prespecified hypotheses. The study rejected the hypotheses of exceeding thresholds for sensitivity and specificity. The other studies, 003 and 304, did not have prespecified hypotheses but did have prespecified analysis plans. However, the prespecified plan for 003 was based on an unblinded read and cannot be considered adequate.

Study 304 has significant loss to follow-up, which was not unexpected because of the 36-month follow-up. A review of some baseline characteristics did not reveal any obvious bias in the follow-up set of patients. Likely, because all studies were conducted in Europe the patients in all three studies were overwhelmingly Caucasian and may not be representative of the US population.

[Slide]

As noted, there was a difference between the

proposed indication of visualizing the DaT protein and the study objectives which were of a diagnostic nature. Input from the committee on the use of the clinical diagnoses criteria used in these studies as a standard of truth for the presence of the DaT protein will be important in evaluating the usefulness of these studies.

Sensitivity and specificity varied by the study population. We saw that the inclusion of the possible DLB patients in study 301 resulted in lower sensitivities. Likewise, study 304, which had early movement disorder patients, had lower sensitivities than study 003 which had patients with movement disorder diagnoses.

The clinical utility needs to be evaluated with respect to both the study patient population and the resulting sensitivities and specificities. This is another area where input from the committee will be important.

[Slide]

Finally, from a statistical perspective, the Phase 3 program was not strong. There was only one study with prespecified hypotheses. There are questions on the use of the particular clinical diagnoses as standards of truth for the DaT protein. As seen in the Walker clinical diagnosis

at baseline for dementia was not seen to have good performance. There were extensive amendments to study 304.

The studies cannot support a diagnostic indication. The question is can they support clinical utility and for what clinical population. Thank you.

Clarifying Questions

DR. ANDERSON: At this point we are open for any clarifying questions for the FDA and their presentation. Dr. Tatum?

DR. TATUM: Let’s come back to the part where you just ended, which is that one of the problems I think we have here is the co-mingling of two different indications. Mostly the conversation right now has been centered on a diagnostic indication and the data, the way you put it forward, is basically being held to the standards of a diagnostic indication which you are saying is needed.

So, where does the bar exist for demonstration of clinical utility in the absence of a diagnostic indication? I guess that is what you want us to decided, from what I just heard, but I would like a little input from the FDA on that.

DR. RIEVES: Well, we are entering the realm of

molecular imaging which is very complicated. It is sort of a unique regulatory paradigm. Dr. Davis gave the example of F18 FDG as an example. If you go to that label and you look and try to find out what the performance characteristics are for that product they are not there. Dr. Davis expanded upon why that product was approved in the manner it was.

That is atypical for our imaging agents, our diagnostic products, because most of them do have established performance characteristicsB-sensitivity, specificity-Bagainst a solid clinically meaningful truth standard, whether that is long-term follow-up or pathology for example in a cancer situation or many other examples.

So, here we are challenged by the situation where the company is asking for a biochemical type indication, yet the clinical studies that we have coming to us are coming with a proposal that we use the clinical diagnosis as a surrogate, if you will, for the biochemical assessment. It is just the opposite of what we usually see in clinical studies where we usually have a biochemical assessment as the surrogate for the clinical. Here we have the clinical diagnosis as the surrogate for the biochemical abnormality.

That is a very difficult situation. This goes

into the realm of judgment. As you will see how we posed our questions, we are asking the committee to consider the totality of the findings, but also to somewhat struggle with this dilemma, like we are struggling with it, particularly in molecular imaging here where the safety concerns do not appear to be all that substantial, perhaps beyond misdiagnosis which again ties back into the indication, the claim related to that.

So, I don't think we have a clear, pat answer. As you know, our guidances on this subject of diagnostic imaging are very long, and they are very complicated to decipher, candidly, and I think the dilemma is somewhat reflected in the length of those guidances.

There is a precedent from FDG for taking a favorable approval action in a situation where the performance characteristics are not definitively established. Again, it is based on the totality of the data, the risk/benefit assessment. That similar scenario may apply here, and that is actually one of the questions we are hoping to get to the committee. If the committee decides no, that paradigm does not apply, that is important information for us to have.

DR. TATUM: Of course, as you pointed out, it is unfortunate you picked FDG because we know it was approved more outside of the FDA than it was inside. So, it doesn't make a good example for what we can really base things on. I noticed that in the material amyloid was another one that seemed to be a much more consistent model, I guess, to go back on. So, I don't know if there is going to be any more discussion of that but I think that would be good.

The totality of the data has come up several times over the last few months. So, the experience with the agent approved in the UK, is that part of what would be considered as possibly showing some clinical benefit outside of the set-up Phase 3 type study with statistical analysis? Or, is that something we should really look at somewhat with a jaundiced eye? That is not an easy question.

DR. RIEVES: They are not easy questions, you are exactly right. The thing that I think we are struck by is, is this the best we have in terms of dealing with the situation. So, yes, we view all clinical studies with some bit of jaundice and skepticism. As I said, that is our job, verification.

On the other hand though, we are taking a look at

those studies and we are hoping the committee will take a look at the studies. The company somewhat took an approach in which they couch the truth standard not so much really as the clinical diagnosis, and I think they will expand upon this, but as it was proposed to us, the truth standard was the presence or absence of striatal dopaminergic deficit, or SDD. It may seem a bit semantic, but it tries to get away from the implicit specificity associated with a definitive diagnosis of Parkinson's disease or MSA for example.

So, conceivably that couching of SDD may be a more reasonable approach to viewing those clinical studies. We have not dismissed this out of hand. We could have and not have been here today, but we did not. We thought it was worth taking an eye, even if it is a jaundiced eye as it should be from our perspective, with respect to these data. But they are definitely not clear-cut. These are atypical features, as Dr. Levenson and Dr. Davis said. So, there is considerable hand-wringing going on with the situation.

We are looking for advice on how to handle the situation. The amyloid was a great experience and we also have the benefit of getting the committee's feedback in the amyloid development program. If you notice, that feedback

did not enter into this development program so we are hoping we can have a little bit more clear pathway with the amyloid situation. But any advice in this area, because we have other products on the tarmac that will come down with these same challenges, we are eager to hear it.

DR. ANDERSON: Dr. van Belle?

DR. VAN BELLE: I actually had a question for both the sponsor and the FDA. One of the issues is that we have a clinical diagnosis and we have a neuropathological diagnosis, and the argument seems to be that there is a possible discrepancy between the clinical diagnosis and the neuropathological diagnosis.

So, from a statistical point of view the question is if we estimate the sensitivity and specificity based on the clinical diagnosis, what is the effect of mis-classification on specificity and sensitivity? So, maybe I should ask the sponsor first, what is your interpretation of that? What does mis-classification, in terms of the clinical versus the neuropathological diagnosis, do to the specificity and the sensitivity of the test? I do have an answer but I would sooner have them struggle with it for a minute.

DR. ANDERSON: Well, what I would like to do is I would like to hear your answer and also the larger answer, but I think at this point they have asked me to help try focus us on clarifying the FDA's presentation and questions from that. We will turn to some of these larger, more expansive issues in the afternoon. So, if you will bring that up again, please. Dr. Katz?

DR. KATZ: Yes, I don't know if this is either a clarifying question. You can decide. A couple of questions for Mark. You mentioned a couple of times that two out of the three studies didn't have primary hypotheses. They had primary analytic plans but not hypotheses. Is that terribly critical in a case like this? Is there a standard for what we would consider acceptable sensitivity and specificity for example?

The one study that did have a primary hypothesis I think set the sensitivity somewhere in the 60 percent-ish and specificity in the 70 percent-ish range. Depending on which analysis you did in the other two studies, they clearly met those standards. So, I am wondering how critical a flaw it is that they didn't prospectively designate a prominent hypothesis. The other one--

DR. ANDERSON: Why don't we let him answer this one and you can come back?

DR. LEVENSON: First of all, for study 301 where they had the prespecified thresholds, that was the only dementia study. So, it may not be fair to say those are the relevant sensitivities and specificities when you are talking about the movement disorders, and everybody else at the table would know better than me about that.

In terms of having a prescpecified hypothesis as opposed to a prespecified analysis plan, first I would say the prespecified plan and the design of 003, the movement disorder study, was not acceptable, even if it had a prescpecified hypothesis. It was based on unblinded readers. The standard of truth criteria, as Dr. Davis can say better, was weak. So, the prespecified plan I don't think buys you anything in that study.

Now, FDA guidance, as you are well aware, generally requires two adequate and well-controlled studies for approval and there are, of course, exceptions to that. Further, guidance explains what a confirmatory trial is and that involves prespecified hypotheses.

So, from kind of a regulatory, statistical point

of view, these studies do not meet the threshold for approval. But there are exceptions. So, we are here because the totality of evidence may overcome that. Does that answer your question?

DR. KATZ: Yes, it addresses the question. Your answer also alluded to my second question which was on 003 which, you said, by design was more or less inadequate because the primary analysis was to be done based on unblinded readings. But there was this panel of blinded readers. I think we saw the results of those analyses presented and the sensitivities and specificities were I think 80-ish to 90 percent. It is true that wasn't the primary analysis but the data are there.

DR. LEVENSON: Yes, well, I have two comments on that. Those blinded readers were chosen from the study investigators themselves. So, there is not the independence that we seek. As the imaging FDA guidance will point out, as a completely independent panel of image reviewers, they do not meet that standard.

The other comment about 003 is especially how it differs from the other movement disorder study. These are patients with existing diagnoses. So, you have to question

the relevancy of this population in clinical practice. Is this the population you want to be looking at when you evaluate sensitivity? I am not going to answer that question but I am going to pose that question.

DR. ANDERSON: Dr. Twyman?

DR. TWYMAN: Actually, my question was on the adequacy of the Walker data set as a performance characteristic measure but that could be saved for this afternoon.

DR. ANDERSON: Dr. Royal?

DR. ROYAL: As I think back on Dr. Perlmutter's presentation, he seemed to accept that there was good data that these tracers work, that they measure what they are supposed to measure or what they are purported to measure, these dopaminergic deficiencies.

He even seemed willing to accept that they had reasonable diagnostic accuracy, although how you are going to sort all of that out when a clinical diagnosis is in doubt is not clear to me.

His objection seemed to be marginal cost effectiveness. So, the question I have for the FDA is what role, if any, does cost effectiveness analysis play in

approving an agent.

DR. KATZ: I am supposed to answer that? I don't think it really plays much of a role. Again, I don't deal in my day-to-day work with imaging agents so I don't know if there are different considerations that are brought to bear there, but as a general matter we look to see whether or not it is effective; whether there is substantial evidence of effectiveness, however that is defined in that particular setting; and whether it is safe in use and we make a judgment whether or not those two factors justify approval. We don't take cost benefit into consideration.

DR. ANDERSON: At this point we are reaching a break. We are going to have the open public hearing and discussion in the afternoon. We have an hour break for lunch. It is 12:17 on the computer up here. We will resume in an hour.

For the committee members, there is a special lunch location organized. There is the hotel restaurant with take-out. We are sort of just on our own to be back in an hour. The room is locked in our absence so if you have something you want to take with you, you are supposed to take it with you now because you will not be able to get

access until we return.

One last admonition is to please not discuss the deliberations or the questions and the issues while you are at lunch. Please restrain yourself until we come back this afternoon.

[Whereupon, the proceedings were recessed at 12:17 p.m. for lunch, to resume at 1:15 p.m.]

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

Open Public Hearing

DR. ANDERSON: Welcome back, everyone. We are going to begin the open public hearing portion of the meeting and I have a statement to read at the beginning:

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 you may have with the sponsor, it's 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 this issue of financial relationships at the beginning of your statement it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy and respect. Therefore, please speak only when recognized by the chair.

Thank you for your cooperation. We have three speakers for today, well, we have four but three presentations. The first two presenters, speaking together, are Dr. Marek and Dr. Seibyl.

DR. MAREK: Thank you. My name is Ken Marek. I am the President of the Institute for Neurodegenerative Disorders and one of the founders of Molecular Neuroimaging. Neuroimaging is an imaging services company which has provided services to GE as well as to competitors in this

area, Alseres Pharmaceuticals, Abbot Radiopharmaceuticals.

I am here with my colleague, John Seibyl, the other co-founder of Molecular Neuroimaging, and I am grateful for the opportunity to address the committee, to provide some additional information with regard to the clinical utility of DaT imaging based on some of the work that we have done over the last decade or so. Could I have the next slide, please?

In the last decade or so we have focused most of our attention on evaluating DaT imaging in Parkinson's disease using Dopascan or beta-CIT, which is a close congener of DaTSCAN. The structure of these molecules and their relationship to cocaine are illustrated here, as has been already discussed.

Over the years there have been a number of studies, and some of these have already been outlined today in the presentations, to really indicate that DaT imaging has been of use as a tool really to mimic what would be the expected pathology in Parkinson patients.

We, ourselves, have done more than 4,000 beta-CIT scans in over 30 studies, really showing that there is a reduction in early Parkinson's disease in the putamen

greater than the caudate; that it is asymmetric, correlating with severity of disease; is able to monitor disease progression. All of these issues have been already mentioned today. But that has also been true in a number of studies using Dopascan as well as DaTSCAN.

The point I would like to make is that in considering the use of DaT imaging as a tool to assist with diagnosis it is important, as is illustrated in this slide, to keep in mind that at the time of diagnosis of Parkinson's disease about 50 or 60 percent of the DaT imaging activity is already gone and so it provides an opportunity really to take advantage of this tool. As Dr. Perlmutter indicated, there is even a loss of imaging activity prior to the onset of symptoms.

What I would like to do very briefly is outline two sets of evidence to suggest that there might be utility of DaT imaging in the diagnosis. Fortunately for me because I have limited time, both of these issues have already been discussed in part by some of the other speakers.

I will focus on two studies that we have done, which I am calling Suspects and SWEDDs, Suspects, meaning a study in which we looked at patients with suspected

Parkinson syndrome really to assess can DaT imaging improve diagnostic accuracy. SWEDDs, again is these subjects who were identified in clinical studies who have normal imaging but have been enrolled in clinical studies as Parkinson's disease subjects really to assess whether DaT imaging can identify subjects who do not have Parkinson syndrome.

This is a study really that Dr. Perlmutter described in some detail and, as I say, has already set the stage. I am going to really provide some of the data that expands on the published work, again, a study which we called Query-PD or Query-PS to try to understand whether DaT imaging can be helpful in diagnosing difficult to diagnose patients with Parkinson's disease or Parkinson's syndrome.

The methods are outlined here. Again, community neurologists were asked to refer patients about whom they suspected parkinsonism but were uncertain. They were brought into our center where they were evaluated by a movement disorder neurologist and at baseline we also obtained a CIT scan and those baseline evaluations were compared to a gold standard clinical diagnosis done at 12 months, blind to the imaging.

The demographics are here, 137 patients from 37

community neurologists; typical demographics one would expect to see in a Parkinson study.

The relevant data is illustrate in this slide. It is a bit small. Certainly I can't see it so I don't know if anyone back here can see it. But if you look at the top panel, the key piece of information is that of these 36 neurologists who referred 137 patients in whom they suspected Parkinson's syndrome only 43 percent actually turned out to have Parkinson's syndrome, at least as defined by a movement disorder expert at a 12-month gold standard. It is only 43 percent.

Among the movement disorder neurologists who evaluated those subjects at baseline, they did better but still their sensitivity and specificity were in the sort of 70-80 percent range, and baseline imaging was about 88 or 89 percent sensitivity and specificity, suggesting that, again, early imaging was the best predictor of the clinical gold standard diagnosis in this larger group.

I would point out that this group really expands the work that Dr. Perlmutter mentioned earlier. It is a larger group. It has a 12-month gold standard rather than a 6-month gold standard. And, we made an effort to have a

more even distribution of people who did and did not have Parkinson's syndrome. Really these are difficult to diagnose subjects, so not people who are typical patients.

The other piece of data that I think is very interesting is that we then asked those same neurologists how this would impact their clinical practice. In this slide you see, if you look at the bottom row, that at baseline about 47 percent of those individuals would have considered treating subjects with dopaminergic medications. Once they learned the imaging in the positive imaging group that increased to 74 percent; in the negative group that decreased to 25 percent, suggesting that at least these neurologists were certainly influenced with regard to their practice by the imaging data and certainly put that into the equation of how they treated patients.

I guess I would disagree slightly with Dr. Perlmutter's discussion earlier in that I don't think that just treating patients with levodopa is an alternative at diagnosis. It is often the case that these patients don't respond to levodopa because they are early in disease or, indeed, that they may have negative effect because of levodopa.

But, in any case, this is data really that reflects the community neurologists' view after they received the imaging data.

I am just going to skip on to the opposite side of the coin. Again, this was mentioned already by Dr. Grosset and by Dr. Stacy. We have uncovered a group of individuals in clinical trials whom we have called SWEDD. My colleague, John Seibyl, is responsible for that term. About 8 to 10 to 12 percent of people enrolled in early clinical trials have what are really normal exams. We have really spent some time defining what those people have or don't have.

This is just a slide you saw earlier just to point out in the PRECEPT study, a study of about 800 subjects, if you look at this histogram which shows the percent of age-adjusted DaT uptake in the subjects in that study, and this is percent age-adjusted compared to a healthy subject database of 100 subjects who have been imaged and evaluated in another study, what you see is that there is a nice peak at about 50 percent of normal in those people who have a DaT deficit. Those are the Parkinson's disease patients. Then there is another peak that centers around 100 percent and those are the subjects we call SWEDD patients.

Just one more piece of data, if we now follow those patients, as we have for 2 years, and image them again and follow them clinically, you can see in these 72 subjects who were SWEDD that there was really no difference in their imaging outcome over this period of time. So, they didn't change. Of course, as expected and as Dr. Grosset pointed out, in the Parkinson's disease patients you do see a change, in this case of about 8.5 percent over 2 years.

Importantly, in the clinical outcomes there is also no change. So, these patients certainly don't behave like Parkinson's disease patients, nor do they require dopamine therapy during this 2-year period by and large. So, certainly they seem very different and, in our view, having followed some of these people for as long as 4 or 6 years, it is very unlikely that they have Parkinson's disease.

I am going to close by saying that, you know, DaT imaging in diagnosis of Parkinson's syndrome, on the one hand, I think the Suspect study suggests that there is need for additional tools for community neurologists for difficult to diagnose patients with suspected Parkinson's syndrome, and that DaT imaging is a useful tool for those

patients.

On the other side of the coin, DaT imaging can identify subjects without Parkinson's syndrome even among subjects who have been enrolled in clinical studies by movement disorder experts although it is early in their disease and DaT imaging is certainly a useful tool to identify patients who do not have Parkinson's disease.

I am going to close there. Thank you very much for your attention.

DR. ANDERSON: Our next speaker is Dr. Norman Foster.

DR. FOSTER: Hello, my name is Norman Foster. I would like to thank the committee for the opportunity to provide my perspective to your deliberations on this new drug application.

I don't have any slides. I did have a statement that I hope you have a copy of. I am representing only myself here today. I have paid my own travel and lodging expenses and have not received any payments or honoraria for my attendance or my comments today. However, in the past I have been a scientific advisor for GE and have many other research support mechanisms that aren't relevant to this

discussion.

As will be apparent from my statement, I have a long-standing interest in molecular brain imaging and in the care of patients with neurodegenerative diseases. As a consequence, I felt compelled to be here today and make some comments. I hope you find what I have to say helpful.

For those of you who don't know me, I am a professor of neurology and a senior investigator in The Brain Institute at the University of Utah in Salt Lake City. I direct the Center for Alzheimer's Care, Imaging and Research at the University of Utah, where I maintain both an active clinical practice and also conduct research. I have been actively involved in the care of patients with neurodegenerative diseases for over 30 years.

At the University of Michigan, in 1984, I developed the first clinic in Michigan devoted to the diagnosis and treatment of dementia. When I moved to the University of Utah, in 2005, I developed the first dementia clinic in the Intermountain West. Today I see patients with memory problems and dementia two days a week in the Cognitive Disorders Clinic.

My research has focused largely on the practical

use of imaging to better understand and manage Alzheimer's disease and related disorders, including progressive supranuclear palsy and dementia with Lewy bodies. I have been involved in the development of radioligands to measure neurotransmitter function, including presynaptic and postsynaptic cholinergic and dopaminergic markers.

Perhaps surprisingly, I have never used the drug under discussion here today. Nevertheless, I understand the rationale for the use of these agents and what is involved in their development and validation.

I am passionate about translating advances in brain imaging to the routine care of patients, not just limiting this work to theoretical research. I led an NIH-funded multicenter study to evaluate the value of FDG-PET to distinguish Alzheimer's disease from frontotemporal dementia. I am currently an investigator in the Alzheimer's Disease Neuroimaging Initiative, and in a study funded by Medicare to determine whether FDA-PET can improve the care of patients with mild cognitive impairment.

My purpose in attending this meeting and making a presentation is to make sure that the committee understands how the availability of an agent to detect loss of

functional nigrostriatal dopaminergic neurons can significantly benefit patients and their physicians.

To illustrate this, I would like to tell you briefly about three patients that I saw recently that illustrate how knowledge about nigrostriatal dopaminergic function can enhance diagnostic accuracy but, furthermore, also improve diagnostic confidence on the part of the physician and also provide more specific and appropriate treatment.

The patients I will tell you about aren't really the kind of patients that typically would be included in research studies. They have too many co-morbidities or atypical features. Yet, I think these patients can benefit the most from the kinds of agents that we are talking about today. Their situations aren't represented in the data the manufacturer has already presented. This kind of information on using imaging will be of greatest help for clinicians in these cases.

The first patient is a 70Byear old man who developed unusual behavior during an overseas trip. He went into a women's restroom and didn't seem to understand what was wrong with that for a while. He also was going through

the customs and couldn’t answer questions. As you can imagine, this was pretty upsetting to the patient’s wife who was with him.

About the same time he began to have nausea and seemed to have a fever. He developed sleep problems and saw a doctor who diagnosed Alzheimer’s disease and started clonazepam to try to help with his sleep. Then he began to act out his dreams and had prominent visual hallucinations.

When I examined him his nausea and fever had resolved, but he still had memory problems and he did not have any parkinsonism, even though I would have suspected that on the basis of the visual hallucinations and his sleep disturbance which sounds like REM sleep behavior disturbance.

Did he have dementia with Lewy bodies rather than Alzheimer’s disease? Of course, this would be possible rather than probable DLB because he didn’t have parkinsonism. Were these problems due to a medical illness and then medications caused the sleep problems, or was this DLB? Dopamine receptor imaging would have helped me answer these questions.

The second patient was a woman who came to me,

again recently, only after 5 years of progressive dementia. On her examination I found that she had bradykinesia, moderate limb rigidity without tremor. Her doctor hadn't noticed this and her family couldn't tell me when these problems had actually begun. The patient couldn't tell me about hallucinations. She was too impaired.

Does this patient have dementia with Lewy bodies or is this Alzheimer's disease in which she had developed these motor symptoms only late in the disease? Is it worth the risk of side effects to start a trial of levodopa? If so, how far shall I go? My confidence is unclear about this. Dopamine receptor imaging would help me answer these questions to manage this patient.

I received a consultation for a third patient after her discharge from our psychiatric unit for disruptive behavior, delusions and hallucinations. They recognized that she had dementia, fortunately, but her previous physician had started treatment with neuroleptics without documenting a neurologic examination. Now she has rigidity but it is unclear whether this is drug-induced or spontaneous.

Stopping antipsychotics isn't feasible because she

still has psychotic symptoms. Does she meet criteria for dementia with Lewy bodies? I can't tell because I don't know whether her parkinsonism is spontaneous or drug-induced. Is this Alzheimer's disease with just drug-induced parkinsonism? Are expensive antipsychotics necessary because this is dementia with Lewy bodies or not? Can typical antipsychotics be safely used? A dopamine receptor scan is the only way that these questions can be answered.

In summary, the approval of an imaging agent allowing an in vivo assessment of neurotransmitter status would be a historic advance in neurology. It would provide a precedent for translating further imaging advances to improve patient care. Furthermore, it would stimulate additional research leading to improved technology with more sophisticated and targeted utilization of imaging in clinical practice.

On the other hand, failure to approve such an agent in the face of considerable evidence available will set back translation of advances that I would like to see happen to help patients and to stunt the development of similar agents.

In your deliberations I hope you will keep in mind

the effects of your decision on patients and on their physicians who need more tools to better diagnose and manage neurodegenerative diseases. Thank you.

DR. ANDERSON: Thank you. Our third speaker at the open public hearing portion is Dr. Thomas Chaly.

DR. CHALY: I am Thomas Chaly from the Weinstein Institute of Medical Research, North Shore Long Island Health System in Manhasset New York.

I came here with the support of North Shore Island Health System in travel and stay in the hotel. I have no special connections to the sponsor nor am I receiving any payment from any other agency.

I was involved in developing imaging agents for Parkinson's and movement disorder for the last 20, 22 years. We have synthesized the FP-CIT, F18 level FP-CIT, in 1996 and we published a paper on that one. It is exactly the same as that compound that they are presenting here today except the level is on F18.

We did the dosimetry at that time and we compared the three compounds at that time, FP-CIT, and the other one is F-dopa and the other one is raclopride. And we found that FP-CIT has 6 times more radiation to the striatum than

F-dopa and 10 times for the raclopride.

The problem with these highly binding receptor compounds--the problem is it goes and it stays there in the striatum. Compounds like cocaine analogue, which has a high affinity for the striatum, it stays in the striatum very long and the dosimetry has to be estimated based on the striatal radiation rather than the whole brain radiation dose, especially in the case of DaTSCAN since it requires 5 mCi dose.

When we did the PET Scan with the F18 FP-CIT, we used 1 mCi considering the fact that the striatal radiation is much higher and sometimes it exceeded the bladder radiation. Therefore, there are some safety issues concerned about these cocaine analogue imaging agents.

On top of that, these patients are very sick. They come to the hospital and they want to get the scan done and get out from there as soon as possible because they are off medication for a long time.

When you look at the study, you can see that the reagent has to be injected into the patient and the patient has to wait 4 to 6 hours to do the scan. They have to be off medication for that. These patients are real patients,

sick patients. There is real public concern regarding that when putting them for 6 hours off medication to do a scan like that.

There is a problem with iodine, also. We have to prevent--some people are allergic to iodine so we have to consider that also into consideration.

So what I want to ask the committee is this, we have other imaging agents for dopamine detection available now for the last 20 years. We are using it routinely clinically and we are given results based on that one to the satisfaction of the physicians. And that is using the best technology, better than that SPECT technology that is using PET.

So, this technology is available. They are now. The only problem is we haven't got the FDA approval for that one. We have been trying that for the last 20 years. I hope that one day we will get it.

But what is the advantage of this particular DaTSCAN over F-dopa scan or any other scan that is presently used for Parkinson's, detection of this DatSCAN, detection of this striatal region of this? What is the advantage there?

Here we have an agent that we can inject into the patient. In 90 minutes time, we can finish the scan. The patient is not going to get much radiation there because 80 percent of the radiation ends up in the bladder and the patient can go to the washroom and the radiation can be removed.

The scanning technique is also very useful in the case of fluorodopa. We inject the patient with the F-dopa, fluorodopa F18, imaging agent and we let the patient go to the washroom before he goes to the scan for 15 minutes on the scanner ...[microphone off.]

DR. ANDERSON: I am sorry to be impolite but I have been told that, since everybody had an assigned time, at this point when the microphone has gone off the assigned time for the open public hearing has been concluded. Thank you, Dr. Chaly.

Panel Discussion/Committee Questions

DR. ANDERSON: At this point the open public hearing portion of this meeting has now concluded and we will no longer be taking comments from the audience. The committee will now turn its attention to address the task at hand, which is the careful consideration of the data before

the committee as well as the public comments, and we are now going to proceed to the questions that the committee has as well as the panel discussions.

I would like to remind the public observers at this meeting that, while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

At this point I guess we are ready to move to the first question. We have four questions before us today, of which only one is a voting question. For the others the FDA is primarily interested in our discussion and our opinions on the issues and it makes, I think, greatest sense to sort of consider them one at a time and after we have sort of come to some settling point I will try to rephrase the consensus for the record.

So, the first question before us today is do the preclinical and clinical data demonstrate that DaTSCAN allows visualization of the dopamine transporter distribution within the human brain striatum?

Is there anybody in particular who feels strongly that they would like to start this up? Perhaps some of our neuroimagers are stronger for these issues? Dr. Royal?

DR. ROYAL: As I said earlier, I haven't heard anyone present testimony saying that this agent doesn't measure what it is being claimed to measure, that is, dopaminergic deficits in the brain.

There are obviously some issues. You know, a disease state is not a binary state. There is going to be a gradual loss of dopaminergic function and where exactly you draw the line between what is normal and abnormal I think is unclear. But I think that is true with almost every disease that we deal with. But, you know, with the animal data and what limited human data is available it seems to me that the drug does what it is claimed to do.

DR. ANDERSON: Dr. Tatum?

DR. TATUM: I think one of the things that we talked about a little bit before was that that is one of the critical pieces of this, and in the example we had with FDG there was a lot of in vitro data that was really important.

However, we really had limited information on the preclinical provided in this. I did go back and dig through some of the literature which was very helpful to me in coming to the conclusion that it really was representing what was being stated now and what they want for the use.

DR. ANDERSON: Dr. Ziessman?

DR. ZIESSMAN: Yes, I would agree with that. I think the evidence does show that the indication for which it is being recommended-Bit does image that physiology and anatomy.

I think one of the things that is impressive about this to me is that, at least looking at the images and reading the literature, this is an easy study to interpret. In fact, I cannot think of another nuclear medicine study that is easier to interpret than this is.

It is not exactly just binary but it is pretty close to that and the only caveat I would put with that is that I guess if this is approved I still would like to have some quantitative method to confirm by visual interpretation of the study. It needs to be a simple quantitative method because really it is mostly right to left differences, although I am not quite sure if it would be limited to that. But I think the clinician out there would need something to help confirm in his mind that, in fact, this is what he thinks it is when he looks at it.

But my impression at this point is that this is an easy study to interpret and I don't think the question

should be whether or not these studies were interpreted correctly or not because I think they probably were.

DR. ANDERSON: Dr. Kieburtz?

DR. KIEBURTZ: I just want to echo that I think the preclinical and clinical evidence is compelling, if not almost unquestionable that this does what it purports to do. I would make the caveat that it can be modified in various ways. The binding site could be modified. There can be competition for binding, whether pharmacologically or not. Plus, transporter could be expressed. There could be more expression of other competing binding sites or transporters for the ligand. So, it is not uncomplicated. That is just a handful of things that could happen but I think unquestionably to what question 1 asks, yes.

DR. ANDERSON: Dr. Herscovitch?

DR. HERSCOVITCH: I would agree that this agent images dopamine transporter on the totality of the evidence, much of it preclinical and animal work very little of which was presented today. So, I guess my question isB-I think I have the answer but how much of the evidence to support that answer has to be in the submission? For example, I personally have concerns about the preclinical studies where

the gold standard of an abnormality of the dopamine system was the clinical diagnosis. This sort of harks back to the discussion that this group had last year with regard to validating an amyloid binding imaging agent.

So, although I would agree with all my colleagues with regard to what this agent does, I have questions, and maybe it is a regulatory issue or committee issue, about how much do we have to have presented to us to critically evaluate versus what some of us may have come to this meeting knowing beforehand from our own reading or the reading that we did of additional papers in the literature to help convince us that this agent does successfully image the DaT?

DR. ANDERSON: Dr. Mattrey?

DR. MATTREY: Yes, I again would echo that I am convinced that it actually images what they claim it images. I think it would be easy to label the DaT on the autopsy specimen, because that is what we are actually imaging, rather than correlated to the number of neurons expressing dopamine, which is an indirect evidence. I think it might answer Karl's question to some degree.

But there is no question in my mind, based on the

data presented, and I am not up on that literature, that it is actually imaging what it is supposed to image. The connection to the clinic is always a difficult question but as a molecular imager I am happy. You know, if they show me that the receptor is down then they are actually telling me that the receptor is down.

DR. ANDERSON: It seems like the consensus is that as far as the first question goes, sort of the demonstration that DaTSCAN is allowing visualization of the dopamine transporter distribution in the human striatum, there seems to be a consensus that that has been demonstrated either by information here or information available to members through their expertise prior to coming.

Were there other issues related to this question, Dr. Rieves, that you would like us to expand upon?

DR. RIEVES: No, we are content with this.

DR. ANDERSON: So, now we have the slightly more difficult transition to question number 2, which is again a discussion question and there may be some more discussion.

There were three Phase 3 clinical studies, that were highlighted today, in the assessment of DaTSCAN images in comparison to clinical diagnoses. There were clinically

diagnosed dementia cases and movement disorder cases.

I will read both sections here together. Part (a), is clinical diagnosis, as formed in these specific studies, a satisfactory diagnostic standard, that is, a standard of truth, for the detection of abnormal dopamine transporter distribution within the human brain striatum?

Does the acceptability of this standard depend at all upon which clinical population was studied, that is, dementia patients or movement disorder patients?

Maybe this would be a time to come back to Dr. van Belle's issue about sensitivity and specificity.

DR. VAN BELLE: So, the question is FDA has raised the issue several times that there is the clinical diagnosis and the neuropathological diagnosis. So, to my mind, the issue then becomes how does the estimate of sensitivity or the estimate of specificity get changed as a function of possible mis-classification?

Now, mis-classification could occur in two ways and that is part of the challenge as well. We have patients and controls at times so is the mis-classification more likely to be in cases rather than controls? If so, that affects the estimate of sensitivity and specificity in a

different way.

So, it really is a very complicated question. The bottom line in my mind is, well, there is always a tradeoff between sensitivity and specificity. You increase one and automatically decrease the other. From a clinical point of view, what is more important for this particular product? Is it to have a high sensitivity or to have a high specificity? In one case you would use it for ruling out disease; in the other case you would use it for ruling in disease.

So, I am not sure what the answers are to these questions in terms of what is more important. So, that is the kind of thing that I am struggling with. I have a fairly simple model that is not too hard to work out that shows that if the mis-classification is only in the cases, not in the controls, which is probably reasonable at first blush, then the estimate of sensitivity remains unchanged versus the autopsy estimate. The precision of the estimate changes. It gets reduced.

But there is also an effect on the specificity, and if there is mis-classification then the specificity typically decreases. So, my bottom line is that if there is

only mis-classification in patients, then the estimate is still valid but it is less precise, but the specificity is increased. That then brings up the question which is more important, sensitivity or specificity?

DR. ANDERSON: Dr. Kieburtz?

DR. KIEBURTZ: Can I go after 2(b)? Because I think it does matter. The standards are a little different in movement disorders and dementia. Being a movement disorders doctor, I am a little more comfortable talking about that.

Just regarding the two studies, 304 and 003, 304 is in the early movement disorders population which used as a standard of truthB-which I think the FDA checked as acceptableB-a consensus panel at 36 months, which is in American Academy of Neurology evidence-based guideline which basically sites that as the most acceptable way to make a diagnosis in life, bearing in mind that there is no better way to do it currently in life. All there is, is a neuropathologic diagnosis.

That meets at least, I would say, a standard in the community of what a reasonable standard of truth is and I think the FDA accepted that, if I understood the check

boxes correctly. So, I think that is a reasonable standard of truth.

For the 003 I think there is a question mark there. That is a little different. That was the baseline diagnosis in individuals who had established diagnoses. I take it to mean, but I don't know for sure not knowing the protocols in depth, that these are individuals who probably carried the diagnosis of PSP and MSA and Parkinson's disease and essential tremor for long periods of time. The likelihood that those diagnoses are accurate, as opposed to the circumstance when, sort of as Dr. Marek proposed, you know clearly Parkinson's syndrome or early on as in 304. That is a different circumstance than when someone has lived with that diagnosis for many years. It is more likely that that is more accurate.

So, I would say I am a little beyond a question mark as that as a reliable standard of truth. I would be more towards the check mark than a question mark. I think it probably is a reasonable standard of truth. I don't know that there is any very good evidence about that, except to say there is the follow-up Hughes article, which I believe is in Brain, 2002, looking at the diagnosis of parkinsonian

syndromes in a specialist movement disorder service. So, this is a follow-up of a 1993 or '92 citation that in the hands of expert movement disorder specialists over time their diagnosis of these syndromes is pretty good, better than the 25 percent or so misdiagnosis rate quoted earlier.

So, I think that those both, even though they are differentB-one was 36 months after the initial in early movement disorder syndromes, and the other is later at baseline in established movement disorder syndromes. I think those are both as good as you get in life in those movement disorders.

I hope I haven't gone on too long, but I think these are acceptable standards from my perspective on those two studies.

The only thing we have evidence in the application about regarding dementia is the Walker study about neuropathologic diagnoses versus clinical versus imaging. I don't think we can use that same level of clinical diagnosis uncertainty in that disorder and apply it broadly to the other two studies. I think it is different.

DR. ANDERSON: Dr. Tatum?

DR. TATUM: So, let's go back to the sensitivity

and specificity question because that is very relevant here. One of the problems we run into, which I think is a bit more of an issue with molecular imaging, is taking sensitivity and specificity in isolation. We don't use ROC curves in looking at documents for the FDA usually, although that is used in Europe.

But the question that was brought up is how is this used in a clinical paradigm? What we heard, and what we got from the experience in Europe, was it wasn't a screening test where sensitivity and specificity becomes very important and sensitivity needs to be high. It was one in which you have already used a decision-making point, which was clinical, to which now you add further gradation, which is an increase in specificity. That tends to be a lot of what molecular imaging ends up doing for many of our patients.

That is a very different paradigm so when I am asked the question I think the truth to that one is no. But the question of does this add clinical benefit or utility, I think that is the scenario in which you have to go back and say does this add something in addition to what the experts already can determine which had a very high sensitivity in

some of these studies but a specificity problem which seems to be documented in the Walker study.

I have to say that that is the way you look at this. Then you have to come up and say, well, do I have sufficient data to show that there is a clinical benefit in relation to a safety profile that is extremely low? So, that is kind of where I am sitting on this related to this point. But it does really come back to your question of which is more important and I don't think that you can take it in an absolute piece. You have to put it into the scenario where you are asking the question about what is the specific abnormality.

I think the real problem we have with this is we don't have a number of different therapies. It is the same problem we have with oncology across the board. We don't have enough selective therapies to allow the imaging which may be robust enough to actually give us the result we need for the true benefit.

DR. ANDERSON: I will make one comment and then I will turn it back over to you. So, I think it probably does matter as well whether it is movement disorder or dementia. I think the notion of incremental information that you are

talking aboutB-well, we heard an example of some of the cases that were discussed earlier from movement disorders and dementia as well, which is that it may not always be feasible to give a drug holiday or just add a medicine as a trial, especially in older patients and demented patients.

So, the idea that you are starting with a certain sort of prior probability and now you have a new piece of information that you don't just take in the abstract but you interpret in the light of what you already know may also be relevant to this issue of diagnostic standards and standards of truth. It may be better rather than considering it an absolute standard that all studies must meet independent of any other information known about the clinical circumstance or the past history of products or applications. It may be worth interpreting it in light of that prior evidence in favor of a hypothesis now to interpret this standard of truth as incremental information gained.

I think, from my standpoint of dementia, even though the Walker study is small, it does provide evidence for me that I think helps me feel like that is a satisfactory bit of information to slant the way I interpret some of the other studies, the ones related to dementia in

terms of their clinical utility and whether they would meet a satisfactory standard for myself. Dr. van Belle?

DR. VAN BELLE: I wasn't going to make this until later on when we talk the clinical relevance. From a statistical point of view, the issue that I think about in terms of clinical relevance is the prevalence of the disease or the prevalence of the entity.

Just to give you a rough idea, if the prevalence is 1/10, so 1/10 of these patients that come into this clinic have the condition that you are interested in with a sensitivity and specificity of 80 percent--I am just doing a rough, back-of-the-envelope calculationB-the predictive value is less than a half. In other words, more than 50 percent of these tests will show false positives. So, the clinical relevance has to be judged in general practice, I guess, as to what mix of patients does a clinician or a neurologist typically see and where would this be used. Then I think the sensitivity levels that we have seen are not as good as I would like in terms of a prevalence of, say, 1 in 10. If the prevalence is even less it becomes even worse.

DR. ANDERSON: Dr. Royal?

DR. ROYAL: Well, there are three comments I wanted to make. One is that I was struck by what Dr. Rives said, that molecular imaging agents represent a new challenge for the FDA and whether the committee approves this drug or not, it is an important decision in and of itself. The whole concept of what we are going to do with molecular imaging agents is, to me, a very important issue.

The second point is I am a little confused about this molecular imaging agent where we are saying that what it tells you is that there is a dopaminergic deficit, and then what we are using as the standard of truth and sort of struggling with is diagnostic accuracy. Because it is not being claimed that this is a drug for diagnostic accuracy, it is being claimed that this is for dopaminergic deficit.

Then, the last thing I wanted to comment on is the relevance for sensitivity and specificity. You know, medicine and diagnostic tests are complicated. The diagnostic test has a whole range of outcomes. The clinical severity of disease has a whole range. And, when you do sensitivity and specificity you make the world binary. The test is either positive or negative and the disease is either positive or negative, and we are actually sort of

fudging a bit on the disease because the disease status is actually determined by other imperfect tests.

So, there are a lot of imperfections about sensitivity and sensitivity and to make too much out of it I just don't think is very realistic.

DR. ANDERSON: Dr. Herscovitch, do you have a comment?

DR. HERSCOVITCH: I would actually just like to ask what specific question we are discussing now because I know we have gone on, I think, to issues of the potential clinical utility of this agent or, as I thought we started out discussing 2(a) about what is the standard of truth to demonstrate that this tracer detects abnormal dopamine transporter distribution.

Also, it may be interestingB-I don't know the answer to thatB-what impact it will have on the subsequent discussion that we started having about clinical utility but if we want to specifically speak to 2(a), I would say that I personally do not thinkB-and we had this discussion last time with the Alzheimer agent-Bthat the clinical diagnoses, even if they were done in a research environment, are an acceptable standard of truth for demonstrating that this

agent detects that biochemical abnormality.

Although I would agree from a clinical research point of view, sort of the consensus panel's subsequent follow-up statement at the end, is the best one can possibly do when one is restricted to using clinical data, are those clinical data still good enough to be accepted as the gold standard for a biochemical abnormality when we have results in the binder showing that the clinical assessments are maybe 80, maybe in some cases 90 percent accurate. In one case we had the 2 expert reviewers having a kappa of 37 and 65 at 18 and 36 months.

All of these things would suggest that the clinical diagnosis is not an appropriate surrogateBusually surrogate is the other way around, but it is not an appropriate surrogate for a biochemical endpoint when, in fact, there are absolute gold standards which would be a biochemical determination of tyrosine hydroxylase, or the DaT or dopamine levels in the striatum at autopsy cases of patients who had premortem exams.

So, although I am not sure how it will affect the ultimate decisions about diagnostic use, I would say personally that I do not feel that a clinical diagnosis,

given all we have heard and read, is an appropriate standard of truth to see whether this agent can make that biochemical measurement.

DR. ANDERSON: So, you are saying that it labels DaT transporter in the brain. We think we understand that. But we now want to know whether it is abnormal and the only acceptable clinical standard of truth would be autopsy confirmation for abnormal dopamine transporter in the brain. Is that a summary?

DR. HERSCOVITCH: Well, I am saying that the state of the art of the clinical diagnoses, even done in a research environment, and this is the data we have been presented, are on the order of maybe 80-90 percent which I don’t think is an appropriate gold standard against which to make that biochemical measurement.

DR. ANDERSON: So, it would be autopsy in brain at this point from your standpoint for this kind of an agent?

DR. HERSCOVITCH: Yes.

DR. ANDERSON: Dr. Fountain?

DR. FOUNTAIN: So, I think that sort of addressed my point too. That is, I would say it is separate for DLB and for Parkinsonian syndromes, and my interpretation would

be that the DLB data satisfies that to a much larger degree. That is, we have evidence of DaT impairment from the DaTSCANs that correlates with clinical evaluation, which they agree isn't very good, but then also in the Walker study correlates with pathologic findings. Even if it is not DaT concentration, it is probably as good a surrogate as you can find, maybe even more relevant, you might say, although not the same thing.

So, I would say for DLB it makes a very linear story to me to say that that is the correlation because then ultimately the gold standard, if it is pathology, has been met except that it doesn't include DaT concentrations.

I think it is a different story though for the parkinsonian syndromes, just as you said. I guess I would find, as I think Dr. Anderson said earlier, that evidence from that is so compelling that I would be willing to apply some parts of that to the argument about parkinsonian syndromes.

On the other hand, I would also say that in life I don't think we know another way to measure parkinsonism other than by clinical evaluations. So, the only alternative that we know of, I guess, is autopsy. If

ultimately patients are treated on the basis of their clinical evaluation, then in a way the clinical development diagnosis is the gold standard, which doesn't apply to whether or not it measures DaT but still, as you suggest, might have clinical relevance.

So, I would say it makes a difference for 2(b)whether or not it is DLB or parkinsonian syndromes, and for DLB I would say it suggests that fairly clearly. I am not sure whether or not the diagnostic standard or the standard of truth for the clinical examination is excellent but I would say it is adequate under the circumstances that are available given the other supportive evidence.

Then just to follow-up on an unrelated comment, I think what Dr. van Belle said that, you know, sensitivity and specificity is how we evaluate tests but in the clinic, once the test is approved, it is the positive predictive value that does us any good. Because you are not sure what someone has; you suspect they have the condition; you get the test; you have a positive test. What does it mean? Or the negative predictive value, how likely is it?

I would think that of most of the people who get the scans a large percentage would have a parkinsonian

syndrome, which would kick the positive predictive value much higher even if the sensitivity is maybe not so high. But I guess that would be a statistical discussion.

DR. ANDERSON: Dr. Mattrey, please?

DR. MATTREY: Yes, I would like to ask my neurology colleagues if you have a patient with a positive scan, meaning they have depressed dopaminergic neurons, is that health or disease? I don't want labels here. I mean, is that person normal or abnormal?

DR. KIEBURTZ: Abnormal. So, that is one vote.

DR. MATTREY: Because it seems to me that the discussion of clinical significance here is going in the wrong direction. You see, you have a test that tells you somebody is abnormal and we are arguing what does that abnormal mean. Is it parkinsonian syndrome? Is it Parkinson's disease? Is it this disease; that disease? The bottom line, it is a disease and without having that indicator we will never be able to do prospective clinical research to understand what is its significance.

So, to me, knocking that test out would hurt the further progression of diagnosis/therapy rather than, you know, providing it and let us collect the necessary data. I

mean, the data from the European literature that we heard today suggests that it was useful to them. But I think, you know, with an indicator like this, then one can understand disease; can understand its sensitivity and specificity in a prospective environment.

That is kind of my feeling about molecular imaging agents where the true connection between finding and disease might not be as clear based on today's knowledge base, but now it provides a basis that will be refined with time so that we understand its significance. That is my comment.

DR. ANDERSON: So, I guess before I let things drift to clinical implications too soon, let me redirect the question back to you. So, we agree that this labels DaT, and we think we have evidence that says that nuclear imaging people can agree on normal versus abnormal as refers to an image that is displayed in front of them. Now we want to make a deduction as to whether that really relates to something going on in the subject's or the patient's brain and we are using these clinical criteria, as described in the Phase 3 studies, to make that conclusion.

Are you persuaded that those clinical standards applied in the study are really adequate for us making the

extrapolation from what the nuclear imager says is abnormal to what is actually happening in the striatum of that particular person?

DR. MATTREY: Well, forgive my lack of knowledge on the neuroradiology side, but it seems the arguments were never is that person normal or abnormal but, rather, the labeling of a disease. So, from my perspective, having a positive scan told me that that person is abnormal and I am convinced, based on the data I heard, that that is true. Whether they have disease (a), (b), (c), (d) or (f) is irrelevant at this point because we never have had a gold standard to understand what that finding means. All it seems to indicate is that there is something bad going on there.

Now, having a normal study here then bifurcates into two groups, the normals and the abnormals. But, again, you know, I don't think there is enough clinical data that has linked in prospect the absence of dopaminergic neurons to disease or that the lack of disease and backward studies looking at autopsies seem to be very convincing.

So, from my perspective, the argument is really nit-picking a little bit as to the specificity of a specific

disease rather than normal versus abnormal. But that is from a sideline perspective of the problem, not being a neurologist nor a nuclear physician.

DR. ANDERSON: Dr. Royal, did you want to comment again?

DR. ROYAL: Yes, I wanted to get back to Peter Herscovitch's call for more human brains, and this is really a question to the committee because I don't know what the answer is, but the question is, is the dopaminergic system in animals different from in humans so that one would need to study human brains as opposed to animal brains?

The data that was presented made it seem pretty convincing that this agent maps the dopaminergic system in animals quite well and there is good histologic proof. So, I am asking the committee is there any reason to believe that it would behave differently in human brain?

DR. ANDERSON: I will take people out of turn. Is there someone who wants to address specifically that question? I mean, I don't want to assert an expertise beyond my own but I don't think that we really have an animal model of diffuse Lewy body disease, and even the MPTP Parkinson model is not really a model of idiopathic

parkinsonism.

So, I think the steps between our current available animal models and the clinical classifications that are given in studies like the Phase 3 studies we are reviewing are still unknown enough that it gives people pause to make that kind of an extrapolation that we can just make that sort of a direct inference from the animal status to the human status. Anyone want to correct me? Dr. Tatum?

DR. TATUM: So, not to be a lumper and a splitter but I think this is important, again, to the precedent that we are setting here. We have answered question 1 and now we are re-answering question 1 with the clinical. Now, which is it?

So, I think that if we use in vitro and available clinical data to answer question 1 and we are satisfied that works, now coming back to this to make this the standard of truth, which it is not, to try to answer that question again is kind of redundant. It really complicates the situation.

Where we are now, my feeling is that now we are at that second level, is there a clinical utility for this study? And, I think that is a whole different question, and I guess we will get to that question as we go forward, but

trying to apply this now back to a population that is a mixed population with and without this disease as a proof standard for what we say has already been proven by the mechanistic and biochemical things makes absolutely no sense and we are going to stay in a spin forever doing that.

DR. ANDERSON: So, are you answering the question I asked earlier? I think you are giving the same answer. You are saying the data that was available for question 1 is really persuasive to you that if the nuclear imager looks at a scan and says this is abnormal, then you feel comfortable concluding that there is something abnormal about that human brain striatum.

DR. TATUM: Absolutely.

DR. ANDERSON: Dr. Herscovitch?

DR. HERSCOVITCH: Perhaps to clarify what I was saying, this is a little bit different than the Alzheimer agent where the binding mechanisms are quite different and not perhaps totally understood. The animal models, the knowledge of receptor pharmacology and movement disorders is much deeper and the binding mechanisms are much better understood.

So, on the basis of that I think we were all, at

least I was but I think we were all pretty comfortable about answering number 1. I still will say that my answer to number 2(a) is no, but I don't have to have a Ayes@ to 2(a) to get to a Ayes@ for answering question number 1. If I am making that clear, I do not think the clinical gold standards used wereB-they helped buttress the argument but are really definitive in terms of being a gold standard to show that this agent biochemically does what it says it does.

But I think, given the totality of the evidence, the other preclinical studies and the fact that this is a totally different system in terms of its binding characteristics than, say, an Alzheimer agent, I was happy to say yes for number 1 but no for 2(a), and I think Jim makes an excellent point that maybe the answer to 2(a) is that the question isn't that relevant, but I would still say no.

DR. ANDERSON: Dr. Rieves?

DR. RIEVES: You know, this discussion may seem very esoteric but I think it is very useful as we move forward in molecular imaging because one of the concerns coming out of the amyloid meeting from last year was that

there might be a perception for all molecular probes and molecular imaging that we are going to need autopsy data.

It sounds, from this discussion today, as if, for example, the answer to question number 1 was that in certain situations in vitro data are very powerful and can be very persuasive. This question I also think is important, and it somewhat touches on the uniqueness of the clinical situation, and I am intrigued by the discussion among the neurologists here.

Whereas last year with amyloid it seemed to me at least that there was a very solid consensus that clinical diagnoses in the dementias were not a surrogate for amyloid. But here I am hearing some of the neurologists say the movement disorders are different from dementia and conceivably clinical diagnosis, particularly if it is based upon assessments over a long period of time, may be more useful in terms of terms of surrogacy for this biochemical marker than the case for dementia.

Does that make sense to you? The reason I am bringing it up is because we are talking about precedents for molecular imaging and we are trying to get the logic as coherent as we can.

DR. ANDERSON: So, I think this partly addresses your question, related to your question, which is the difference between looking for a marker for something that may not be a normal constituent and may or may not be related to a disease versus looking for something that marks a normal sort of human element for which there may be a better understanding of its disease relevance. Is that an important distinction between the debate we are having now and the debate we had over sort of the labeling of the amyloid? Or, is it just sort of idiosyncratic with agents we are talking about?

DR. HERSCOVITCH: No, I think that is a good point. There is a tremendous body of knowledge with regard to receptor pharmacology and radiopharmaceuticals that bind to receptors and are used to study receptor systems pre- and postsynaptically, which, you know, is partly behind this application. This is sort of the tip of the iceberg. There is a huge iceberg underneath, a knowledge base to support this type of use and the specific use where it didn't particularly exist with the Alzheimer agent. But still there is a lot to be said for autopsy, direct biochemical verification of what an imaging agent does.

DR. ANDERSON: Dr. Frank?

DR. FRANK: So, there must be a dozen, 15 drugs approved for Parkinson's disease. In those studies, correct me if I am wrong, we used the clinical diagnosis of Parkinson's disease to get those drugs approved. So, I am wondering why the answer to 2(a) is no since the investigators for the studies here used established, up-to-date clinical criteria, and measured by movement disorder specialists by the UK PK Brain Bank criteria or the NINDS criteria for PSP, and administering those criteria by movement disorder specialists isn't good enough? I guess I am questioning that.

DR. HERSCOVITCH: Like I said, that is probably the absolute best that there is, especially when it is done very well. But I think Jim raised the question that a test like this could perhaps enrich the population of patients for clinical trials so that one had a greater certainty that the subjects actually had the disease. But I guess was there another way of doing those drug trials, other than the very best clinical standards?

DR. ANDERSON: Let's let the FDA come in here.

DR. KATZ: Just from the point of view of approving

drugs to treat Parkinson's, of course, it is true patients are enrolled into those studies entirely on the basis of clinical diagnostic criteria. The outcomes in drug trials are clinical outcomes as well. We don't really particularly care too much about the underlying pathophysiology or anatomy. We don't judge drugs on whether or not there is some interaction with the dopamine transporter protein. Either patients are better clinically or they are not.

So, when we are talking about imaging agents it is an entirely different outcome measure and you have to first figure out if it is actually imaging what you think it is imaging. And, from the point of view of drug approval, for the most part, those aren't particularly relevant issues. It is entirely clinical diagnostic as well as outcome.

DR. ANDERSON:. Dr. Mattrey, please?

DR. MATTREY: Yes, I would like to respond to the amyloid versus this particular thing because they are actually different. So, when you have a molecular imaging test that can be positive in normal people you need to evaluate it differently than when a positive test can only be in abnormal people.

From my perspective, the amyloid story was that

you can find amyloid in an otherwise normal, aging person. But in this condition, here, you can not find lack of dopaminergic neurons in the setting of a normal person. So, in other words, if I have a positive test here there is disease. The question is which disease is it, and I think that is, you know, the task of future research.

So, I think in this setting the false positive is not a consequence vis-a-vis presence or absence of disease but, rather, a consequence of differential diagnosis. In the setting of amyloid there was a false positive because you could have amyloid in otherwise normal people that would be mislabeled and all the consequent events, you know, regarding prognosis and quality of life, etc., that may follow that.

So, I think each product has to have its own criteria vis-a-vis, you know, the connection between the study being positive or negative to the ultimate presence of a disease. That is my perspective and that is how I view them differently.

DR. ANDERSON: Dr. Kieburtz?

DR. KIEBURTZ: I just wanted to come back, just to reiterate my Ayes@ answer. I think postmortem material is

really the gold standard. The question, as I read it, is, is this an adequate standard of truth even though it may not be the most definitive gold standard? Is there a standard of truth that is different than autopsy material? Is there a circumstance in which something other than autopsy material could be used as a standard of truth?

That is how I read the question and my answer to that is yes when you have a diagnosis, clinical diagnosis with good information that the positive predictive value is over 98 percent. The way this was deployed this is a very positive predictive value kind of diagnosis for Parkinson's disease. Now, in 003 Parkinson's disease made up more than 80 percent of the diagnoses. So, 20 percent of them are PSP and MSA for which the positive predictive value is lower. But the bulk of it was ED.

I don't know that much about the regulatory processes for these kinds of things but it would strike me that it would be important to identify circumstances when something short of autopsy material would be sufficient and try to understand or develop a process by which you identify what that is. Here Parkinson's disease done this way is pretty darned close to the pathology. It is not the

pathology but pathology is always going to be better. But is it acceptable? To me, the answer to that is yes. Is it as good as pathology? No.

DR. ANDERSON: Dr. Tatum?

DR. TATUM: So, Dr. Rieves, this comes back to the question of how much of it is a diagnostic application for which, in fact, clinical trials are absolutely required and studies are required, and you are doing that and you are tryingB-and the same thing with the Alzheimer's, the same problem versus the application you are looking at here, which is a biochemistry thing and you say is there any clinical utility with being able to assess this marker?

There is where the drift for me occurs as to how much of this is required and how many clinical trials are required versus the power of the in vitro data to document it on the other side. It is up to the sponsor to decide where they want to put it on their curve for you, and then what data you are going to need to get there.

DR. ANDERSON: Dr. Holmes, please?

DR. HOLMES: Yes, I would certainly agree with everyone that question 1 was answered positively. If we all agree with that, then I think it becomes the standard of

truth. So, when I am looking at these studies, the clinical studies I am just sitting there thinking, man, we have a diagnostic test here that can tell us a lot about the dopamine transporter but maybe we are not very good clinically at picking up these disorders.

So, I think the standard is probably going to be the scan itself, not the clinical diagnosis. If you are going to do that, I think if you really want something you really have to do the autopsies to get a direct measure. But what I am learning from here is that maybe we do not understand the clinical manifestations of defects of the dopamine transporter as well as we thought we did.

DR. ANDERSON: Dr. Green?

DR. GREEN: Yes, I also think that the amyloid issue is really quite different. When we spoke about that about a year ago I think a lot of us expressed the concern that the beta-amyloid would become an active comparator going forward that might be very widely used, which is really very different from what we are talking about in terms of a test which would have therapeutic implications tomorrow.

And, I think it has been clear from some of the

presenters that it is not an academic exercise confusing Lewy body disease and Alzheimer's. There could be treatment errors made which could have serious implications and, perhaps not quite as serious but to some degree, essential tremor versus Parkinson's because therapeutic trials of a medication are not very adequate.

DR. ANDERSON: Dr. Twyman?

DR. TWYMAN: Just a couple of comments from an industry perspective, I think the point about using it for differential, helping in differential diagnosis in someone suspected of a parkinsonian syndrome is well taken. But I think the performance characteristics need to be evaluated around that.

Similarly, I think from the industry standpoint there would be a very strong interest in agents that could potentially identify patients at risk because we know that there is already a loss of neurons before the symptoms actually manifest. So, I think there would be a very strong interest, from an industry standpoint, for having a diagnostic aid there but it would be very nice to know that, in fact, the agent is, indeed, visualizing the dopaminergic system as it is indicated to be so.

So, I am wondering right now from a performance characteristics standpoint, is the autopsy data that is collected to date which may not be Parkinson's disease but actually visualizes a pathological deficit in the dopamine system, is it sufficiently adequate from the standpoint of establishing performance characteristics in the in vivo situation for humans and correlated to their autopsy, and sufficient from the standpoint of saying, okay, we know now that, indeed, in a living human being we can see a deficit in the dopaminergic system that correlates to this pathological change, and do we need to do that in all types of syndromes? Can we just sufficiently use the pathology that is already collected to date?

Because in the amyloid situation we did not have that. There were very few actual autopsy correlations to the amyloid binding with the imaging there. In this situation we already have--what--27 now? There were 22 in the original package. There are 27 cases now.

Is that a sufficient number to do this correlation? I pose that to the FDA. I mean, it will help with regard to the sensitivity and specificity as related to what is seen in the imaging much better than the diagnostic

criteria that is being challenged right now.

DR. RIEVES: To a certain extent I think we are touching on labeling type issues and how to describe those data. We also regard them as important and they are regarded as a component of the overall package. Again, I think we have all been very impressed by the background data, the in vitro, the mechanism of action data in that context. Having the Walker study there, from our perspective is bolstering the argument there.

Of course, we conventionally prefer more solid Phase 3 confirmatory clinical studies but, as we discussed this morning, there is a precedent, FDG for example, of imaging agents that have been approved, with the risk/benefit ratio accepted as favorable, without definitively establishing their performance characteristics. That somewhat was the expectation for these type products we were told to follow.

So, the usefulness of the Walker data overall is a little bit hard to say right now, but knowing that generally, and I have a suspicion that our consensus is that it is very useful, I think that will impact how we use that moving forward.

DR. TWYMAN: I was just going to say, I mean, if an independent pathologist reviewed that data, blinded to what the scans were because I think if the pathologist knew what the scan results were, if an independent pathologist looked at that data it would not be sufficient correlative data to help him in the decision.

DR. RIEVES: It would be useful but, as other folks have pointed out, it probably would be more desirable actually to have DaT staining, if you will, on that tissue as opposed to using the pathology correlates. But, nonetheless, I think we all recognize it as an important study.

DR. ANDERSON: But that probably exists. I mean, there is probably half a hemisphere sitting frozen somewhere. They could probably do that after the fact if there were 29 heterogeneous cases with DaTSCANs and DaT transporter labeling in a frozen hemisphere. Is that what you are looking for?

DR. RIEVES: I think that would be very useful, yes, if that is feasible. Now, that is a question for the sponsor.

DR. ANDERSON: So, we have a lot of clinical things

to discuss and I am perfectly willing to keep the discussion going here, but if people feel like they are sort of done with the standard of truth I can move us to the next question. If people want to make more comments on the standard of truth issues, then we can do that now. Do you want to defer? Dr. Ziessman?

DR. ZIESSMAN: Yes, I have a very brief statement. I think what Dr. Rives said is very important about FDG. Approval of FDG allowed the performance characteristics to be determined at a much, much more rapid rate than they would have been if it was still an investigational drug. So, I think FDG is an excellent example that shows that approval based on something else besides anatomy or performance characteristics moves science and clinical medicine along very nicely.

DR. ANDERSON: I have been asked, sort of in my role, to provide sort of a summary of our discussion for the record. So, if any of you, when I am done, feel that I have sort of distorted the conversation, please object at that point.

On question 2(b), it seems to me that there is a general consensus that the disease population under

consideration is a potentially relevant consideration for the standard of truth that is applied, and it may very well be different between dementia and movement disorder as relates to these studies and may also relate to the advancement of the disease, and all those factors should be taken into account as opposed to applying a single standard of truth across all clinical domains.

As to question 2(a), there are perhaps two different sort of themes for which there are strong advocates. One is that if you want to make a claim about the abnormality of a protein in the brain, then you need to basically be looking at the brain in one way or another. That is the acceptable standard. So, in that way sort of clinical diagnoses are either inadequate or irrelevant.

There is another advocacy that feels that the use of established clinical standards of diagnoses, while imperfect, as long as they meet the objectives and sort of rigors of what is the current standard of expert practice should be satisfactory. In this case there is an advocate that the movement disorder populations, both early and late, met those expectations. Does anyone have strong difficulties with the way I worded that?

[No response]

DR. ANDERSON: I have been asked to make sure we do have our short break. We can take it now at this juncture. Why don't we just take our 15-minute break now and we will resume again in 15 minutes to pick up question 3.

[Brief recess]

DR. ANDERSON: I will call us back to session here for the last two questions. Just before we begin them I guess we have one or two residual comments, one of which came up regarding the autopsies and I have been asked to make sure that people are aware that the neuropathological diagnoses were done blind to the other data. Then we have a couple of questions or comments from our FDA members.

DR. LEVENSON: Is it possible to get my slide 18 up? Thank you.

[Slide]

As far as the Phase 3 data is concerned, in addition to whether clinical diagnosis provides an adequate standard of truth, I what is also revealing is the actual sensitivities and specificities, regardless of any hypothesis testing, that come out of this.

We see that this is dependent on the patient

population. So, the left-hand side of this slide that I showed during my presentation was probable DLB versus non-DLB. The right side includes the possible DLB in sort of the positive category. You can see that actually the sensitivities go down.

So, I think we would still like to use the Phase 3 data, if not confirmatory of whether it visualizes the DaT protein or not, but whether it provides clinical utility. I think the point I am trying to make here is it does vary by the patient population and if you are to answer that question you have to keep in mind what patient population you are talking about. I mean, it would seem likely the possible DLBs are the patients you might be most interested in.

Again, as I said in my presentation, we see similar phenomena when we compare the 2 movement disorder studies. We see higher sensitivities in study 003 where we saw more confirmed diagnoses as opposed to early stages in study 304.

So, if there is still time for discussion about the clinical utility do these numbers provide any information? Would this be useful based on these numbers

for these populations? So, I think we would like to use the Phase 3 data for those purposes. Thank you.

DR. ANDERSON: So, when I read question 3 in a moment, if the panel will keep in mind as they are discussing the favorable risk to benefit profile to, please, include and make comments on the relevance of the Phase 3 studies for your decision and deliberations.

Did you want to bring up something, Dr. Davis?

DR. DAVIS: No.

DR. ANDERSON: At this point we can begin the discussion for our voting question. There are two subsidiary points that they have asked us to consider after we have made the vote. So, the format is the same. We can have our same discussion but then at the end of this one we will be asked to sort of vote up or down on the specific question, which reads as follows:

Do the available data indicate a favorable risk to benefit profile for use of DaTSCAN as a tool to assist clinicians in the evaluation of patients with symptoms or signs suggestive of dopaminergic neurodegeneration?

Is there anyone who would like to open that? Dr. Rudnicki?

DR. RUDNICKI: So, as a clinician I could see using it as he suggests certainly. Unfortunately, the data kind of suggests that that is not its strongest use, that if you look at early people with Parkinson's disease and early people who may or may not have diffuse Lewy body disease you don't have quite as high a sensitivity as when you see them later on.

So, that is a bit of a shortcoming. Again, as a clinician who sees neurology patients, it would also be the patient whom you have treated for a while and are not getting a response, and it looks like, you know, because they have been treated for a while the data would be more sensitive at that point.

The other thing would be, in terms of management, that we haven't really seen a study that looked at that. In my mind, the management issue--you know, it doesn't make a difference in management-Bwould be a 2-arm study, one of which is treated purely clinically based upon clinical bindings and the other group who are scanned and treated according to both clinical and scan findings and seeing outcomes in a year or two years, and do they differ substantially. So, I don't think that has been answered

yet.

DR. ANDERSON: Do you want to call the vote on this? It is pretty straightforward, isn't it?

DR. ANDERSON: Okay, does everyone else think that it is all that straightforward or does anyone else have something that they would like to comment? Because I don't want to belabor the discussion if there isn't really one to have. I guess we can at least get to Dr. Levenson's point here. Are the Phase 3 studies sort of critical for our conviction on this point or not? I mean, are they crucial to that or are we sort of using all the other totality of evidence available to us to reach this conviction?

DR. TATUM: I think it is part of the totality of evidence, and it is exactly what we have been talking about, or at least I have been trying to talk about. That is, it does depend on the clinical paradigm and that is going to change the prevalence of disease that you are looking at in the population and it is going to change what the decision-making is.

In the absence of not having ROC curves and not looking at disease populations with different prevalence you can't reach that conclusion. So, I think, yes, you are

correct. The data does tell us something very important but I think it confirms what we are seeing in the clinical application as it exists now.

The question I don't think we have an answer to is can it really identify very early disease. That is the hidden piece. That is the important piece to drug development in the future and we don't have any answer to that question, but that is not part of what we are being asked right now at this point.

DR. ANDERSON: Yes, Dr. Fountain?

DR. FOUNTAIN: I agree that it is part of the whole totality, and I would say that my interpretation of all of it is that for a movement disorders expert it seems like it might make a difference in maybe 5 percent of people who are relevant, people with parkinsonian syndromes or maybe DLB, and for the general practitioner I think it might make a difference in more like 15 percent of people.

So, I guess I conclude from everything that has been said that, if that is set in my mind, I would say 5 percent of people is an important number for movement disorder specialists and 15 percent of those in question would be important for the general practitioner. And, part

of that comes from the Phase 3 studies in which you can kind of take the sensitivity and specificity and sort of extract out a little bit to a positive predictive value if you guess the incidence in the population.

DR. ANDERSON: Dr. Herscovitch?

DR. HERSCOVITCH: I guess my question is in what clinical groups. I found several of the examples that we have heard today, specific examples from Dr. Foster and some of the data that were presented from Glasgow, quite compelling, especially in very specific groups where patients have received a rather thorough evaluation by at least a neurologist, if not necessarily movement disorder specialist where the presentation isn't clear, where things aren't working out the way you thought this movement disorder patient should be responding to the therapy or diagnosis where you wouldn't want to withdraw a neuroleptic medication but you would still like to know what is going on.

So, I guess, on the other hand, if somebody walks into a GP's office with a bit of tremor, should they be getting the scan? So, although I found many of the examples and also case series that we have heard about quite

compelling for useful applications of this agent, what exactly are we saying yes to in terms of how it would be used once it is approved?

DR. ANDERSON: Dr. Kieburtz?

DR. KIEBURTZ: Yes, I think it does have a favorable risk to benefit ratio. The risk seems very low; the benefit seems tangible.

I respect Dr. Perlmutter's comments earlier but I would disagree to a certain extent. I think medication challenge which he posed as a potential to assist in a diagnostic conundrum has problems of its own. We have heard from others about both commission and omission and therapeutic misadventures that could happen in poorly diagnosed people.

So, I mean, the wording of this question, to me, is very critical in arriving at a Ayes@ answer, which is, is the risk to benefit favorable to assist clinicians in the evaluation of patients? The answer to that I think is yes, almost without a question. We have heard a lot of examples of that. And, as a movement disorder clinician I could, you know, amplify on those. I am sure there are many circumstances which I can think of and imagine of actually

happening where this would come into play. But I think Dr. Foster and others have already elaborated on those.

DR. ANDERSON: Well, then we won't belabor it and we will call the question, whatever the right parliamentary term is. Since we have some members who are new to the committee, the voting procedure is that we will make a relatively sort of simultaneous, independent vote by these instruments in front of us, which have Ayes,@ Ano@ and Aabstain.@ After those have all been recorded, so that we don't influence each other's votes sort of by peer pressure, we will then go around the table for everyone who has a vote and ask them to state their name, state their vote to make sure it was accurately recorded by the computer and then, if you choose, to give sort of a brief synopsis of why you voted the way that you did.

At this point let me reread the question? Do the available data indicate a favorableB-yes, sir?

DR. HERSCOVITCH: I hate to be repetitive but I am just concerned about what exactly we are voting for in terms of the clinical utility if we say yes or no to that because in some cases some imaging agents are approved for specific applications. For example, in Alzheimer's disease FDG is

approved, at least by CMS, for specific issues of differentiating between FDG.

Again, in this case there are many compelling clinical situations which we have heard of today which Dr. Fountain says may represent a relatively small group of patients with movement disorders. So, if we were to vote yes, in what types of patients are we voting yes for? I might feel more comfortable with some groups of patients and less with others.

DR. ANDERSON: I think, from my understanding of what I have been told, they would like us to give an assessment on this general term. Then there are a couple of follow-up questions. One of them is if you voted yes, is your recommendation limited to a specific set of patients or indications?

So, there should be an opportunity for all of us to elaborate which subset we think best reflects, or the only subset that actually represents our affirmative action. But this is more in any circumstance is there actually a case in which we feel that there is a benefit to assist the clinician? So, if you do you should vote affirmative and then we will have a chance for you to elaborate on the

specifics or circumstances.

DR. TATUM: Would it be good just to read the label indication that specifies what we are really talking about, the original indication labeling?

DR. ANDERSON: So, I have been asked to put back up the slide showing the actual language for the requested indication.

So, I will reread the proposed indication and then I will reread the question and we can vote at that point if there are no more objections.

The proposed indication reads DaTSCAN is indicated for visualization of the dopamine transporter distribution within the striata by single photon emission computed tomography imaging in patients presenting with symptoms or signs suggestive of dopaminergic neurodegeneration.

The question is do the available data indicate a favorable risk to benefit profile for use of DaTSCAN as a tool to assist clinicians in the evaluation of patients with symptoms or signs suggestive of dopaminergic neurodegeneration? At this point if people will vote.

[Electronic voting]

LCD NGO: We are still missing two votes. Just

vote again, please. There should be 14 votes. Let's do that one more time. Push again.

[Electronic voting]

DR. ANDERSON: The results are 11 in favor; 2 opposed and 1 abstention. At this point we will go around the table, I guess starting from my right, for voting members to state their name, state their vote and, if they choose, to give a brief statement of the reason for their vote. Dr. Ziessman, I guess you are up.

DR. ZIESSMAN: Harvey ZIESSMAN. I think that perhaps many of us would like more and better data but I think the sum of the evidence is positive. I voted yes.

DR. HERSCOVITCH: I voted yes as well. I believe it images what it purports to image, even though we didn't necessarily see all the data today, and I believe there are several clinical situations, many of which we have heard about today, where it is useful except, as I said before, I have reservations about how widely and in what clinical situations it might be used beyond those.

And, I perhaps would like to hear later, if we can discuss it, from any of the movement disorder experts. We have heard figures of 5 percent, 15 percent of patients that

they see or general neurologists may see in which this would be useful, and I think it would be very important to characterize this and I would be concerned if this became widely available so that anybody with a suspicion of a movement disorder who sees their family doctor might get one of these tests to, quote, see if they have Parkinson's disease rather than perhaps a more restricted set of applications relating to what we have heard of today. I am sorry, I am Peter Herscovitch.

DR. FOUNTAIN: Nathan Fountain. I voted yes and I agree that the totality of the evidence, whether stronger or weaker, for different indications supports the statement.

DR. VAN BELLE: Gerald van Belle. I abstained. I do agree that there is evidence that links DaTSCAN to characterize the dopamine transporter system in the brain. I was not convinced by the evidence that there is potential clinical evidence, but I am not a clinician so I decided to abstain.

DR. ROYAL: Henry Royal. I voted yes for the reasons stated by others.

DR. MATTREY: Robert Mattrey, and I voted yes.

DR. DECAMP: Wilson DeCamp, patient representative,

and I voted no and I think I owe my FDA colleagues bit of an explanation here and I will make some comments for the benefit of the company.

I was thinking about what would I do if my Parkinson's physician came up to me and said here is this procedure, FDA has just approved it and I want you to go through this. I look at the safety aspects or risks. If you are looking here at a favorable risk to benefit profile, there is no question abut the benefit but I think that the risk to the patient may have been underestimated.

The reason for this is that looking at a few of the slides, specifically starting at C-50 if you want to pull them up and look at them, you have 942 subjects that are evaluated in their claim about the safety profile of DaTSCAN. This compares with their estimated exposure of 216,000 patients as of last June.

Now, surely, there is more to be learned from those in a quantitative way than is shown here. Looking at C-51, there were 5 deaths. None was considered related to DaTSCAN but I question whether that determination was made by somebody who was closely involved with the development of DaTSCAN or by an independent physician who had no interest

in whether the death was related to DaTSCAN or not.

Now, there were 36 serious adverse events. The same problem is there. In looking at C-52, they say they have added a couple of things to the proposed USA label but we haven't seen what that draft label looks like.

So, I think that there is some more work that needs to be done in looking at the post-marketing safety data to see that it is adequately reflected in the USA labeling. Thank you.

DR. KIEBURTZ: I am Karl Kieburtz. I voted yes for the reasons I already stated.

DR. ANDERSON: I am Britt Anderson. I voted yes. I can certainly see particular patients for whom I feel this information would have provided clinical usefulness for me.

DR. GREEN: I am Mark Green and I voted yes for the same reason. I think there are specific conditions where it may have therapeutic implications.

DR. FRANK: Samuel Frank. I voted yes. I also feel that there are certain situations where it might be very helpful. Even as a movement disorder specialist, if there are 5 percent of my patients that could benefit from a more exact diagnosis and better treatment, that is worth it.

I think that looking at the data, if the sensitivity and specificity is approximately close enough, so to speak, to movement disorder specialists, then I wonder what it would be like for a general neurologist or even an internist and a test like this might be helpful.

I do have one concern and that is in the wording, and I agree with Dr. Kieburtz that it is very important to look at the wording. It is to assist clinicians, and I don't think that this substitute clinical judgment based on what is in front of people. So, I think that a little more work needs to be done on that.

DR. TATUM: I am Jim Tatum and I voted yes. I think you have heard enough from me today, but I want to point out that the safety profile of this drug is excellent.

DR. HOLMES: Greg Holmes. I voted yes. I think this is really an exciting compound. I think the potential is incredible. I think it is a great biomarker for a disease process that we need to know a lot more about so I am very in favor of it.

DR. RUDNICKI: Stacy Rudnicki. I voted no because of reservations of how it is going to be used clinically.

DR. ANDERSON: I think all our voting members are

now on the record. So, let's go to the next subset of questions please.

If you answered no, discuss the types of clinical data that would be necessary to change your opinion. If I understand correctly, it is not really that there is more data that would change your mind; it is more an issue of application. Dr. DeCamp had concerns about safety and the rigor with which it had been evaluated.

Do you have some elaboration you wanted to make? If you have a point, that is fine. Could you sort of keep it modest in duration?

DR. BROOKS: Yes, the deaths involved were things which would not normally be associated with a radiopharmaceutical like this, bronchial carcinoma or cancer. In 2 cases patients had broken hips which probably was related to the disease. Sorry, I am blanking on the other causes of death but they are things which would not normally be considered related and the investigators themselves who evaluated the subjects did not feel that they were related to DaTSCAN.

[Slide]

DR. SHERWIN: This summarizes the overall

experience.

[Slide]

So, bronchial carcinoma, pneumonia, fractured left femoral neck, ischemic heart disease, ventricular failure in one subject, septicemia in another subject and another fractured femur.

Also shown here are the times between death and the time that the patient had received the DaTSCAN previously. So, you can see 46 days, 89 days, approximately 200 days, over a year for septicemia and 3 days for fractured neck of the femur. So, the long duration for most of the cases probably argues against any causality and this assessment was made by the investigators.

DR. ANDERSON: Thank you.

DR. DECAMP: May I add something?

DR. ANDERSON: By all means, sir.

DR. DECAMP: I think that the question is also how this applies to serious adverse events that were named post-approval in the European studies. So, you have a much larger database than just the 942 subjects in the clinical trials that we have heard about.

DR. SHERWIN: Would you like me to respond?

DR. ANDERSON: Would the panel like to hear additional information upon sort of the monitoring of post-approval adverse effects from Europe at this point for our deliberations, or does the panel feel like we would like to go to the next question?

[No response]

DR. ANDERSON: Thank you for your offer, but no thank you.

The next portion of question 3 which I hope people will comment on is, for those of us who answered yes, and it sounds like many of us have sort of ideas about which sets of patients or which subgroups of patients we feel the favorable profile applies to, and this is sort of the time for people to go on record and to give their opinions.

If you answered yes, please discuss whether the favorable profile applies to all patients or only specific subsets, for example, dementia or movement disorders or other subsets. Are there folks who would like to now weigh in on that? Dr. Mattrey?

DR. MATTREY: I will start, and it is neither. I think having a positive or a negative test, from my perspective, is sufficient and then we will figure out what

that means. Obviously it is disease, you know, whether it is movement or dementia or some third disease that might crop up that has dopaminergic issues. I don't think the clinical side is ahead of the curve here.

DR. ANDERSON: Dr. Royal?

DR. ROYAL: I don't think that this committee was presented with any data that would help them decide what groups of patients it would be useful in. I mean, it sounds like we are asking for a practice guideline and it just makes me nervous to go there because I don't think that we are constituted to do a practice guideline, nor do we have the right expertise on the committee.

DR. ANDERSON: But isn't there some middle zone? I mean, do you think it should be a screen test? Do you think there should be some effort made to sort of allow, permit or restrict its use sort of in the mall to diagnose your Parkinson's disease while you are shopping?

DR. ROYAL: I do think there should be some effort to identify which group of patients it is most useful in, but it sounds like we are asking for off-the-cuff opinions as opposed to evidence-based medicine.

DR. ANDERSON: Well, if it were approved though it

is going to be available for use whether there is a practice guideline or not, and that might draw from the same clinical expertise that the FDA uses when they bring us together. I feel like maybe you are shortchanging the idea that there might be some useful, practical guidance that we could give short of issuing a specific standard of practice or care. But if that is the way you feel, that is the way you feel.

DR. TATUM: So, you are asking to change from what the indication says there. I think that is pretty good. It is Aassist@ which has been pointed out, which I think is very important, and for a patient population in which this test would be applicable for adding information. That seems pretty good to me.

So, are you asking do we broaden that or do we collapse it down even more? I don't think so. I think it is a great starting point and I think it is about all we have got for information to justify its use at this point. Obviously, a screening test is out. Then we are back to the diagnostic study and we really do need big studies to show that we actually have good sensitivity and specificity and ROC curves to make sense. We are not there. Also, I am not sure what you would do with that data.

There is one point though, at some point, and I think it is going to have to be a trial, I think we are going to need to know whether this can be a predictor of early disease, and I have harped on this before today, so that it can be used as a stratification to bring patients into trials with enriched populations where we would have therapeutics, hopefully, that will be developed. As I look at the slides that I saw this morning, I think there is some potential there. Those will be tested and there will be a smoother transition to know whether they are useful or not. With it is ever used then after that as a screening of the drug, it may no; it may drop off at that point.

DR. ANDERSON: Dr. Fountain, did you have a comment?

DR. FOUNTAIN: I think it is understandable that you ask the question would we restrict it to dementia for the question of DLB or movement disorders because I think the data for DLB is direct and linear, and sufficiently accurate and precise because we have the autopsy correlation. So, I feel good about that.

I would also say though that in movement disorders we just have so much either indirect or maybe circumstantial

evidence that I still think we have to maintain that.

I guess I am really just saying what Dr. Tatum said, the broad indications is good. But the second part of this question is Aother studies@ and I think it would be relevant and important to bring up sort of the next logical use of this test, which would be whether or not it has any predictive value or diagnostic value early in the course of a question of Parkinson's disease in particular.

DR. ANDERSON: Were there other issues related to this 3(b) question that we can touch upon or that you might have us bring up at this point? No? Okay. I am sorry, Dr. Kieburtz?

DR. KIEBURTZ: I was just going to echo what was just said regarding 3(b). I think it applies to all patients and I wouldn't suggest sub-parsing it.

DR. ANDERSON: All right, then I guess we have our final discussion question here which has been touched upon briefly, which is to please discuss any considerations you regard as important for labeling or for subsequent clinical studies that you believe should be performed.

We have heard some about screening and early diagnosis. Are there other issues that people think they

would like brought up? Dr. Holmes?

DR. HOLMES: Yes, I think the labeling is pretty important. I like the way it is worded here because I think we don't want to get into a bind by making this now the gold standard for the diagnosis of Parkinson's disease. So, I think it is really important that it remain the way it was stated. This cannot be the comparator from now on because they haven't proved that.

DR. ANDERSON: Dr. Fountain?

DR. FOUNTAIN: Just one last comment, I am a neurologist/epileptologist but I look at SPECT scans a lot, ictal SPECTs and interictal SPECTs for epilepsy which are also not quantitated, and we call those cotton ball images and we guess, sort of through the tea leaves, what is positive so I see a lot of them. And, it strikes me that while the nuclear medicine radiologists can detect what seemed to be subtle changes very easily, for the rest of us it is difficult.

So, I wonder if it wouldn't be important to know, particularly because this would be presumably a widely used test, whether or not quantitative assessment is valuable beyond the qualitative visual assessment of the image as

something to consider for the future that could give it at least more standardization, I don't know about more accuracy or anything else but at least more standardization. Maybe there are reasons why that shouldn't be but it seems kind of self-evident to me.

DR. ANDERSON: Dr. Royal?

DR. ROYAL: We have a saying in nuclear medicine that we can generate numbers faster than you can prove that they are useless. I think, you know, quantitation is over-emphasized. I mean, look at PET scanning for tumors. When you look at the sensitivity and specificity of determining whether a lung nodule is malignant or benign, in general visual assessment comes out as well as any quantitative measure.

So, numbers always sound much more concrete than a subjective visual interpretation, but a subjective visual interpretation can take into account so many things other than where a region of interest is drawn.

DR. ANDERSON: Dr. Ziessman?

DR. ZIESSMAN: An example that was given is probably the opposite extreme but clearly diagnosing a focus of epilepsy is very difficult and requires a lot of

experience. This, as I mentioned earlier, seems to be a very simple test to interpret, so simple that I would worry that some of the neurologists here will talk to their GE reps about buying a SPECT camera after this meeting.

But on the other hand, I think that it would be useful to have at least some data that validates the ability to look at images and make an interpretation, yes or no, and either a study or even perhaps some simple quantification that the clinician can use in his practice, the imaging clinician can use in his practice in order to confirm what he thinks by looking at it.

I suspect it will turn out that looking at images is just as good as quantification, but it is always nice to have that data.

DR. ANDERSON: Dr. Mattrey?

DR. MATTREY: As a molecular imager, I vote for quantification, validated quantification because without it you cannot predict early detection; you cannot predict response to therapy; you cannot predict prognosis. If it is a yes/no it is of lesser value than if you actually can quantify disease because if you want to look at progression or arrest progression, then you don't have much dynamic

range with a yes/no answer. If quantification is possible and can be validated, of course, I would vote for quantification.

DR. ANDERSON: Dr. Tatum?

DR. TATUM: I think as we talk about seeing if it is an early, early detector and there is some signal you are going to fall into, whenever you do that trial I think you will figure out how to put some kind of quantitation in it.

But coming back to Harvey's question, in the large experience in Europe you might have some of that data, I would think, about what the reading is like across the spectrum and how much reliability and those kinds of things which would be really interesting to find out or extract that data although, obviously, it is not very well controlled, but it would be an interesting study to look at those 200,000.

DR. ANDERSON: Dr. Kieburtz?

DR. KIEBURTZ: Just regarding considerations that might be important for labeling, just the proposed indication versus vote for question 3, whether in the indication that language about assisting the clinician and evaluation of patients presenting with symptoms or signs,

that is not in the proposed indication and that might contextualize why visualization of the dopamine transporter distributionB-what that is for, and might be relevant to actually be in the indication.

Regarding subsequent clinical studies, something about the pragmatic deployment of this normal/abnormal differentiation and/or how that training is to be accomplished. Some people echoed, I think tongue in cheek, but it could well be true that people might read as normal or abnormal who have no training and might feel that they could do that. Neurologists often feel they can read images that they maybe shouldn't be reading sometimes.

So, I think what those training standard are and what the pragmatic deployment of a normal/abnormal, or if there is a more quantitative reading of that, I think that would be relevant fodder for future studies.

DR. TATUM: Question for FDA, when you put together an indication that says something like Aassist@ or something else, how does CMS interpret that? Do they use that in making a determination or not?

DR. KATZ: I really have no idea. I am sureB-well, I am not sure, let's put it that way, but I imagine they

could try to interpret it according to, you know, their own purposes but I am sure they look at what the label says. But how in an individual case that is going to be interpreted I think would be very hard to predict.

DR. TATUM: Because that is your check on these sheets right there.

DR. ANDERSON: Dr. Herscovitch?

DR. HERSCOVITCH: Is there anything with regard to any type of medication, either parkinsonian, anti-parkinsonian medication or other medication which could potentially interfere with the study. I guess if the patients are on maybe Ritalin it might be an issue, but is there anything with regard to cross-effects with medications these patients might be on and whether they should be withheld?

DR. ANDERSON: Dr. Kieburtz?

DR. KIEBURTZ: I can’t answer that about DaTSCAN but I know that in other research studies we have done with beta-CIT that Dr. Marek is familiar with there was at least the suggestion that you could change imaging measures with the initiation or discontinuation of experimental medications. So, clearly, the signal is modifiable by

pharmacologic agents. That doesn't fully answer your question but I think it is at least relevant that that can happen. Whether it happens with routinely administered anti-parkinsonian therapies like levodopa and dopamine agonists, and I guess that is what you are leading to, might be a worthy thing to study so that clinicians know what potential interference those are providing.

DR. HERSCOVITCH: Definitely in a lot of research studies involved with fluorodopa, sort of the anti-parkinsonian medications are withheld over night, and so forth. That works very well in research settings, not particularly practical perhaps but I think that whole issue has to be explored. Definitely there are other medications that could almost certainly interfere with the binding of this agent. So, that should be considered.

DR. ANDERSON: Do you want to make a very brief commentary on that about the other medications that might be used for Parkinson's disease that could affect the DaTSCAN?

DR. BROOKS: As I said, Ritalin, methylphenidate or any cocaine agents can directly block it. Other anti-parkinsonian agents have very little effects. COMT inhibitors have none. Levodopa, as far as we know, had

none. MAOB blockers, possibly a mild effect, a few percent. So, it is a very benign tracer.

DR. ANDERSON: Thank you. Other items on question 4? Dr. Mattrey?

DR. MATTREY: There was data presented on the effect of dopamine therapy by Dr. Earl Mirro[?]--I don't know how to pronounce his name--sorry, who taught us about the clinical implications. It was this bar graph, percent reduction of beta-CIT uptake. There is no page number and there is no slide number. There was data that the high dose of L-dopa affected the study by decreasing the beta-CIT uptake by 7 percent.

DR. KIEBURTZ: Could I just clarify since I was a co-investigator on that? That is just what was measured. It doesn't mean that levodopa caused that reduction. In the groups that were assigned a placebo, 150 mg, 300 mg and 600 mg, those are the observed, over 9 months, decrements but whether or not levodopa directly modulated the ligand binding is unknown.

DR. MATTREY: It looked as though there was a dose response of 0, 150--

DR. KIEBURTZ: Does that just mean that disease

progression was faster in those groups? It is unknown whether that is just faster disease progression or some pharmacologic modulation of ligand binding. So, it isn't a direct measure of what levodopa did to binding.

DR. ANDERSON: All right, then the consensus of the comments seems to be that most people felt fairly positive about the labeling, with perhaps some amendation to provide the context of assistance for patients with symptoms and signs, to help with that.

There was a lot of discussion abut the potential value of quantification and whether that might be particularly relevant in studies to be done for early diagnosis or sort of preclinical diagnosis.

Lastly, there was sort of no particular suggestion that it would be particularly limited. I don't remember hearing any particular other studies proposed. It was mostly the pre-screening and some of the wording that seemed to be in favor.

If that is an accurate summary and no one else has any other additions, then I think that concludes the business for th meeting and we stand adjourned.

[Whereupon, at 3:45 p.m., the proceedings were adjourned]