FOOD AND DRUG ADMINISTRATION

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MEDICAL DEVICES ADVISORY COMMITTEE

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NEUROLOGICAL DEVICES ADVISORY COMMITTEE

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THIRTEENTH MEETING

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FRIDAY

MARCH 31, 2000

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The meeting was held at 10:00 a.m. in the Plaza Ballroom of the DoubleTree Hotel, 1750 Rockville Pike, Rockville, Maryland 20852, Dr. Alexa I. Canady, Panel Chairperson, presiding.

PRESENT:

ALEXA I. CANADY, M.D.	Panel Chairperson
PERRY D. COHEN, M.D.	Patient Representative
EVERTON A. EDMONDSON, M.D.	Voting Member
RICHARD G. FESSLER, M.D.	Voting Member
CATALINA E. GARCIA, M.D.	Consumer Representative
MARK HALLETT, M.D.	Deputized Voting Member
SALLY L. MAHER, ESQ.	Industry Representative
STEVE G. MASSAQUOI, M.D.,Ph.D.	Voting Member
MARC R. NUWER, M.D.,Ph.D.	Deputized Voting Member
STEVEN PIANTADOSI, M.D.,Ph.D.	Deputized Voting Member
CEDRIC F. WALKER, Ph.D.,P.E.	Voting Member
LUCIA J. ZAMORANO, M.D.,Ph.D.	Deputized Voting Member
JANET L. SCUDIERO, M.S.	Executive Secretary

P-R-O-C-E-E-D-I-N-G-S

(10:05 a.m.)

MS. SCUDIERO: Good morning everyone. We're ready to begin the 13th Meeting of the Neurological Devices Panel. My name is Jan Scudiero and I'm the Executive Secretary of this panel. I'm also the Classification/Reclassification Team Leader in the Division of General Restorative and Neurological Devices. First, we have a couple of housekeeping matters.

If you haven't already done so, please sign the attendance sheets that are on the tables by the doors. There are agenda and other information at these tables also and you can pick up information about the Advisory Committee web site. Before I turn over the meeting to Dr. Canady, I'm required to read two statements into the record. The Deputization of Temporary Voting Members and the Conflict of Interest Statements.

First, the appointment to temporary voting status. Pursuant to the authority granted under the Medical Devices Advisory Committee Charter, dated

October 27th, 1990, and amended April 20th, 1995, I appoint the following as voting members of the Neurological Devices Panel for the duration of this meeting on March 31st, year 2000. Mark Hallett, M.D., Mark R. Nuwer, M.D., Ph.D., Steven Piantadosi, M.D., Ph.D., Lucia J. Zamorano, M.D., Ph.D.

For the record, these people are special government employees and are consultants to this panel under the Medical Devices Advisory Committee. They have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting. David W. Feigal, Jr., M.D., MPH, Director of the Center for Devices and Radiological Health on March 15th, 2000. The next statement is the Conflict of Interest Statement prepared for this meeting.

The following announcement addresses conflict of interest issues associated with this meeting and it made a part of the record to preclude even the appearance of an impropriety. To determine if any conflict existed, the Agency reviewed the submitted agenda and all financial interests reported

by the committee participants. The Conflict of Interest Statutes prohibit special government employees from participating in matters that could affect their or their employers financial interest.

However, the Agency has determined that the participation of certain members and consultants, the need for whose services outweighs the potential conflict of interest involved is in the best interest of the government. Waivers have been granted for Dr. Richard Fessler and Steven Piantadosi for their interest in firms and issues that could potentially be affected by the Committee's deliberations.

The waivers allow these individuals to participate fully in today's deliberations. A copy of these waivers may be obtained from the Agency's Freedom of Information Office, Room 12A-15 of the Parklawn Building in Rockville. The Agency took into consideration other matters regarding Drs. Everton Edmondson, Richard Fessler and Cedric Walker. These individuals reported past and/or current financial interests in firms at issue, but in matters not related to the topic to be discussed by the panel.

The Agency has determined, therefore, that they may participate fully in today's deliberations. The Agency would also like to note for the record that Dr. Perry Cohen, who is the panel's Patient Representative today, has acknowledged personal financial interest with the firms at issue. In the event that the discussions involve any other products or firms not already on the agenda for which an FDA Participant has a financial interest, the Participant should excuse himself or herself from such involvement and exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness, that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon. Thank you. I would now like to turn over the meeting to Dr. Canady.

CHAIRPERSON CANADY: Good morning. My name is Alexa Canady and I'm the Chairperson of the Neurological Devices Panel and I'm Professor of Neurosurgery at Wayne State University and Chief of

Neurosurgery at the Children's Hospital of Michigan. At this meeting, the panel will make a recommendation to the Food and Drug Administration on the approvability of Pre-Market Approval Application P960009, Supplement 7, for the Medtronic Activa Parkinson's Control System. An implanted, deep brain stimulator to treat Parkinson's Disease.

Before we begin the meeting, I would like to ask our distinguished panel members who are generously giving their time to help the FDA in the matter being discussed, as well as other FDA members seated at the table to introduce themselves. Please state your name, your position, affiliation and your area of expertise. Will start with Dr. Witten on that end.

DR. WITTEN: I'm Dr. Celia Witten, I'm the Division Director of the Division of General and Restorative Devices at FDA.

DR. PIANTADOSI: My name is Steve Piantadosi, I'm a Clinical Trialist from the Johns Hopkins Oncology Center.

DR. FESSLER: I'm Rick Fessler, Professor

of Neurosurgery, University of Florida. My specialty is spinal surgery.

DR. MASSAQUOI: Steve Massaquoi, Assistant Professor of Electrical Engineering at MIT and a Neurologist at Mass General Hospital in Boston.

DR. NUWER: Marc Nuwer, I'm a Professor of Neurology and Department Head for the Clinical Neurophysiology at UCLA Medical Center in Los Angeles.

DR. EDMONDSON: I'm Tony Edmondson and I'm a Neurologist, Neuro-Oncologist and Pain Management Physician practicing at the Texas Medical Center in Houston.

DR. HALLETT: My name is Mark Hallett, I'm Clinical Director of the National Institute of Neurological Disorders and Stroke.

DR. ZAMORANO: My name is Lucia Zamorano, I'm a Professor of Neurological Surgery and Radiation Oncology, Michigan, Wayne State University and my area of expertise is Stereotactic Surgery, Image-Guided Surgery.

DR. COHEN: My name is Perry Cohen, I'm a Health Care Management Consultant and I'm a

Parkinson's Patient.

DR. WALKER: Cedric Walker, Professor of Biomedical Engineering at Tulane University and Chairman of Engineering Science with a research interest in implantable devices.

DR. GARCIA: I'm Catalina Garcia and although a physician I'm not here in that capacity. I believe I represent my past history involvement in women's issues and Latino's issues and aging issues.

MS. MAHER: Sally Maher, I'm the Director of Regulatory Affairs and Clinical Research at Smith & Nephew and I'm here as the Industry Representative.

CHAIRPERSON CANADY: Thank you. I would like to note for the record that the voting members present do constitute a quorum as required by 21 CFR Part 14. Now that the formalities are done, we're going to ask Ms. Heather Rosecrans, who is Director of the Pre-Market Notification Staff, to explain the least burdensome provisions.

MS. ROSECRANS: Thank you, Madame Chairman, and members of the panel, it's a pleasure for me to be here today to speak briefly to you about

the least burdensome provisions of the Food and Drug Modernization Act of 1997, that President Clinton signed into law in November of that year, and I know you've all been trained on this provision.

Many people think that this piece of law is the most significant piece of law for FDA since the Medical Device Amendments of 1976. We have a lot of information on our web site about this Food and Drug Modernization Act of 1997, including more detailed information, a whole web site on least burdensome. So we would be happy if you would look at that and the audience as well. Next slide, please.

I'm going to go over briefly the references to least burdensome from the law and the mechanisms we've used at the Agency to implement where we are today in understanding what Congress wanted us to do with least burdensome. Next slide, please. The two references that are in the Food and Drug Modernization Act and now in the Food, Drug and Cosmetic Act on least burdensome are specific to premarket approval and premarket notification, the two major types of applications used to get a device,

review a device to go to market. Next slide, please.

The first provision talks about premarket approval applications and that's going to be the one you'll be most familiar with, that you usually receive premarket approval applications before the Advisory Panel. This section says in clinical data, including one or more well controlled investigations, specified in writing by the Secretary for demonstrating reasonable assurance of device effectiveness shall be specified as the result of a determination by the Secretary that such data are necessary to establish device effectiveness.

And again, this is specific to effectiveness. The Secretary shall consider, in conjunction with the applicant, the least burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval. And again, this is for premarket approval applications. Then next slide, please. This section of the law is specific to premarket notifications of 510(K)s.

And you're probably most familiar with

those as homework assignments because they don't come before an Advisory Panel in a meeting that often, but they do on occasion. And again, this section says whenever the Secretary requests information to demonstrate that devices with difference technological characteristics are substantially equivalent, the Secretary shall only request information that is necessary to make substantial equivalence determinations.

In making such requests, the Secretary shall consider the least burdensome means of demonstrating substantial equivalence and request information accordingly. So these two, as you can see, these two provisions of the law are somewhat different relating to substantial equivalence and effectiveness for approval of a PMA. Next slide, please.

Now it's very important to recognize that this provision of the law did not change the standard for the way we review premarket clearance and approval. The way we evaluate valid, scientific evidence for a PMA is still reasonable assurance of

safety and effectiveness with the intended use of the device, and for a 510(k) it's substantial equivalence, but the device is at least as safe and effective as other legally marketed devices of that type.

So absolutely no change in what criteria we need to meet. Now what have we done to implement and try to define what Congress wanted us to do? The first thing we did was when the law, as I said, had gone into effect in November, '97, the first thing we did on least burdensome is we held an open, public meeting in Rockville. It was a half-day session. There were industry people there, consumer groups, Agency people and professional societies.

And it basically was just an open discussion of what was meant by least burdensome. Next, we came out with a draft Agency guidance, that's available on the web. It came out the first of September last fall and the comment period ended in November. As you can see, there's the web site. We're still evaluating the comments and working on revising this guidance. Next slide, please.

There was an industry task force proposal

on the least burdensome requirements of the law as well. I mean they met separately and the industry came up with what they thought should be a guidance document. That industry task force proposal is an attachment to our guidance that was on, is on the web and was out for comment last fall. So you, so the comments were still directed at the industry proposal as well.

Currently, there is still an industry task force going on and they have FDA representation on that task force as well. And it's represented by many different parts of the industry including the invitro area. I know we sometimes get questions saying were the invitros included. And again, it's attached to the guidance. Next slide, please. We have come up, at the Agency, with an interim definition of what we think Congress meant by least burdensome.

Again, this is not final and we believe it means a successful means of addressing a premarket issue that involves the smallest investment of time, effort and money on the part of the submitter and FDA. Again, not changing our standard for review. Next

slide, please. Now, did the least burdensome requirements require a change in FDA's culture? There is debate on this matter. However, we have gone out and done training internally, within the Agency, and we're not done doing that, but as a first step we did this last fall.

And we told everyone inside, as we're telling you, that we need to recognize that there may be multiple approaches to satisfying the regulatory requirements. That we need to communicate, collaborate and compromise in the interest of public health. But not, again, not lowering our standard. Understand not just the letter of the law, but also the spirit of the law on least burdensome. One might say just a common sense approach to the type of information we need to make a final decision.

And to think about time, effort and money in our decision making. Next slide, please. Now, does least burdensome compromise our scientific integrity? That's not where we're going at all. We believe that all scientific endeavors are affected by the availability of resources, whether inside the

Agency or at a learning institution, etcetera. That good science includes cost effectiveness, no one has unlimited budgets. And compromise is a necessity for successful research.

Lessening the regulatory burden may say, I'm sorry, may serve to enhance scientific progress and may advance medicine in a more timely fashion. Next slide, please. Now some of the mechanisms we believe to lessen the regulatory burden, we are thinking, why did Congress put this into law? Was it to streamline the process and to make sure that the burden was less. Some of the ways we've thought of this are ensuring that all of our regulatory decisions are made in accordance with obviously development statutory criteria.

That we should use the tools provided by the Food and Drug Modernization Act and the re-engineering that we've done with the Center. And some of those examples in the 510(K) premarket notification area are exemptions from 510(K) where there is no value added specifically to the review of some very simple Class 1 devices. In some Class 2 devices they

may be exempt, but they may be, have a special control saying to follow a recognized standard, a guidance document, etcetera.

And if they did that, they would be exempt. If they didn't do that, they would not be exempt. But we meet in early collaborative meetings and decide the most simple and effective way of helping a product make its way to market and also our third-party review program has lessened the burden for the Agency. That's where an outside group recognize by the Agency is able to review a 510(K), certain types of 510(K) applications.

I saves us resources so we can work under more complicated premarket approval applications and hopefully it saves the industry time as well. And we have to factor in all relevant, publicly available information in the decision-making process, whatever that information might be. Next slide, please. We also are relying on non-clinical testing for decision making when possible.

Often times from bench testing we can be very precise information or hopefully always get very

precise information and rely on that as much as possible. Rely on conformance to recognize standards and decision making, when a company declares conformity to a standard or a certain part of the standard, rather than asking for that data, if the standard describes the data, we just simply take the reliance on the declaration.

When clinical data are needed we need to consider alternatives to randomized control trials, where we can rely on literature or other, or non-active controls. And to use surrogate endpoints whenever possible to demonstrate effectiveness, to think of what is the closet endpoint we can use to feel that the device has reasonable assurance of safety effectives and PMA and get to market but not compromise safety and effectiveness. Next slide, please.

The bottom line where we are today on least burdensome is to factor the least burdensome concepts into all of our premarket activities, even though it's only specific to premarket approval in 510(K). We need to be, we at the Agency, need to be

thinking about that in developing guidance documents, their use and the development, in the development of regulations, thinking about what might be exempt from 510(K), etcetera, and our Advisory Panel reviewing recommendations.

We need to remain open-minded to alternative proposals for satisfying our regulatory requirements. Obviously listening to the companies when they come back and say, how about doing it this way? And lastly, we believe that Congress wanted us to inject a degree of common sense without diminishing the least, the level of safety and effectiveness that we ensure the American public. Thank you very much, and I'll take any questions if you have any.

CHAIRPERSON CANADY: Thank you very much. Our next phase is going to be the open meeting portion. We are going to give an opportunity to a number of people who have already identified themselves to address the panel. Following which, if there are other burning comments that people wish to make, we'll have a short period of time, perhaps, for those.

We're going to begin with Dr. Anthony Porter. I would like to remind people that they need to identify themselves and their affiliations, if any, as well as identifying any financial interest they may have in the product. Dr. Porter, Dr. Arthur, rather.

DR. ARTHUR: Good morning. My name is Anthony Arthur and I've been asked by Medtronic to speak to you regarding my personal experience with deep brain stimulation. Medtronic has paid for my room and board and transportation to come down here. I contracted Parkinson's in 1985, at which time the therapy for this was anti-Parkinson's drugs which offset my symptoms in the beginning, but as my symptoms got worse the medication had to be increased. And increased to the point where I got dyskinesia and I was a walking zombie.

At this point in time, my Neurologist, Dr. Olanow, Head of Mount Sinai Medical Institute, suggested I participated in work study, clinical study on deep brain stimulation for the treatment of advanced Parkinson's Disease.

MR. ARTHUR: I'm his son, Michael Arthur.

I was not paid by Medtronic to come here, I wish they did, though, it would have been nice.

(Laughter.)

MR. ARTHUR: My dad is a little nervous. There is a lot of people here and a lot of doctors and it's a little overwhelming. So I'll let him get a chance to catch up and get his thoughts and he'll jump right back in. I just want to thank you guys for letting me speak here. It's a great opportunity for me. Without this device -- yeah, you have to jump back in.

(Laughter.)

MR. ARTHUR: My father wouldn't be here right now. What the device did, it gave back his life. Before this happened -- sorry about this. The drugs were just overcoming him. His life, he was just so medicated he was just becoming, like he said, a zombie. He would just become comatose and there was no quality of life. And people say that you should know how it affects him, but it affects all of us.

Parkinson's becomes a family disease. The doctors, the drugs, the care. It becomes so time-

consuming to take care of him and what the device did, it brought back his life. Because like I said, he would not be here right now. He would be at a home, 24-hour care, you know. Not a nursing home, but we would take care of him, but our lives would be totally changed. No vacations, no family life.

Right now he can spend time with his grandkids, he can play, he's not going to go out and run around the blocks, but he can go out and about. He goes to movies. He can do stuff with my mom, they have a life together. They can enjoy the quality of life and he can, he's added ten or 15 years to his life right now. And you are seeing him with a cane now, that's not because of the Parkinson's Disease. He just had two knees replaced.

(Laughter.)

MR. ARTHUR: So he's got it all going now, so that's why I'm just kind of hoping to come up right now. But the next, that's not the Parkinson's. But for him to go on vacation, to come to Washington to speak to you, is amazing. Before this, he would barely get out of the house. And I want you to know

that, that it affects the whole family. And the device has turned our family around. Are you ready now? I'm done.

(Laughter.)

DR. ARTHUR: Thanks, Mike. Since I've joined the group to participate in the clinical study they agreed to have the surgery in the fall of 1997, and the fall of 1998, where the neurostimulator was inserted at Mount Sinai Hospital. The immediate affects of the neurostimulator were as follows. As far as my eating habits goes, my hand/mouth coordination improved. My dressing, I was able to put my own clothes on, I could do everything but tie my shoes. Speaking. The stimulator had an effect on my speech.

I had to weigh the pros of getting rid of my tremors or should I have an interruption of my speech. I chose not to have interruption of my speech, that's why I have a residual tremor today. Because I made that decision based on what the stimulator could do for me. The rigidity of my body has changed immediately. As soon as it was inserted

and they programmed me I could turn in bed which I usually could not. I could not drive, and now I'm looking forward to driving in the next six weeks.

Overall, the stimulator has made me a better, given me a quality of life which I never could have had before.

CHAIRPERSON CANADY: Thank you very much, Dr. Arthur, thank you very much.

MR. ARTHUR: If I could just say one thing. I just them to know that with this device we have a father back. It would be nice if other people, too, could.

CHAIRPERSON CANADY: Mr. Larry Wistrom, who is a Parkinson's Disease study patient from the University of Kansas Medical Center is going to talk with us.

MR. WISTROM: Thank you for letting me come here today and speak to you. Medtronic paid my way up here and I appreciate that very much. I had Parkinson's strike me when I was 33 years old, and I've progressed with it since that time in 1977. It's completely got worse and by the time I was 49 years

old I was plum out of control. I had no control of me at all. I was offered a chance at having the deep brain stimulator to see what would happen.

I had taken every test that was known at the time. To this day, you may not believe me, I even go hunting and fishing, you can beat that.

(Laughter.)

MR. WISTROM: I would like to have my wife to say a few things for me.

MRS. WISTROM: Thank you for letting us speak here because if it had not been for Medtronic I wouldn't have had a husband. And my children and I are so thankful. I had to feed him, dress him, take care of him for eight and a half years. He had no control of his limbs, he had no control of the tremors, and now we do have a life. And we thank that all to Medtronic and Dr. Wilkinson.

CHAIRPERSON CANADY: Thank you very much.

MR. WISTROM: Thank you.

CHAIRPERSON CANADY: Mr. Jeffrey Martin, who is a Parkinson's Disease patient.

MR. MARTIN: Good morning. I'm 46 years

old, I have two teenage daughters and I live here in Rockville, so nobody had to pay my way. In fact, welcome to my home town. I split my professional time among three activities. I'm a partner in a Washington law firm, I'm an Executive of a retail company, Saks, Inc., which owns Saks Fifth Avenue, and I'm a Parkinson's Advocate because for about two and a half years I've been diagnosed with Parkinson's Disease.

There are approximately one million Americans with the progressive disease known as Parkinson's. It's relentless. Absent more effective therapies that now exist, this disease will cripple and disable and ultimately kill people. I'm here, not as a scientist, I'm not a scientist, but to place your deliberations in a real world context and I think you've already had more eloquent testimony than I can possibly give, from the two previous witnesses.

But you need to understand that existing treatments of Parkinson's Disease provide only symptomatic treatment and on temporarily. The principle drug therapy, Levodopa or Sinemet, causes dyskinesia as a long-term nasty side affect. However,

deep brain stimulation in the subthalamic nuclei offers hope of a better therapy. I actually spent a little time learning the science in this area and went around trying to develop an understanding of the science.

I met with a lot of scientists and determined to actually -- you asked about financial involvement, nobody has paid me anything and I haven't paid Medtronic anything. But I have used my family money to support academic centers to get together to drill up something called the Deep Brain Stimulation Study Group which involved Vanderbilt, Emory, Stanford, Dr. Benabid in Grenoble, France. There is people to get together and plan a, plan for a grant application at NIH in order to do a long-term, a large-scale clinical study of DBS in the STN.

I think the promise that that has, it's not a cure, it's not the end game, but it has, there's some tantalizing evidence, particularly from Dr. Benabid in Grenoble, that indicates the possibility that not only will it provide symptomatic relief, but it could even be neuroprotective. It could slow the

progression of the disease. And nothing now does that. And we don't know whether that's going to be the case. We know it's effective for symptomatic relief, but it has the potential for actually being neuroprotective.

And so I believe that this tool should be available to those patients who are fully informed about the risks and benefits of it and who are in the hands of very qualified, very trained Neurosurgeons. Now this is not your role, but I would say, I do not believe that Neurosurgeons should dabble in DBS. It should be, you should go to the centers that have a lot of experience with this, where there are teams of people that work on this. That's for purposes, if any patients who will hear this, go to the best, go to the experienced people. Because it's not for every Neurosurgeon.

So the approval of this procedure for Parkinson's indication would allow future studies to build on a basic foundation and learn about the benefits of DBS. In conclusion, people with Parkinson's Disease face a very difficult future. It

is a family, it is a family illness in the sense that the people, that this procedure, while it's not a long-term cure, it's not going, it's not going to restore the brain function which is gone.

It's not going to replace the neurons. There's a need for much more effective therapies than this, but it is the most promising immediate therapy for some patients. Some early stage patients and some advanced patients. So I think it should be available and an option for people with Parkinson's Disease.

CHAIRPERSON CANADY: Thank you very much, Mr. Martin. We have Mr. Robin Elliott, President of the Parkinson's Disease Foundation to speak with us also this morning.

MR. ELLIOTT: Thank you members of the panel, distinguished physicians and others. My name is Robin Elliott, I'm the Executive Director of the Parkinson's Disease Foundation in New York. Neither a patient not a scientist, my role is somebody who speaks, probably as much as anybody, with hundreds of lay people and patients and families in the course of my work. And this perspective was deemed appropriate

by this panel and we appreciate the opportunity to make some comments.

I have prepared a statement which the members of the panel have. Out of respect for their busy schedules and others in this room, I will not read the whole thing, but simply take a few excerpts from it and of course be available for questions. I should also say that in terms of the relationship with Medtronic, we are neither compensated for this testimony nor is our travel. That is a policy of the Foundation in matters of this kind, we have other funds to fulfill this and we feel this is the appropriate way to do that.

The, speaking not here as a scientist, I canvass opinions from those who really do know this business. I've read the articles on this and suffice it to say that as for the technique we're talking about, the consensus of scientific opinion at the Parkinson's Disease Foundation strongly supports the use of deep brain stimulation in competent and practiced surgical hands as a valuable option for people with Parkinson's.

Especially, though not necessarily limited to, those in the later stages of the condition. People with Parkinson's have been waiting a long, long time for genuine relief from their daily trials and challenges. The medical interventions we have today are certainly much better than those that were available before the release of Levodopa more than 30 years ago, but the medical advances have been slow, incremental and too often accompanied by their own debilitating side affects.

In part underlying this slow progress has been a lack of attention, on occasion, among leadership, even in the leadership of the scientific leadership in government to Parkinson's Disease. And it's been a lower priority on the list compared with other better publicized and perhaps more prevalent diseases and Parkinson's and languished for many years and has not had the attention of science that people in the community feel that they are entitled to.

Thanks to the visionary leadership of the current administration of the National Institute for Neurological Diseases and Stroke, and their efforts

and their initiatives over the last three months, which have been really spectacular, this is clearly beginning to change. And we expect to know, five or ten years from now, a great deal more about the causes and progression of Parkinson's than we do now.

But for most of us that live with and struggle with Parkinson's today, the hope is scant and the options are few. We need to take advantage of every opportunity we have and one of these is deep brain stimulation. For people, for those people who, and it's clearly for only a relatively small portion of those who suffer with Parkinson's. A leading clinician told me the other day who has had one of the largest patient groups in the country, maybe as many as 5,000. He said, one percent, two percent, maybe as many as five percent, we're talking about relatively few people.

But for those, for whom it is appropriate, for those who are candidates for this procedure, for those who would otherwise be forced into early retirement, it can save careers. For those already in retirement, it can preserve options for recreation

enjoyment. For those in the later stages of retirement and Parkinson's, it can rescue an acceptable, dignified quality of life. And we certainly heard that eloquently from the first two witnesses this morning.

For all of these people, deep brain stimulation surgery can indeed serve as a quality of life belt. The one cautionary note, I'd like to echo something that my colleague just spoke to a second ago. The issue as to who does it and where. It's perhaps obvious to the distinguished physicians and other medical experts around this panel that any high tech, invasive procedure of the kind we're talking about, the safety and success depend in great part on the experience of the medical personnel, the availability of sophisticated and important services, such as brain mapping to go along with the surgery, and the quality and scale of the institutional backup that comes with this.

For this reason, the Parkinson's Disease Foundation and our Scientific Director and Committee believe that patients who are interested in looking

into the possibility of deep brain stimulation check first with those medical centers that have specialized resources and personnel dedicated to the procedure. We also hope, incidentally, not incidentally, essentially, that these centers will be involved in long-term studies of the efficacy and safety of these procedures over time.

With this caveat and this sole caveat the Parkinson's Disease Foundation believes that deep brain stimulation is an excellent option for certain people, some people who live with Parkinson's. And that its prompt approval and release for use in connection with a battle against Parkinson's is very clearly merited. We appreciate this opportunity. Thank you.

CHAIRPERSON CANADY: Thank you very much. We have also two statements that were sent to us by persons who could not attend that are going to be read by Dr. Garcia.

DR. GARCIA: The first statement is from the University of Southern California, Department of Neurologic Surgery, Dr. Dogali and Dr. Young. And

because they are not here to choose what to read, I shall read the entire letter. As per our conversation, we respectfully request that our thoughts and concerns be presented to the Neurological Panel reviewing expanded indications for deep brain stimulation and Parkinson's Disease.

Our Center is actively involved in the medical and surgical management of individuals with Parkinson's Disease. At the University of Southern California our daily Movement Disorders Clinic has more than 3,000 patient visits per year and approximately 100 surgical procedures per year. The surgical procedures include both ablative and stimulation procedures. In the past year we have implanted approximately 60 deep brain stimulators.

We believe that the deep brain stimulation of the subthalamic nucleus or the globus pallidus interna will prove to be significant and important therapy for control of advanced Parkinson's Disease. However, we have concerns about the present level of scientific information which would be necessary for widespread general implantation of stimulators into

these nuclei. We agree that the deep brain stimulating system, as manufactured and sold by Medtronic, Inc., is a safe device for intracranial use.

However, the Food and Drug Administration has insisted repeatedly that the device must also be demonstrated to be efficacious. We are presently embarking on a double-blinded, randomized study of the effects of deep brain stimulation in the globus pallidus and in the subthalamic nucleus in advanced Parkinson's Disease under a recently granted FDA IDE. This study is funded through HCFA and has secondary support from Medtronic, Inc. The stated purpose of our study is to determine the efficacy and safety of deep brain stimulation in these areas in the blinded, control manner.

We certainly would not be undertaking such a study if these questions had not already been adequately addressed. We have concerns, particularly with subthalamic stimulation. While some European reports indicate that the subthalamic nucleus is the preferred target for stimulation, there have been both

objective and anecdotal reports of significant morbidity with this target.

In deed, while our French colleagues have chosen to focus on the subthalamic nucleus, the Spanish group in Madrid stimulates exclusively the globus pallidus. And through personal communication reported that they made that decision on the basis of adverse affects with subthalamic nucleus stimulation. There have been anecdotal reports from a variety of French Centers regarding depression and personality alterations with STN stimulation.

There obviously have also been studies, both from North American and European colleagues, of dramatic, clinical improvement with such stimulation. Including a reduction in the need for Levodopa. A paper to be presented at the upcoming meeting of the American Association of Neurological Surgeons indicates that similar results can be achieved with globus pallidus stimulation. An abstract is included.

In addition to the lack of scientific information about the ideal site for stimulation, we lack the knowledge of optimal patient selection

criteria. We are all aware that Parkinson's Disease presents with a number of different symptoms. And while we group Parkinson's patients into a large class for clinical purposes, there appear to be clinical subsets of patients, as judged by progression of the disease, major disabling symptoms and responses to therapy.

Which subset of patients is best treated by which type of stimulation? It is our impression that the majority of Parkinson's patients have undergone either GP or STN stimulation tend to be younger onset patients. In reality, the vast majority of Parkinson's patients have the onset of their disease in the late fifth or early in the sixth decade and become significantly refractory to medication in their 60's and mid-'70's. It is this population which would potentially be the large group needing surgical therapy.

We feel there is insufficient data on the morbidity and mortality caused by stimulation in this more advanced age group. Finally, many of our outstanding and exceedingly competent colleagues have

devoted significant time to studies of stimulation in these nuclei. We point out that they represent the best, both in terms of scientific ability and surgical expertise. At the same time, it is generally accepted within the neurosurgical community that at present there exists a significant void in the ability of most neurosurgeons to carry out stereotactic procedures.

Particularly, those that are functional in nature. There is an even greater void of expertise which would be needed for deep brain stimulation in the globus pallidus or subthalamic nucleus. While there are perhaps more neurosurgeons capable of targeting and successfully stimulating the GPI, the subthalamic nucleus will present significant problems for many Centers due to the lack of both experience and available equipment.

General approval of deep brain stimulation in additional nuclei for advanced Parkinson's Disease may result in improved patient outcomes in the short term. But it may have undesirable affect of subjecting a substantial number of patients to a surgical procedure for which the indications and

efficacy are not completely understood. Placing them in the hands of surgeons, who, at present time are not technically competent for the procedures described. This may result in substantial, unnecessary cost to taxpayers.

As to our own Center, we would benefit substantially from a general approval of deep brain stimulation because we have many patients who potentially would be candidates for deep brain stimulation in these nuclei, but are definitely not candidates for our study. Thus in spite of what we believe would be a significant benefit to us, we strongly urge the panel to exercise due caution in this circumstance where therapeutic enthusiasm appears to outrun scientific underpinnings. Dr. Dogali and Dr. Young.

CHAIRPERSON CANADY: Thank you very much. Do you have a second statement, Dr. Garcia?

DR. GARCIA: Yes, I do. It's from the President of the Parkinson's Action Network, Joan Samuelson. And also I'll read hers in its entirety. In 1987, after being diagnosed with Parkinson's

Disease at the age of 37, I left my career practicing law to begin the Parkinson's Action Network. The Network, a nationwide advocacy organization, was formed to provide a voice for the Parkinson's community.

The central objective the Network is to promote a level of research support sufficient to produce effective treatments and a cure. Until the objective is accomplished, the secondary mission to provide an informed, organized and effective voice on public policy issues affecting the search of a Parkinson's cure. Although I'm familiar with the procedure of deep brain stimulation in Parkinson's patients and know people who have undergone this treatment, I am not qualified, nor do I have the necessary scientific data to make a statement about the safety or efficacy of this procedure.

However, I am qualified to testify to the extremely urgent need for effective therapies for Parkinson's and the great suffering and economic loss caused by the disease. Parkinson's Disease a progress neurologic disorder. Approximately one million

Americans are currently afflicted with the disease, with 60,000 more diagnosed each year, one every nine minutes.

Currently there is no cure for Parkinson's Disease and the cause of the disorder is unclear. Parkinson's victims become increasingly incapacitated over many years until they become totally disabled. The disease slowly destroys the body's ability to function, taking away the physical abilities necessary to daily life while leaving the mind like a prisoner inside the body.

Presently, medication is often used to control Parkinson's symptoms, but it does not entirely alleviate them. Conventional treatments of Parkinson's revolve around pharmaceutical substitutes for dopamine, such as L-dopa and drugs that temporarily enhance the cells' dopamine production. Unfortunately, these have many side affects and often do not take affect immediately. Even with newly developed agonists and inhibitors, drugs that increase the effectiveness of L-dopa therapies, these measures lose their effectiveness over time.

Generally, four to eight years after diagnosis, victims begin to notice their symptoms are less controlled by the medication. Eventually, patients are left unable to move, speak or swallow. Parkinson's Disease is estimated to cost the U.S. about 25 billion per year. In addition to the health care costs, there is a significant loss of productivity and tax revenue due to reduced or loss employment and early retirement.

Costs are spread among afflicted families, health and disability benefit providers, SSI and SSDI, Medicare and Medicaid. According to Roger Kurlan, M.D. at the University of Rochester, even a ten percent slowing in the progression on Parkinson's will save 327 million per year. If deep brain stimulation is found to be effective and safe for Parkinson's patients, I strongly urge the FDA to act immediately to make this treatment widely available as soon as possible.

Once a safe breakthrough therapy has been developed, it is essential that it does not become buried in regulatory approval. The process must be

efficient and effective, I'm sorry, efficient and expedient. People with Parkinson's do not have the luxury of time to await potential life-enhancing therapies. This from Joan Samuelson, President, Parkinson's Action Network.

CHAIRPERSON CANADY: Thank you very much, Dr. Garcia. We will be having an industry presentation, but I'd like at this time to invite any other comments from the public. Would the Panelists like to ask any questions of any of the public? If not, then we'll bring this portion of our meeting to a close, and we will proceed with the industry presentation. The open panel discussion on the PMA Supplement P960009/S7 for the Medtronic, Inc. Activa Parkinson's Control System. We will start with the Sponsor's presentation to the panel, and then after the lunch break, there will be an FDA presentation to the panel.

The panel will then deliberate on the approvability of the PMA Supplement. Before the panel votes on the approvability of the PMA Supplement, there will be another open public hearing and a time

for both the FDA and the Sponsor summations. I would like to remind public observers at this meeting, that while this meeting is open for public observation, public attendees may not participate accept at the specific request of the panel.

We will begin with the industry presentation by Medtronic. The first Medtronic speaker is Ms. Lisa Pritchard, Principle Product Regulation Manager, Medtronic Neurostimulation.

MS. PRITCHARD: Good morning. As Dr. Canady indicated, my name is Lisa Pritchard. I am a Principle Product Regulation Manager in the Neurostimulation Division of Medtronic. I'd like to thank each of you for the flexibility you've shown in your busy schedules to be here with us today to discuss the safety and effectiveness profile of Activa Parkinson's Control Therapy.

The data that we'll present to you today, clearly supports that Activa Parkinson's Control Therapy is safe and effective in controlling the symptoms of Parkinson's Disease that are not adequately controlled with medications. In addition,

the data supports that Activa Parkinson's Control Therapy is effective in controlling the dyskinesias and motor fluctuations associated with medical therapy for Parkinson's Disease. Next slide, please.

To review the data that has been collected by Medtronic, I will begin with a brief history and chronology of the events that have been completed to date associated with the Activa therapies. I will then provide a brief description of the main implantable components of the Activa Therapy Device and then turn the presentation over to Dr. C. Warren Olanow.

Dr. Olanow is one of the principle investigators involved in our study and he will present a brief background on Parkinson's Disease and then present the compelling study results obtained within the study. To conclude our presentation then, I will then introduce all of the physicians and Medtronic personnel that we'll have available to answer any of your questions. Next slide, please.

The Activa System, as a brief history, was reviewed by this panel approximately three years ago

for the treatment of Essential or Parkinsonian Tremor with stimulation in the ventral intermediate nucleus of the thalamus. Following the panel's recommendation, the Activa System was approved for the treatment of Unilateral Essential or Parkinsonian Tremor in July of 1997. Specifically related to the Activa Parkinson's Control Therapy, Medtronic obtained initial approval of the investigation of the exemption back in May of 1995.

The first U.S. study patient was then implanted in July of 1995. Following the collection of data in the study, Medtronic submitted, back in September of 1999, the premarket approval application supplement that included data collected in the study through August of 1998. Following that initial submission, we followed up with updated information on the safety data in the study that followed patients through August of 1999.

We then submitted responses to FDA questions in January of 2000. Next slide. Activa Parkinson's Control Therapy uses the same device components previously approved for the Activa Tremor

Control Therapy. The Activa System uses an implantable, programmable neurostimulator that applies control electrical stimulation to specified targets within the brain. The primary implanted components of the system include a lead, a neurostimulator and an extension.

For Activa Parkinson's Control Therapy, the electrodes on the distal end of the lead, and you're going to see them there, are implanted either within the subthalamic nucleus or the internal globus pallidus. The leads and extensions are implanted underneath the scalp to the neurostimulator implant location which is typically in the subclavicular region as indicated on this diagram. Next slide, please.

Currently, we do have two leads that are available for use with the Activa Parkinson's Control Therapy. The Model 3387 lead on the top, includes four electrodes on the distal end that are spaced 1.5 millimeters apart. We also have another lead, Model 3389. This lead also includes four stimulating electrodes which have a closer spacing of 0.5

millimeters. The two leads are really available just to accommodate physician preference on the spacing of the electrodes.

The neurostimulator used to deliver the stimulation for the Parkinson's Control Therapy is the ITREL II, Model 7424 Neurostimulator. This neurostimulator contains the electronics and battery necessary to deliver the electrical stimulation to the target location. Next slide, please. At this time I'd like to introduce Dr. C. Warren Olanow. Dr. Olanow is one of the principle investigators involved in the evaluation of Activa Parkinson's Control Therapy. He's Professor and Chairman of the Department of Neurology at the Mount Sinai School of Medicine in New York. Dr. Olanow.

CHAIRPERSON CANADY: Good morning, Dr. Olanow.

DR. OLANOW: Good morning. Thank you all for allowing me to be here today to discuss the results of our study with you. Let me begin by saying that I have no financial interest in Medtronic, but I have served as a Consultant to that organization and

they have paid my expenses to come here today. If I could have the first set of slides, please.

What I would like to do is to describe for you the results of our clinical investigation testing the Activa System as part of deep brain stimulation of either the subthalamic nucleus or the globus pallidus pars interna in patients with advanced Parkinson's Disease. In doing this, I'd like to give you a brief review of Parkinson's Disease and the problems that we're trying to control.

Then I will review with you the methods and the results of our study and conclude with risk benefit analysis and along the way I'd like to show you some patient videos. Next, please. To begin with, as you've already heard, it is estimated that Parkinson's Disease affects approximately 500,000 to one million people in the United States. And as you've also heard, the average age of onset is approximately 60 years.

Because of the aging of the population and the increasing number of people who will be 60 years or older in the future, we have predicted that the

various drugs that are currently available for the treatment of Parkinson's Disease, and as I've mentioned, they are largely based on trying to replace dopamine in the striatum.

This has led to marvelous advances, as I will show you in a moment. But to spite this long list of medications that are available today, there are a number of limitations, as I will also show you in one moment. Next, please. So firstly, just to review Levodopa as the gold standard of medical therapy today, you should appreciate that it remains the most effective anti-Parkinsonian agent and that virtually all Parkinson's Disease patients do respond in some way to this medication. Clearly, it reduces disability.

It allows patients to maintain independence in their activities of daily living. And even to remain employed. And finally it prolongs their life. The problems, however, are listed on this side, and these problems are important and they're common. After as little as five to ten years of levodopa treatment, more than 75 percent of patients

have begun to develop adverse events which now lead to increasing disability.

The most important of these are motor problems. First, motor fluctuations, and second, dyskinesia. Motor fluctuations refers to the fact that when you give a patient a dose of levodopa early on, they get an extended benefit which lasts for a considerable length of time. As the disease progresses, the duration of benefit gets shorter and shorter and shorter, so that patients now begin to cycle between being good and responding to drug and begin bad and the drug affect having worn off.

Now to make matters even worse, they also experience dyskinesia or involuntary movements which complicate the on or the drug effective stage. Here they will experience wild writhing movements which are usually dance-like or choreaform in nature. So that what happens to the vast majority of Parkinson patients is after five to ten years they are beginning to cycle between periods in which the drug works, but they have involuntary movements that complicate them.

And then the drug stops working and they

become frozen and unable to move, what we call sometimes akinetic. In addition, probably because of the fact that these patients have a high risk of developing dementia, Levodopa and other dopaminergic agents tend to increase confusion and cause hallucinations. And finally, it should be appreciated that there remain many problems that are very important for Parkinson's patients, like freezing, postural instability, dementia, etcetera, that just are not adequately controlled with levodopa. Next, please.

Well, what do we do when a patient starts to develop these kind of problems? And again I want to emphasize to you, this is the majority of patients. When a young person walks in the room with early Parkinson's Disease and only a slight tremor, I can tell you that five to ten years from now 75 to 80 percent of them will have this problem. Well, one thing we can do is try to manipulate their drugs, use the wide variety of agents currently available.

But I can also tell you, as an experienced clinician, this is most unsatisfactory for most

patients in the long-term. This is what has led to the resurgence of interest in surgical therapies. The inability to control these problems with medical therapy. And here one has a variety of options, ablative procedures, including thalamotomy and pallidotomy which provide some benefit but necessity making a destructive lesion in the brain with all the side effects that are associated with that, particularly when the procedures are done bi-laterally.

More recently, as you've already heard and know, there has been the advent of a new technique called deep brain stimulation. This is based on observations in the laboratory suggesting that two critical areas in the Parkinsonian brain are overactive. The subthalamic nucleus and the globus pallidus pars interna. And what deep brain stimulation allows is an electrode to be placed into these targets and to simulate the effect of a lesion but without having to destroy brain tissue through a damaging brain lesion.

What are the advantages of this technique?

It voids the necessity of making a destructive brain lesion. It can be adjusted at any time after the procedure in order to try and maximize benefit and to minimize adversity. It can be used bilaterally with relative safety and it avoids the bilateral problems that are so commonly seen with bilateral destructive procedures, such as speech disturbances, cognitive disturbances and swallowing disturbances.

And then finally, as we continue to advance in developing new therapies that may be even more effective, it does not preclude their use by having destroyed part of the basal ganglia, which may prove to be necessary for some future therapy. At this point, what I'd like to do is show you a videotape that gives you a brief sense of what these patients look like and what the therapy we're about to describe can do for them.

So here is the first patient and I'm going to show you what he looks like when he's not on medication. He's been implanted with a stimulator, but the stimulator is turned off. And this is what the medication-off state looks like. When the drug

isn't working they become frozen, they can hardly walk. And this gentleman is not the worst that you can see. Patients can be so bad they can't even get out of a chair or get out of bed.

They can't move, they can't go to the toilet, they are stuck. And he illustrates the kind of problem that patients might have when they are off and when the medicine isn't working. Now in contrast, when the stimulator is turned on in a patient like this in the off state, it restores motor function to him in a way that no other medication that I have ever seen has been able to do. And here you can see the tremendous improvement that this patient has been able to enjoy with stimulation and the medication on-off stage.

Now the other side of the problem is what happens if they take medicine to try and improve their clinical condition. Well, they develop a series of involuntary movements and I think you recognize this cap. And here you can see some of the kinds of dyskinetic involuntary movements that complicate the on. So you get a sense that Parkinson's patient's

cycle between being on with these involuntary movements and off with in which they are frozen.

And in a second I'll show you the results of what happens when you stimulate a person who is in the medication-on state and what you will see is, he's being turned on as you can see and this will continue for just one second. We'll do the other side in a moment. But the bottom line of this is that by turning on the stimulator in the on state, he not only enjoys the benefit of having on, but his involuntary movements have been markedly improved.

If we could go on then to the next slides, please. So the study that we performed to evaluate these new treatments are summarized as follows. We've performed a prospective, 12-month, multi-center trial to evaluate the efficacy of the Activa System using high frequency deep brain stimulation in the two targets I've described, the subthalamic nucleus or the globus pallidus pars interna, and all patients have advanced Parkinson's Disease.

The study was open-label, but it included a double-blind, randomized, cross-over study of the

effective stimulation at the three-month time point in both the STN and GPI groups. I point out to you that in this study patients were not randomized to one treatment group or another, physicians had the right to choose which target the preferred to use. So this study was not designed to directly compare STN and GPI.

The primary endpoint was chosen as a 25 percent reduction in the motor subscore of the unified Parkinson's Disease rating scale. This is a standard endpoint in patients with Parkinson's Disease and has been used routinely as an endpoint for many of the pharmacologic areas or pharmacologic therapies that we have tested. And this is tested as our primary endpoint in the double-blind phase of the study where they are randomized to a sequence of either stim-off and then on, or stim-on and then off.

Secondary endpoints in this study were again the UPDRS motor subsets, but now over the course of the study at different visits in all combinations of medication and stimulation-on and off, as I'll show you in just a moment. Next, please. Other data that

was collected, including the activity of daily living subset of the UPDRS. Home diary assessments of percent time spent in the following motor conditions. Off, when the medication is not working. On, in which the medication is working, but they have dyskinesia, the involuntary movements you saw. And on in which they are working but they have no dyskinesia.

And obviously, this is the condition that we would most like to have our Parkinson's patients in. The way these home diary assessments are performed is the patients are given a home diary that records every half hour or hour how they are doing in respect to each of these conditions, and they are filled out for two days prior to each visit. And patients are trained to recognize and identify these conditions and to fill out these calendars before the study is initiated.

And again, these have been used as primary endpoints for several medications that have recently received FDA approval. Other data that we collected, including the dosages of Parkinsonian medications, global assessments of disability as determined by both

the physician and the patient, and stimulation settings and device information, and of course adverse event data. Next, please. The study included patients who had been diagnosed as having idiopathic Parkinson's Disease based on Capit criteria and who had a good levodopa response which we feel is inherent to a diagnosis with Parkinson's Disease.

In order to ensure that they had a certain level of disability, we looked at several other measures of Parkinson's severity and ensured that they were Hoehn and Yahr Stage 3 or greater, that their UPDRS total motor examine score was 30 or greater in the medication-off state, and we required that either motor fluctuations of dyskinesia or both were present in all patients.

Medication has to be stable for at least one month before enrollment. Patients had to have absence of dementia and be able to give proper, informed consent. And they had to be free of psychiatric symptoms and hallucinations that would confound their participation. They could be 30 to 75 years of age, either gender and any race. And they

had to have no medical problem that was considered to be clinically significant that might interfere with the study.

Exclusion criteria of course included those who withheld consent, anyone who had an atypical or secondary Parkinsonism, people who had had previous intracranial neurosurgical procedures, demand cardiac pacemakers or other conditions that required repeat MRI, a history of substance abuse, major psychiatric problems, and anyone who for whatever reason was deemed to be an appropriate surgical candidate. Next, please.

At the time of pre-implant or baseline, patients underwent two visits which were completed within one month of implant. At baseline they were evaluated in both the medication-off and medication-on states. The medication-off state, as determined by the Capit protocol, is what's called the practically defined off state. And what we're trying to do is get a handle of their underlying Parkinsonism.

Patients were withdrawn from medication overnight and thus were off medication for

approximately eight to 12 hours and then their motor scores were evaluated. The medication-on state was evaluated after their morning medication and we tried to obtain their best on state which was usually approximately 60 minutes after the usual dose of medication.

So in this way we were hopefully getting records of how bad they could get and how good they could get with current medical therapy. Follow up assessments were performed at one, three, six and 12 months after the second lead implant. And the two lead implants had to be performed either simultaneously or within three months of one another, for those who wish to stage. And in the follow up state, patients were evaluated in four conditions.

Medication-off, as the defined here, with stimulation-off. Medication-off with stimulation-on. Then subsequently, medication-on with stimulation-off, and medication-on with stimulation-on. So I've defined medication-off and on here. For purposes of this study, stimulation-off evaluations were performed after overnight withdrawal of stimulation, which again

was generally eight to 12 hours. Stimulation-on evaluations were performed when the stimulator had been on for at least 30 minutes. Next, please.

DR. EDMONDSON: Excuse me.

DR. OLANOW: Yes.

DR. EDMONDSON: Could you just review the permutations again, with regard to medication-on with stimulation-off, what both --

DR. OLANOW: We captured the four conditions that could exist.

DR. EDMONDSON: Okay.

DR. OLANOW: Medication-off with stimulation-off and with stimulation-on. And then medication-on with stimulation-off or stimulation-on.

DR. EDMONDSON: Okay, so they're randomized to those four --

DR. OLANOW: No, no, no. These are in our routine open evaluations and follow up visits.

DR. EDMONDSON: At follow up visits?

DR. OLANOW: Right.

DR. EDMONDSON: Okay. And so for each of those four subgroups, if you have someone with a

stimulation-off overnight, medication-on or off, then you turn it on and you wait an hour?

DR. OLANOW: Thirty minutes.

DR. EDMONDSON: Thirty minutes. And in the same time course if they are off medication, give them medication, wait an hour?

DR. OLANOW: What would happen is overnight they would be off both. You would now score them. So that would be medication-off, stimulation-off.

DR. EDMONDSON: Right.

DR. OLANOW: You would now turn the stimulator on. You could now make a recording 30 minutes later and have medication-off, stimulation-on. Okay? At another setting you could then have them overnight without medication, give them their medication, get their best response and score them medication-on, stimulation-off. Then turn on the stimulator, wait 30 minutes and score them medication-on, stimulation-on.

DR. EDMONDSON: Okay, got to go slower. All right, let's take one session, stimulation-off,

medication-on, let's just take that for a second.

DR. OLANOW: Okay, well, for that a person would be withheld from drug overnight. They would be given their medication.

DR. EDMONDSON: Right.

DR. OLANOW: They would turn on, but the stimulator would be left off. They would be scored. That would be considered medication-on, stimulator off.

DR. EDMONDSON: Okay.

DR. OLANOW: The stimulator would then be turned on. They would then be scored. That would be considered medication-on, stimulation-on.

DR. EDMONDSON: Okay. And the time interval?

DR. OLANOW: Thirty minutes.

DR. EDMONDSON: Thirty minutes after you turn it on and score.

DR. OLANOW: Correct.

DR. EDMONDSON: Okay. And that takes into account that if you give them medicine, the interval there is 30 to 60 minutes after you give them the

medication as well?

DR. OLANOW: Correct. The medication is given. The patient turns on, you score them. You then turn on the stimulator, wait 30 minutes, score them again.

DR. EDMONDSON: Okay.

DR. HALLETT: Warren, while we're interrupted, can I just clarify what the blinded part was compared to the unblinded part. There is only one blinded observation and all the rest of the observations are open, as I understand it.

DR. OLANOW: That's correct.

DR. HALLETT: And the only blinded observation is done at the three-month point.

DR. OLANOW: Correct.

DR. HALLETT: And could you clarify what the specific observations were that were made blinded and were those then duplicated for the unblinded portion at that same visit or was there only one set of observations made at that visit of those particular observations?

DR. OLANOW: Patients at three months had

their routine evaluations, as I've just described. In addition they had the following which constitutes the randomized double-blind cross-over. First of all, they were evaluated in the medication-off state. That is overnight off-medication, off-stimulation. They were then randomly assigned to one of two sequences. In Sequence 1, they would be evaluate first with stimulation-off and then with stimulation-on.

In Sequence 2, they would be evaluated first with stimulation-on and then with stimulation-off. The two periods were separated by two hours. Both of these evaluations were performed in the medication-off state and it was the UPDRS motor evaluation that was used as the endpoint. And both the patient and evaluators were blinded as to both stimulator status and the sequence that the patient was undergoing.

So if you look at this consort diagram, no, I guess it's not, it's just a diagram of the randomization. Here they're randomized and they would, those who are randomized to stimulation-off would be evaluated 30 minutes after not turning on the

stimulator. They would then go two hours, the stimulation would be turned on, and 30 minutes later they would be evaluated stimulation-on in Period 2.

Now the opposite effect, I apologize, for this it was two hours, not 30 minutes. For those randomized to Sequence 2, they would be randomized to stimulation-on, it would be turned on, two hours later evaluated, then it would be turned off, two hours later evaluated. So in this way, patients in Sequence 1 have evaluations in off and then on, and the opposite for those in Sequence 2.

DR. HALLETT: All right, and then the, then the unblinded examinations of that same visit were done on a separate day?

DR. OLANOW: On a separate day.

DR. HALLETT: And was that always done before or after or did that vary? In terms of the unblinded assessment on the time of the three month visit?

DR. OLANOW: We, they were always done before the unblinded.

DR. HALLETT: The unblinded were done

first and the blinded were done second, is that correct?

DR. OLANOW: Yes. Question?

DR. COHEN: Yeah, I had a question. Were both of those situations done with medication-off and medication --

DR. OLANOW: Yes. All of these were in medication-off.

DR. COHEN: All of the medication-off?

DR. OLANOW: Correct.

DR. COHEN: Did you also do it with medication-on?

DR. OLANOW: No, we never did the blinded in medication-on.

DR. MASSAQUOI: Question?

DR. OLANOW: Yes.

DR. MASSAQUOI: Can you review any sort of scientific basis or argument for what would be an adequate amount of time for washout of stimulation effect? In particular, why it might be chosen that one leaves a stimulator off overnight and then later has a cross-over in which the stimulation is off only

for a short amount of time before the subsequent testing?

DR. OLANOW: There really is not excellent data on that and it is an important point. We did a study in our own group for slightly different reasons. We were looking at neuroprotection issues in trying to use medication-off, stimulation-off as a baseline Parkinson's state and we wanted to see if that was changing over the course of time in the STN group. In that study what we did is we brought people into our GCRC. We turned off STN stimulation in the medication-off state and then scored them blindedly, we actually randomized them to be on or off and scored them blindedly evaluating them over 12 hours, every 30 minutes.

What we found in our study was that patients deteriorated maximally in 30 minutes and then remained the same over the course of the next 12 hours. Now we did not carry them out seven days. And as you probably know, in the levodopa situation it's conceivable that there could be increasing fall off over seven days. We have no data that that either

does or doesn't happen with STN, but at least in our group when we stopped it, the maximal effect was at 30 minutes and it remained constant over the next 12 hours.

So at least for purposes of the blind, it appeared that it would be satisfactory.

DR. MASSAQUOI: And the one other question is that if the, if it is the case that one of the primary intended uses of the stimulator is in conjunction with medication, why was it chosen to study the medication-off period as a primary situation in the randomized study?

DR. OLANOW: I think I can show you that better when I start to show you the results. Because maybe if I can just say, in a simple way, the problem with levodopa has never been that it doesn't work and that it doesn't give good benefit. The problem with levodopa is you pay a price for that. So I think any one of us as clinicians, if you could tell us I'll give you levodopa and it works all the time and it's best and you'll never fluctuate and you won't experience dyskinesia, we would take that right now

and our Parkinson's patients would be very well managed.

The problem with levodopa is not how good it gets, it's that it doesn't stay there, it cycles back and forth. And that when it's good, it's complicated by these involuntary movements. So one of the things we wanted to be able to show was that in fact we could get substantial benefit with deep brain stimulation because, as you'll see in a moment, we're able to obtain that without these complications and get it to sustain.

So you might argue that this is a surgical way of giving the best levodopa and maybe that's true, because as you'll see, the best of deep brain stimulation is very similar to the best of levodopa. But it's the absence of the problems that confound levodopa that make this so appealing.

CHAIRPERSON CANADY: I would remind our panelists that there is going to be some questions at the end and he does have a long presentation. So if you would, if you need to question for purposes of absolute clarification, please go ahead. Otherwise,

if you could hold your questions to the end. Thank you.

DR. OLANOW: Next, please. So I wanted to point out to you that for purposes of statistical analyses, all data were analyzed by target site depending whether the STN or GPI was used and by laterality, that is to say bilateral or unilateral. I can tell you that the data I will present you is going to be exclusively the bilateral data, but I believe in your packages you also got the unilateral data.

I can also tell you that the way we designed the study was primarily with the intention of people doing bilateral, but with the idea that if somebody felt a result was adequate with unilateral or for whatever reason they didn't want to proceed to bilateral, they didn't have to. So you will see that the vast majority of the patients had bilateral stimulation. The primary endpoint was evaluated using non-parametric tests, the Wilcoxon Rank Sum and treatment period and carryover affects were assessed.

The other effectiveness data were

evaluated using paired comparisons with Wilcoxon Signed Rank Test. P values were established at .05 for significance and all adverse events in all patients who participated in the study, regardless of whether they underwent any surgery, let alone bilateral surgery, were included and were tabulated. Next, please. These are a list of the Centers that participated in these studies.

There were 18 different Centers. You can see that they come from across the wide spectrum of the globe. I can tell you that of the 18 different Centers, the beneficial results that I am going to show you were analyzed by Center as well as by group and that in more than 90 percent of Centers the benefits that I'm going to show you for the group were seen in the individual Centers. Next, please.

The patient demographics are shown here. As in so many of the clinical trials we do, the majority of patients who participated were male. As someone pointed out earlier, many of the people who undergo these procedures are relatively young, so you can see that there is a relatively young age of onset

of Parkinson's Disease in the 40's. You can see that at surgery most of them were in the 58 to 60-year range.

But I will point out to you that approximately ten or more patients were 70 years of age or over, and we have done analyses comparing how older patients did compared to younger patients and basically they did identically. All of the patients, of course, had Parkinson's Disease symptoms. Almost 100 percent had motor fluctuations, and the large majority, 90 percent, had dyskinesias or involuntary movements. Next, please.

These are flow diagrams showing you what happened to the patients. For STN, 105 patients were entered into the study. Ninety-five of whom received bilateral implants. The implant was not performed in four and was performed unilaterally in six, either for reason of physician decision or because there may have been a complication. The database was cut for purposes of doing these analyses so the reducing number does not reflect dropout and you can see that we actually did extremely well, losing only six

patients to follow up of 105 over the course of this one-year rather complicated study.

You can see the same kind of information with GPI. Fifty-four patients, more of them had unilateral, 15, and again only two patients of the 54 eventually dropped out over the course of the study. Next, please. So I would like to talk to you about the effectiveness of bilateral stimulation and the claims that the company has made based on this study include the fact that it improves the motor features of Parkinson's Disease, the total motor features as well as the individual cardinal features.

But it decreases dyskinesia which is measured primarily by an increase in percent on-time without dyskinesia, which as I mentioned to you before, is the hardly desirable state that we want our Parkinson's patient to be in. That it allows them to regain independence and functional ability. In the case of subthalamic nucleus patients most could reduce Parkinson's medication and global assessments of disability were improved according to both physician and patient. Next, please.

So I'll begin this portion of the presentation talking only about subthalamic nucleus bilateral stimulation and then go on after and show the results of GPI. Firstly, with respect to motor features, we used the UPDRS total examine firstly in the randomized double-blind cross-over assessment that we described and then in the four conditions at each of the follow up visits. Next, please.

Here are the results of the double-blind cross-over study. Patients in Sequence 1 were randomized to off and then on. Higher scores on UPDRS means worse function, lower score means improved function. You can see that patients randomized to off did better with stimulation. Patients randomized to on did worse when the stimulation was turned off and there were significant differences not only for these various treatment effects, but also when analyses were performed comparing those randomized to off and those randomized to on in Period 1, there were no period or carryover affects.

The magnitude of improvement in motor score was 48 percent, for those who had stimulation-on

compared to those who had stimulation-off. And in the Parkinson's Disease world where we're dealing with patients with very advanced disability, this is a very dramatic and marked improvement in the level of motor score improvement. We wanted 25 percent improvement with stimulation as the endpoint, and you can see that 77 percent of patients met that criteria. Next, please.

Now here I can show you the four conditions that we talked about before. Here is the medication-off, stimulation-off score baseline and then at each visit over the 12-month course of the study and you can see that basically it didn't change. Look now at the medication-off state when you turn on the stimulator and you can see that you get a very dramatic and robust improvement in their motor score which persists over the 12-month course of the study.

The dotted line you're seeing here, excuse me, represents medication-on, stimulation-off, so this is the best of levodopa and other anti-Parkinson agents. And what you can see is that the anti-Parkinson affect of stimulation is approximately equal

to that which is obtained with medication. And in fact when you add stimulation to the medication-on effect you attain additional benefits in what we call the medication-on, stimulation-on state so that there is overall improvement with stimulation in both the medication-off and medication-on states.

The magnitude of improvement matched that which we saw in the double-blind phase about 44 to 52 percent improvement and this was highly significant. At 12-months, the comparison to baseline 25, excuse me, 84 percent of these patients had at least a 25 percent improvement in UPDRS score in comparison to their original medication-off baseline state. In the medication-on state the benefit was a little less pronounced, but it was nonetheless significant.

One of the things you should take note of in analyzing this data is that one of the reasons the medication-on score may have drifted up or worsened a little, is that with stimulation we were able to reduce the levodopa dose some. So this may be a slightly unfair comparison here because the dose had been reduced and that may account for why medication-

on, stimulation-off was a little worse, and why there was such a big difference between medication-on, stimulation-on. Next, please.

This just shows you the difference for each of the cardinal features of Parkinson's Disease. The magnitude of improvement in tremor was dramatic, about an 87.5 percent increase, and this was at a level that was approximately the same as what we obtained with deep brain stimulation of the VIM nucleus, which has been approved for this. Here you can see the improvement in rigidity score, the improvement in bradykinesia and the improvement in postural instability and there are the percentages ranging from 33 to 87.5 percent. Each of those was statistically significant. Next, please.

Now, this is the part that for me I found most intriguing as a doctor, and it reflects the time when the patients are on, responding to drug, but not experiencing the bad complications. And this information was really recorded largely through home diaries where patients record every 30 minutes what their motor state is. And if I can see the next,

you'll get a sense of what I believe this procedure can really do.

The gray represents when they're asleep. So if anything, it's, it makes the results seem less dramatic. The orange represents the period of time in which the patient is off, excuse me, on without dyskinesia. This is what we want. We don't want them off because they can't move very well and we don't want them on with dyskinesia because they have those complicating involuntary movements.

This is what we want. And you can see, I've just shown you here the results of three and 12 months, but you can see the tremendous increase of on-time without dyskinesia that patients experience in the presence of stimulation and the tremendous reduction in the time of day they experience dyskinesia and the time of day in which they are off.

The other thing that's really striking about this and represents something we've never been able to achieve with any medical therapy is when they're off, not only has there been a dramatic reduction in off time, but the yellow represents their

UPDRS when off and their UPDRS score off has begun to approximate their on-time. So that effectively they're on all day almost without dyskinesia. And that short time they're off, their off score is not all that much different than when they're on.

And this is really what allows us to say that their function has been so dramatically increased. The daily on-time without dyskinesia at baseline was five hours. And that was increased to 11 to 12 hours at follow up visits. The daily on-time with dyskinesia fell from four to one to two hours and the daily off-time went from eight hours to three hours and was associated with a marked improvement in motor function so that the off wasn't as severe, and all of these were highly significant. Next, please.

In order to talk about independence, we use the ADL component of the UPDRS. Again, this is the a standard instrument that we routinely use in clinical trials in Parkinson's Disease. Next, please. We evaluate this in their off and on state and basically what we do is just ask the patient, how do you perform this act when you are at your best? How

do you perform this act when you are at your worst? And that's sort of how we try to determine on and off.

Here you can see their score when they were at their worst at baseline, here when they were at their best at baseline and here you can see what they call their worst and best in the presence of stimulation. It's important to remember, by the way, that most of these patients left their stimulators on virtually all the time. So that these represent something that they experienced literally all during the course of the day.

So basically they just didn't do much worse than this, which is a big difference between what they were experiencing at baseline, and again was highly significant. Next, please. With respect to medication, because they were on different drugs, we tried to calculate levodopa dose equivalents.

And we used the formula that Tony Lang had developed in which he added the Levodopa dose plus .75 of controlled-release levodopa plus ten times the dose of bromocriptine and 100 times the dose of pergolide. Next, please. When you look at that you find that the

levodopa dose equivalence is reduced by about 25 to 37 percent. This improvement, or excuse me, this reduction in dose may have contributed partially to the improvement in dyskinesia.

But as you'll see, we saw the same kind of thing with GPI and there wasn't a dose reduction, raising the possibility that by interfering with the firing of STN neurons we may have done something more fundamental in terms of reducing dyskinesia. Interestingly, approximately 27 to 36 percent of patients had at least a 50 percent reduction in their dose of levodopa equivalent. Next, please.

To assess this ability we use global assessment which is another standard tool we use and we asked physicians and patients to merely remark on their level of disability ranging from zero to four severe, and it's a very simple scale. Next, please. Here to the results were very dramatic. As you can see before the study started, 74 percent of patients and physicians rated Parkinsonism severe, either severe or marked. And you can see that that fell to nine to 14 percent at the time of the end of the

study.

And you can see that the huge majority had moderate, and in many cases mild or no disability according to determinations of both doctors and patients. Next, please. So now I'd just like to briefly show you the results in the GPI which are very similar to what you've seen with STN. Next, please. First of all, with respect to the primary endpoint, the double-blind, randomized, cross-over study. Again, you see that those randomized to off had a higher UPDRS score than those randomized to on.

When they were stimulated they were improved. Those who were, stopped stimulation deteriorated. The treatment affect was highly significant and there was a significant affect even in the group in Period 1, where we could do that analysis of just those patients. The magnitude of improvement was 38 percent for those who received stimulation-on and 67 percent of patients had at least a 25 percent improvement with stimulation-on, no significant period of carry-over affects were observed. Next, please.

Here you see again the drawing or the

diagram of the four conditions. The dotted line at the top represents medication-off, stimulation-off and again the stimulator improves their condition very substantially, approximating but not quite reaching the level of improvement that was, excuse me, the state with levodopa and other anti-Parkinson medications. And again, you can see with stimulation-on there was slight improvement even in the medication-on state.

The magnitude of improvement was very similar again to what we saw in the double-blind component, 31 to 39 percent, and this was highly statistically significant. Looking at the benefit of stimulation both compared to the off state at baseline at each visit and compared to the medication-off, stimulation at the corresponding visit. At the 12-month time point, 71 percent of patients had at least a 25 percent improvement over their original medication-off baseline score.

In the medication-on state the improvement was less, nine to 31 percent, and it was significant, however, and again both in comparison to baseline and

to each visit. Next, please. Here you can see the affects of GPI stimulation on the cardinal features of Parkinson's Disease. You can see that there was 35.4 percent improvement for tremor, 28.3 for rigidity, 35.9 for bradykinesia. It looks like there's improvement for postural stability, but when you calculate the median it was zero. And this was the only one that wasn't significant. Next, please. Next, please.

If you look at these home diaries, which again I think is really a great way to evaluate how the patient is doing, you can see that the on-time without dyskinesia went from five hours at baseline to ten to 12 hours at the time of the final visit. And you can see the corresponding reduction in off-time and in the time with dyskinesia. And as with STN, you can see that even when they were off, the magnitude of off score was less than what it was at baseline. Next, please. Next, please.

Here you can see the results of ADL scores. ADL scores were improved by 35 to 38 percent in the off periods and they were improved by 28 to 43

percent during the on scores. And these are reflected here indicating again that according to UPDRS activity of daily living evaluation, treatment with stimulation provided benefit that was significant. Next, please. Next, please.

Here, as you can see, I indicated before that the levodopa dose equivalents were not changed in the GPI group and yet there was a dramatic reduction in dyskinesia suggesting that either the levodopa dose reduction does not account for that benefit in STN, or that the mechanisms are different in the two structures. Next, please. Next, please. And again, if you look at how patients and physicians rated themselves, 75 percent were thought to have severe or marked disability at the start of the study and only ten percent at the end of the study, with again the vast majority being moderate, mild or none. Next, please. Next, please.

With respect to the stimulator settings at six months, and these are the mean stimulator settings, just to give you a sense of what was happening. They were not all that different between

the group. The average voltage was 3.0, a frequency of 154, pulse width of 75.2. The majority in STN shows monopolar stimulation. You can see that they use the stimulator an average of 23.5 hours per day.

In the case of GPI, they use slightly higher voltage of 3.4, their rate was 152.7, they used a somewhat higher pulse width of 114.7. There was about a equal split between whether the electrode configuration was monopolar or bipolar and again they used the stimulator almost all of the day. Next, please. So let me know go on and talk to you about the adverse events that were associated with obtaining this level of efficacy. Overall, 139 of 159 patients or 87 percent experienced at least one adverse event.

I should explain to the panel that the way we obtain adverse events is to just ask patients openly and broadly, has anything new happened to you? Have there been any problems or any worsening of problems that have occurred since the last visit? And those are recorded. We do not probe for individual adverse events. I say that because in the trials we do in Parkinson's Disease, the idea that 87 percent