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ATDEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

NEUROLOGICAL DEVICES PANEL MEETING
OF THE MEDICAL DEVICES ADVISORY COMMITTEE
NINTH MEETING

Friday, March 14, 1997

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at

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Gaithersburg, Maryland

MILLER REPORTING COMPANY, INC.
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Washington, D.C. 20002
(202) 546-6666

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P R O C E E D I N G S

Introductory Comments

MR. KEELY: Ladies and gentlemen, welcome to the Ninth Meeting of the Neurological Devices Panel. I am Levering Keely and I am the Executive Secretary for the panel.

First is a housekeeping item which will be repeated later. At the conclusion of the meeting, please confine all trash to appropriate containers within the room and deposit them or take them with you, please. If you have not already done so, please write your name legibly on the attendance sheet that is outside the back door so that we can have an accurate record of those who have attended today.

In addition, there is a packet of information containing an agenda and identification of the panel members which is available outside the room if you have not already picked it up.

Let me call your attention to the format of the meeting today. The first session is open to the public, hearing concerns from the public from persons who have identified themselves to speak. Anybody who has made a prior notification to speak as outlined in the Federal Register dated February 28, 1997, will be given an

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opportunity to address the panel at that time.

There has been one such request. Following this, anybody else who wishes to speak will be recognized.

Following the open public hearing, there will be an open committee discussion of the issues at hand. The involved firm will be given time for the presentation. The FDA will make a presentation and the panel will discuss and vote on the issue at hand.

Following the open committee discussion and vote this afternoon, there will be a brief break when all members of the public must vacate the room and the panel will reconvene for a closed session to discuss proprietary data.

For the panel members, you have a panel packet in front of you that contains, if you look at the table of contents, an agenda, some panel questions which are similar to the questions which you have had mailed to you prior to this meeting. There are reviewer summaries from the different members of the panel who have made them available and you have a list of the panel participants and panel affiliations.

Also included are enclosures and handouts. If you do not have them, they will be made available prior to that time. There will be summaries of slides or the actual slides themselves that are being presented by the people at

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the Food and Drug Administration, if you wish to make notes on them or refer to them. They will be provided before that discussion.

I would like, at this time, to introduce Dr. Harold Wilkinson, the Chairperson of the panel who will be presiding.

DR. WILKINSON: Thank you, Levering. For those of you who are not familiar with how these panels are constituted, I might just tell you, very briefly, the panel consists of a core group of regular members of the panel who are full voting members. Then, for each individual device that the panel reviews, there are deputized experts in the area who are given voting privileges for that meeting only.

There is also a group of consultants who are asked to participate as experts on the topic, a representative from industry and a representative of the general consuming public.

I would like to now go around the table and have each of the members of the panel introduce themselves. When you introduce yourself, if you would give your name, your place of work, your credentials very briefly, why you are here, kind of, what your area of expertise is. We don't need a bibliography, thank you.

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I am Harold Wilkinson from the University of Massachusetts Medical School in Worcester, Massachusetts, Professor of Neurosurgery at that institution.

DR. CANADY: I am Alexa Canady. I am Associate Professor of Neurosurgery and Vice Chairman of the Department of Neurosurgery at Wayne State University in Detroit, Michigan.

DR. GONZALES: I am Gilbert Gonzales. I am at the Mayo Clinic in Scottsdale, Arizona. I am a neurologist.

DR. HALLETT: My name is Mark Hallett. I am at the National Institutes of Health. I am a neurologist interested in movement disorders and clinical neurophysiology.

DR. GATSONIS: I am Constantine Gatsonis. I direct the Center for Statistical Sciences at Brown University.

DR. SCHMIDT: Edward Schmidt from the National Institutes of Health. My area is brain stimulation--that is, cortical stimulation--for areas of visual prostheses.

MR. SPYKER: My name is Dan Spyker. I am a surrogate for Tom Callahan. I am the Deputy Director for DCRN.

DR. GOORAY: I am David Gooray. I am a cardiologist. I am the consumer rep. I am associated with

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Howard University in Washington, D.C.

MS. MAHER: I am Sally Maher. I am the industry rep. I am the Directory of Regulatory Affairs for Johnson & Johnson Professionals.

DR. GWINN: I am Katrina Gwinn. I am a neurologist with a subspecialty interest in movement disorders at the Mayo Clinic, Scottsdale.

DR. EDMONDSON: I am Edward Edmondson. I am also a neurologist with a subspecialty interest in neurooncology and pain management. I am in private practice in Houston.

DR. NUWER: I am Mark Nuwer. I am full-time faculty at UCLA in neurology and clinical neurophysiology.

DR. KU: I am Andrew Ku. I am assistant professor of radiologic sciences at Allegheny University Health Sciences. I have a special interest in interventional neuroradiology.

DR. AMINOFF: I am Michael Aminoff. I am professor of neurology at the University of California at San Francisco. I direct the Movement Disorders and Parkinson's disease and I direct the Clinical Neurophysiology Laboratories.

DR. WILKINSON: I don't quite know how to address all of this brass over here, Mr. Keely.

Conflict of interest

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DR. KEELY: The following announcement addresses conflict of interest issues associated with this meeting and is made 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 interest reported by the committee participants.

The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employer's financial interests. However, the agency has determined that participation of certain members and consultants, the need for which services outweigh the potential conflict of interest involved is in the best interest of the government.

Limited waivers have been granted for Drs. Michael Aminoff and Katrina Gwinn because they have interests in firms which could potentially be affected by the panel's deliberations. The waivers permit these individuals to participate in the review and the discussion of the PMA before the committee but excludes them from voting.

A waiver has been granted to Dr. Alexa Canady permitting participation in all matters before this panel. Copies of these waivers may be obtained from the agency's Freedom of Information Office, Room 12A-15, of the Parklawn Building.

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We would like to note for the record that the agency took into consideration certain matters regarding Drs. Michael Aminoff, Constantine Gatsonis, Mark Hallett and Andrew Ku. Dr. Aminoff reported a past financial interest in a firm at issue and current interests in matters unrelated to the agenda of today's meeting.

Dr. Gatsonis has reported that his wife has a pending involvement with the firm at issue, however on a matter not related to these deliberations. Since the matter is not related to the specific issues before this panel, the agency has determined that Dr. Gatsonis may participate fully.

Dr. Hallett has reported a speaking engagement at a recent workshop sponsored by the PMA sponsor--however, on the scientific issues and not the subject of the PMA device. The agency, therefore, has determined that Dr. Hallett may participate fully in the committee's deliberations.

Dr. Ku reported an interest in a subsidiary of the PMA sponsor--however, on a matter not related to the specific issues before the panel. Therefore, the agency has determined that Dr. Ku may participate fully in today's deliberations.

In the event that the discussions involve any other products or firms not already on the agenda for which

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the FDA participant has a financial interest, the participants should exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask, in the interest of fairness, that 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.

Old Business

DR. WILKINSON: There was an item of old business from the last panel meeting.

DR. KEELY: The last panel meeting was held in September. It was a matter relating to the approval of a neuroprosthetic device. That panel recommended that the neuroprosthetic device be approved based on certain conditions. Those conditions are being answered currently by the manufacturer and the sponsor of that PMA and have not been completed as yet.

DR. WILKINSON: Thank you. For the members of the panel, we would like you to jot down some tentative dates for the next three meetings. Let Mr. Keely or myself know if there are major conflicts with those dates. The next meeting may need to be a two-day meeting so these are all

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double dates.

June 22 and 27, a Thursday-Friday. October 30 and 31 which, unfortunately, is Halloween. I don't know if that is appropriate or inappropriate. But that date possibly could be moved a week earlier or a week later. The third date, January 29 and 30, 1998, also a Thursday and Friday date.

So if you would let us know if there are any major conflicts that you come across for those dates.

Open Public Hearing

DR. WILKINSON: The first item of business is the open public hearing. According to the Federal Register, people were asked to notify the FDA in advance if they wished to speak.

There has been one such request received. I understand there are people here today who, perhaps, don't read the Federal Register but who have been asked to speak. So we will allow additional input.

Could I just have a show of hands of how many other people there are? Joan Samuelson followed the rules, but how many other people wish to speak. There seem to be three hands. We would ask that you make your comments succinct. These are important comments but we do need to move along.

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So keep your comments worthwhile, please, not rambling, if you could. Each speaker will need to introduce himself or herself, what your affiliation is and, as you just heard, any conflict of interest of any proprietary interest, you need to put on the record before you make your talk.

So, Ms. Samuelson is the first speaker.

MS. SAMUELSON: I will report to my mother that I followed the rules and she will be proud. Her training stuck to some extent.

I have a written statement. What I suggest is I pass it out to you. If I didn't get enough for each side, let me know. I have some extras.

As I said, my name is Joan Samuelson. I am a lawyer from the San Francisco Bay area and president of the Parkinson's network which is located there. I was diagnosed with Parkinson's ten years ago in 1987. I am the founder of the Parkinson's Action Network which is a nationwide advocacy organization intended to provide a voice for the Parkinson's community to try, in every way we can, to hasten the cure of Parkinson's and/or effective therapies as fast as is humanly possible.

DR. WILKINSON: Do you have any proprietary concerns?

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MS. SAMUELSON: None. Perhaps, that is unfortunate. To this audience, I probably don't need to go into detail about the effects of Parkinson's disease, but let me just briefly reiterate them so that it is clear how important new effective therapies are.

Parkinson's is an extremely debilitating disease and it can be from the very outset. Of course, there is medication that can, in some cases, quite miraculously eliminate or largely control the symptoms of stiffness and tremor and slowness of movement which are the three basic cardinal symptoms in addition to which there is the enormous problem of postural instability which, in combination with the rest of those, can become the most debilitating of all in some cases.

I am afflicted with all three symptoms, just for the record. Sinimet, which essentially is the primary drug used to control Parkinson's symptoms, works quite well in my case, or it has up to this point. But I am reaching the point, at ten years post-diagnosis, where it is ceasing to be effective in many instances and you may see signs of that during the course of my remarks.

I will talk a little bit later about why tremor-control therapy could be important in my case as well as specifically in the cases of other people that I know.

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Often, all of those symptoms combine in a person but there are cases in which tremor is the primary overriding, very difficult symptom.

For example, there is a member of the Board of Directors of my organization, our treasurer, John Dodge, for whom tremor is the major symptom. Medication is not working in his case for a combination of reasons, either it doesn't work at all or it causes other debilitating side effects, difficulties with cognition and so on, which he can't afford to have impeding his life and his work.

So, as a consequence, he lives with a terrible tremor. Recently, I got together with him to try to talk about Parkinson's Action Network business. We often try to meet for lunch because it is the best time in our busy day to be able to conduct that business. He has extreme difficulty eating. He is limited to a tiny portion of the menu because he simply cannot use a fork because his tremor is so severe that he can't control the use of it, even trying to pick up something with his hands, which is a grosser movement so it doesn't require as much control. In fact, it is extremely difficult for him to be in public, especially in a crowded situation.

Picking up a glass is impossible. He needs to

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order straws and so on. That is just one example of how his tremor affects his life. At this point, there is, essentially, no alternative therapy for him. He could consider a thalamotomy which is a surgical procedure you probably also are familiar with which involves a lesion of the brain.

He declines to do that. He is fearful in two ways. One is the possible serious side effects of a lesion to the brain. He is not willing to undergo that risk. I, personally, know of people who have suffered serious side effects from a deep-brain lesion which is a risk they decided to undergo because they had no alternative therapy. He has decided not to do that.

The other reason he is concerned about it is that a lesion, of course, is permanent. There are other possible effective therapies that are still in development for Parkinson's such as, for example, cell transplantation which could be rendered inappropriate because of a permanent lesion which could interfere with the effects of the other therapy.

He wants to hold out for those therapies so he doesn't want to have a permanent lesion in his brain. As a result, there is no alternative for him. The deep-brain stimulation, like the Aactiva tremor control, could be a

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possibility for him and he is extremely anxious to have that up and available so that he could try and see if that is appropriate in his case.

Let me just, for a moment, touch on the other impacts of Parkinson's. What I am describing is some of the short-term effects, short-term in the sense of intermittent effects that we suffer from Parkinson's when the medicine is still working.

But, eventually, it stops working and it can become ineffective altogether. In my case, for example, Sinimet, the L-dopa therapy, has been working essentially well throughout the day from the point when it so-called kicks in. At the beginning of the day, I have serious problems of tremor and slowness of movement and stiffness but, eventually, it begins to work.

At ten years post-diagnosis, however, I am discovering that the I have times during the day when it won't work very well at all. It seems to correspond with diet. There is a developing understanding of that which seems to indicate that the metabolism of animal proteins interferes with the delivery of the dopamine precursor to the brain.

As a consequence, I am finding that I have to eliminate all meat, chicken, fish, et cetera, and any dairy

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products from my diet for fear that, at some point during the day, I will become extremely symptomatic. This happens often and so I have to be very careful about that which, obviously, is a very difficult thing to do with the American diet.

The symptom that seems to emerge most prominently when that happens is tremor. I don't know why but that is what I am observing. Given how difficult it is to try and manage that diet problem, it might be that a tremor-control therapy would be something that I could use in combination with medication to even that out in my day.

The reason for that is not simply that these symptoms are a hindrance. It is terribly difficult to conduct my working life with these symptoms. That is why Parkinson's is not only a terrible burden for people who suffer from it in the family. It is also a terrible financial cost to that country.

If I were to have to stop working because all of these symptoms combined to the point where I simply am not able to work, then I am not only paying taxes, I am some form of combination of private disability insurance system and I am drawing more heavily from government-subsidized medical care.

We have begun to assess the costs of Parkinson's on

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the country, and it is many billions of dollars, conservatively estimated. That is another reason, a financial reason, in addition to the enormous human cost, why getting the delivery of effective therapy to the market as soon as it is humanly possible is essential.

Obviously, you are going to hear from many other witnesses who are going to describe with precision the safety and efficacy of this particular therapy and why it is appropriate to proceed with processing it through the rest of the approval system.

Equally obviously, I am not sophisticated enough about the safety and efficacy of this therapy to be able to speak to it. You have plenty of data before you, I'm sure. But what I would just urge you, though, to be aware of is the enormous importance of this to the Parkinson's community.

People are flocking to pallidotomy and thalamotomy. We hear about a thousand-person waiting list, people waiting years to be able to get a pallidotomy or a thalamotomy despite the enormous inherent risks, and risks for future availability of other maybe more effective therapies. It is simply because they are desperate. They don't have any alternative and they are losing their jobs, they are going on public assistance, and they are dropping

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out of their society because they can't go to a restaurant and eat with their friends and their colleagues.

So that is an indication of the demand, I would say. There is an enormous demand for this to be made available to this patient population. So I would simply urge you to have that in mind when you think about how urgently this is needed and how swiftly we would like the FDA to review this particular product.

Thank you.

DR. WILKINSON: Thank you, Ms. Samuelson. The majority of the panel are neurosurgeons and neurologists and they are familiar with Parkinson's, but it is always important to realize the human side of this disease. The fact that this is an important session today is why we are all here.

We hope it is important enough that we can try to insure that what is done is done right, that what is done is done as well as possible. So that is why we are all here, I think.

MS. SAMUELSON: I understand.

DR. WILKINSON: There was a second speaker right behind you, I believe.

MR. SCHAEFER: My name is George Schaefer. I come from Fort Myers, Florida. I have got Parkinson's disease

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and also tremor. I was sent here by Medtronic and no influence on what I say has anything to do with that.

Before I had my operation--I have had this deep-brain stimulation installed in me. Before that, I couldn't eat very well. I would splatter things all over the floor. I couldn't button my shirts, tie my shoes. My writing, I couldn't do at all. It just didn't work. Not that I am a good writer, but it didn't work at all.

At work, I was a salesman for a food-service company. I would go out to meet a customer and I got a bad hand shaking and tremor, and I couldn't sell the product. You can't sell like that. You can't sell while shaking in front of somebody and give them confidence.

After the operation, I was like a new man. I even made a model airplane to see if I could do it, small intricate work. After that, I made three or four candlestick holders. I still have Parkinson's, but I say I have got 50 percent of it beat.

I had this operation about three-and-a-half years ago. I was the first one in the United States to have it. I say if there is anybody that should be a judge, or could be a judge, on whether it is needed or not, I don't know of any other one better than I am.

It is a wonderful miracle.

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Thank you.

DR. WILKINSON: Thank you, Mr. Schaefer. Again, the human side of this disease is so great that we need all to keep that in mind. The tremor, itself, can be a major symptom. Thank you.

There is another speaker behind Mr. Schaefer.

MR. LONG: Hello. My name is Maury Long. I have essential tremor. Medtronic has paid my way here and handled my expenses but they have, in no way, compensated me for these remarks.

Essential tremor began exhibiting itself in me in 1982. I was the district manager of a financial-services company. Part of my job description was putting on seminars in front of groups about managing money. It is quite difficult to get up and write on a board and secure people's confidence when they can't read what you are saying.

It was impossible to meet a person one-on-one and make notes on what I wanted to get across to them because they could not see what I was trying to write. It got so bad that I had to resign from that position.

So I went out to my farm and helped my son farm. I got along pretty good driving a tractor-combine, but as soon as I had to weld something, use a wrench, put a nut on a bolt, use a screwdriver, drive a nail, it was impossible

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because of the tremor.

Further, I got to the point where I had to use two hands on the tablespoon while I was eating. I couldn't carry a try. I would carry a tray and it would spill everything. My writing got atrocious. I had to drink coffee with a straw.

I am an avid golfer. You can imagine. It is kind of difficult to have four puts on every green.

I was fast becoming a hermit because I was too embarrassed to go out and could always depend upon my wife to cut my food, to bring my tray to me. It seemed that stress and pressure made this uncontrollable and even worse.

When the medication I was taking was not effective, my neurologist sent me to Kansas University Medical Center where I was evaluated. In May of 1996, I had my first surgery, a deep-brain implant. If you can imagine, two hours after surgery was over, I was eating peas with a fork.

It solved the tremor in my right hand so well I could read a newspaper and I could read the right-hand side, but the left-hand side of the paper, I couldn't because it was still shaking. So, in November, 1996, I had the second side done. Now I am able to do all the things others take for granted.

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I eat soup for the first time in 14 years. I can drink coffee from a cup. I go out. I can meet in the public and be happy and enjoy life. One good thing about this type of surgery and the implant is you can turn it on and off. It is great. You can go to the golf course, have your device off, get on the putting green and get all the bets made, and then turn it on.

I got control of my writing so much that last Christmas I was able to, and wanted to, write checks to the kids of Christmas. I hoped they would keep them as a souvenir and not cash them, but they did.

Following this miracle surgery, I am now as good as ever. Now I eagerly look forward to the rest of my life. All I can say is thank you.

DR. WILKINSON: Thank you, Mr. Long. Medtronic has obviously picked good spokespersons for their human side of this discussion. It is important to recognize that Parkinson's isn't the only disease for which this device is offering promise.

There was one more speaker, I believe.

MS. LEE: Good morning. My name is Jeanne Lee. I am the administrator of patient programs for both the United Parkinson's Foundation for the past 19 years and, also, for the International Tremor Foundation since its inception in

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1988.

Yes; my hotel and travel expenses were paid Medtronics. They did not suggest what I was to say today nor how I was to say it.

The International Tremor Foundation was formed to meet a very specific need, the need of essential tremor patients to learn about their disorder. One of the things that I learned very early on in the course of my career with the United Parkinson's Foundation is that the more educated a patient is about his or her disorder, the better able they are to cope with it in the long-term especially with the progressive nature of both disorders.

Patients also have other needs that are currently not being met. We provide the educational information. We have respected clinicians in many parts of the world and in this country who can provide the diagnostic and the current treatment options that are available to patients.

We have scientists who are dedicating their careers to finding new advances. But what the patients need is hope today, very desperately, possibly more so in essential tremor than in Parkinson's disease, not because it is any more devastating a disease.

It is hard to compare two illnesses that can create so much havoc in an individual's life, probably more

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so because there is less available for the essential tremor patient today and because the embarrassment quotient in essential tremor is so much greater, I think partially because the disease is not as well-recognized as Parkinson's disease is.

Patients frequently tell me when they call my office or e-mail me or write to me that when they try to explain what they have, people look at them dumbly. They make rude comments about, "Oh; you must be just nervous, or something must be wrong with you."

The embarrassment factor is tremendous. They need something that they can look forward to either now in combination with current therapies or in the future, for themselves, as the disorder progresses or for their children who now have the disorder and will grow up and the disorder will progress, and it will become more disabling for them.

They need these options. As the other individuals talked about, we need to allow these patients to continue to work, to want to go further in their careers without embarrassment, to try for new careers in the younger patients so that they are not restricted by their tremors and what they want to do with their lives, so that they don't become hermits and stay away from restaurants, movies, the enjoyable things in life, either in retirement or while

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they are functioning as they are growing older.

We need this device. We need another option. Patients need it desperately. Their families need it. And we hope that you will give it to them.

Thank you.

DR. WILKINSON: Thank you very much. As a clinician, I would like to thank both Ms. Samuelson and Ms. Lee for the work they are doing and their organizations are doing to support people with these diseases that all of us clinicians encounter in the office. Those folks have lives beyond the medical sphere and it is important to have someone working with that aspects of their lives.

I think that was the last speaker who asked to speak representing the public.

Unless, there are patients with irritable bladder syndromes, let's move right ahead with the panel discussions.

Open Committee Discussion

Premarket Notification: Implantable Deep Brain Stimulator for the Treatment of Tremor due to Parkinson's Disease and Essential Tremor

DR. WILKINSON: The next part of the activities this morning are presentations from the firm. I would ask those who are representing the firm to identify themselves

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and your area of functioning within the firm. I don't have a list of names.

Firm Presentation

Introduction

DR. HARKNESS: Good morning. My name is Donald Harkness. I am an employee of Medtronic and manage the deep-brain stimulation for tremor clinical programs. We are here today to present data and answer your questions about an exciting new option for the treatment of disabling tremor due to essential tremor and Parkinsonian tremor.

[Slide.]

These are the topics that we wish to discuss today regarding deep-brain stimulation for the treatment of tremor.

[Slide.]

The indication that we are asking for is as follows: thalamic stimulation using the Medtronic 3382 DBS lead and the Medtronic ITREL II stimulation system as indicated for the suppression of tremor due to essential tremor or Parkinson's disease; unilateral or bilateral stimulation as indicated for the suppression of tremor.

[Slide.]

Five investigators for this clinical trial are here today to present the data and to help answer questions

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regarding this therapy. They are all neurologists or neurosurgeons specializing in the medical and surgical treatments of movement disorders particularly tremor and Parkinson's disease.

They are Dr. William Koller from the University of Kansas Medical Center, Dr. Warren Olanow from Mt. Sinai Medical Center in New York, Dr. Andres Lozano from the Toronto Hospital in Toronto, Canada.

[Slide.]

Also, Dr. Steven Wilkinson from the Department of Neurosurgery at the University of Kansas Medical Center, and Dr. Jeanne Hubble, as associate professor in the Department of Neurology from the Ohio State University in Columbus, Ohio.

[Slide.]

I want to briefly review the regulatory chronology to date for this particular device and the therapy.

[Slide.]

An IDE submission was done in December of 1992. After reconsulting with our medical advisors and consulting with FDA, we resubmitted the IDE and received approval for it in June of 1993. The first patient was implanted in October of 1993. Medtronic submitted the PMA on April 30 of 1996.

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From April 1996 through August or September of 1996, FDA conducted clinical site audits, a Medtronic facility inspection and did a clinical audit of Medtronic's data for this submission. Obviously, today, we are here before the advisory panel.

[Slide.]

The CE Mark in Europe was granted for this therapy and this indication in December of 1994. The therapy and device are currently commercialized in Europe, Canada and Australia and they are commercialized for the treatment of tremor due to essential tremor and Parkinson's disease.

Since the device has been commercialized outside the U.S., more than 2,000 tremor patients have benefitted from this therapy.

[Slide.]

I want to take a moment to describe the device for which we are asking approval. The system for the treatment of tremor consists of three components that are implanted in the patient. Additionally, the physician programs the implantable pulse generator via a console programmer.

The model 3382 DBS lead is implanted in the ventral intermediate nucleus of the thalamus. The ITREL II implantable pulse generator is implanted in the pectoral region near the clavicle. The extension is literally a

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cable that connects the IPG to the lead.

Again, the physician programs using the programmer and software to program the pulse generator.

[Slide.]

The lead is a quadripolar lead--that is, it has four contacts on the end. This is the end that would be implanted in the ventral intermediate nucleus. Those contacts can be selected by the physician to maximize tremor suppression in the ventral intermediate nucleus and to minimize side effects as necessary.

[Slide.]

The Model 7424 ITREL II implantable pulse generator is shown here with an extension connected to it. Down in the bottom of the photograph, you can see that the extension is connected to the lead.

The implantable pulse generator has been commercially available in the United States since 1989 and our experience indicates that it is highly reliable. The indication for which it has been available is spinal-cord stimulation for the treatment of chronic intractable pain.

Essentially, we are requesting an extension of the indications of this device to cover deep-brain stimulation for the treatment of tremor. Labeling has been incorporated to caution about charge-density issues for certain

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parameters and to minimize exposure to the potential of transient, unbalanced stimulus pulses. The extension has also been marketed in the United States for quite some time.

The consult programmer is used by the physician to prescribe the appropriate dose of stimulation and to treat tremor and to minimize the side effects.

The physician can program amplitude, pulse width and frequency. They can, as I mentioned before, select the appropriate contacts on the end of the lead again to maximally deliver the stimulation. Compliance data can also be determined from the IPG using the console programmer as can measurement functions for the pulse generator.

The patient has control over the IPG, or the implantable pulse generator, using a hand-held magnet. They can turn the stimulation off with the magnet and turn the stimulation on with the magnet.

[Slide.]

This illustration shows the device implanted bilaterally. The pulse generator is implanted near the clavicle. These are the implantable pulse generators. The collar bone is right there. It is connected to the extension. Again, the extension runs up, is implanted subcutaneously and connects to the lead.

The lead is implanted in the ventral intermediate

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nucleus using standard neuroimaging and functional stereotactic neurosurgical techniques. Again, this represents the tip of the lead being in the ventral intermediate nucleus of the thalamus.

The lead is held in position using a burr-hole ring and cap to anchor the lead. It is a device that is placed in the burr hole that the neurosurgeon forms at the time of device implant.

[Slide.]

We provided information to FDA from five different clinical studies to support our PMA submission and to support the indication for which we are requesting your approval. The first is the U.S. tremor IDE study. It is a multicenter, Medtronic-sponsored safety and efficacy study with a randomized double-blind assessment at the three-month follow up.

The European tremor Study was a multicenter Medtronic-sponsored safety and efficacy trial conducted throughout Europe. The European long-term study was a multicenter Medtronic-sponsored efficacy study with a randomized, double-blind assessment, in patients who had completed the 12-month follow up from the European tremor study.

The European basic study and the DBS for pain IDE

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study both provide safety data to support the indications.

[Slide.]

We want to turn to the unmet medical need and the clinical results for this particular therapy. To do that, Dr. William Koller, Professor and Chair from the Department of Neurology at the University of Kansas Medical Center will discuss the unmet medical need and discuss the clinical results for this therapy.

Dr. Koller.

DR. WILKINSON: For the panel members, if you have questions of the speakers, now would be a good time to ask, at the end of each speaker's presentation. Obviously, this is not a time to get involved in any extensive discussion. If you have questions about the presentation, itself--any questions now?

Unmet Medical Needs and Clinical Results

DR. KOLLER: My name is Bill Koller. I am a neurologist from the University of Kansas. I am a consultant to Medtronic. It is my distinct pleasure to be here at this very important deliberation.

I am going to say some brief comments about tremor disorders, show a video of several patients so we get a feel for what these patients look like and what the therapy can do, and then review with you the results from both the

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United States and the European tremor study, and then conclude.

[Slide.]

Tremor, as you know, is an abnormal involuntary movement. It is defined as shown here. It is a rhythmic oscillary movement that is caused by contraction of antagonistic muscles. The rhythmic oscillation allows tremor to be easily distinguished from other abnormal movement disorders.

[Slide.]

Just to say a few words about essential tremor. It is probably the most common of all the movement disorders. We don't know the exact prevalence of this disease. It is, by some studies, even five to ten times more common than Parkinson's disease. We know that there are probably at least several million that have symptomatic tremor that needs treatment.

Unfortunately, we have a very poor idea of the etiology and the pathophysiology of this disease. In fact, the drugs that we have to treat essential tremor, serendipity found these drugs for us. There is really no concerned scientific approach to drugs because we have such a poor understanding of pathophysiological mechanisms.

We know, however, that the disease runs in

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families. Probably most cases of essential tremor have at least some hereditary basis. The disease is characterized by tremor. In that sense, it is a monosymptomatic disease of tremor only. Tremor can affect a variety of body parts, the hands being most common, but it can affect head, trunk, legs, voice, other body parts.

There are only two drugs that have been shown to be effective, in essential tremor. These are betaadenergic blocking drugs like propranolol and the anticonvulsant, primidone. It is also effective in some patients.

Essential tremor, in the old textbooks, has sometimes been referred to benign essential tremor. It is certainly benign in the sense that it doesn't shorten life expectancy. However, as has been pointed out by Mr. Long very elegantly, it certainly can disturb one's life and serious affect the quality of one's existence.

[Slide.]

This group and the panel are certainly well knowledged in Parkinson's disease, just to say a couple of general comments. It is a very common disorder. We probably don't know the exact prevalence of this disease, either half a million, a million, a million and a half. Sometimes, when we are applying for grants from the government, we say there are 2 or 3 million people affected

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with this disease.

It is certainly a very common disease. In this disorder--I can't say I could say anything more eloquent than Joan Samuelson describing this disease. It has many symptoms, slowness, stiffness, poor posture, gait problems. Certainly, tremor is a major symptom.

We do have treatment for the disease. Sinemet is the best drug we have but it fails us, as Joan pointed out, long-term. Its effectiveness is lost. Patients begin fluctuating from the med working. The medicine is not working and, for these patients, we need additional therapies.

[Slide.]

Just to say some general comments on Parkinson tremor. The majority of patients with Parkinson's disease certainly suffer with tremor. The tremor is usually in the rest position. It can also be in the postural position. If you look at the major symptoms of Parkinson's disease, slowness and stiffness, they clearly respond better to levo-dopa therapy than does tremor.

Tremor, in some patients, is drug resistant, at least drug-resistant in the fact that we would have to give some much medicine and suffer toxicity before we could reduce the tremor. Certainly, the tremor causes problems,

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both the rest and the postural tremor. Embarrassment is a major issue, as we have heard already. The postural tremor can interfere with a variety of functions.

So Parkinson tremor is certainly an issue which we haven't quite addressed properly with our current drugs.

[Slide.]

We have many patients with Parkinson's disease whose tremor is a major problem and, as Joan Samuelson pointed out, some patients have what we call tremor predominant Parkinson's disease. Tremor is really the main problem more than the other aspects of the disease.

For these patients, often the drugs don't work. Similarly, for essential tremor, the two drugs we have, the two classes of drug, often fail the patient. A publication of a multicenter study that we did several years ago that was published in the Annals of Neurology found that only 40 percent of patients who presented with essential tremor were adequately treated with either propranolol, primidone or both drugs together.

The question is, what do we do with these other patients that present to us. How do we treat them?

One option in the past has been thalamotomy, a destructive lesion of the thalamus. Problems with this exist in that it is a destructive lesion and also most

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neurologists did not advocate bilateral thalamotomy because of the high incidence of speech abnormalities.

Many patients just didn't want a destructive lesion of the brain. When you told them this was an option, they declined this form of therapy. We now have another option that we can offer these patients and that is deep-brain stimulation. This procedure, at least in my mind, has several advantages.

One, it is reversible. We haven't destroyed part of the brain. Two, we can, as Dr. Harkness pointed out, change the stimulus parameters much like we dose the drug. We can increase the stimulus to get better efficacy, control of tremor. We can decrease the stimulus to decrease adverse reactions.

Thirdly, the procedure can be done bilaterally without the same fears we have with bilateral thalamotomy.

At this point, I would like to show the video.

[Video shown for the benefit of the panel.]

The video shows two patients, one with Parkinson's disease and one with tremor. I know most of the panel is very familiar with these disorders but, for those of you who aren't, this will at least give you a look at what these patients are like and we can get a preview of the marked efficacy of this procedure.

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This is a rest tremor. This shows the postural component of the tremor. This is the so-called action component or kinetic component. We look at tremor in three positions; rest, posture, during movement, kinetic or action.

This shows a patient with Parkinson's disease, stim off. This is the patient with a unilateral implant, right side of the body for control of left-sided tremor. Stim on with, I want to say, immediate reduction in the tremor.

Again, stimulation turned off. Marked tremor returns. One can also notice the severity of these tremors. We will talk about clinical rating scales. This would be a marked severe tremor. Again, with stim on and, sometimes, there is almost total abolition of tremor.

This shows a patient with essential tremor with a deep-brain-stimulation implant. You can see the postural component. Usually, in essential tremor, there is not much risk component but there is a postural and kinetic component or action component and it is shown here.

In Parkinson's disease, there is usually a rest and postural component without much action or kinetic component. This is stimulation off. A lot of patients with severe essential tremor really can't write at all or can't

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drink at all. They just can't do it.

Often, the deep-brain stimulation, as we have heard already today, can restore these activities. This is our pouring liquid from one cup to another. Again, for the severe essential tremor patient, this is very difficult to do, even just to get the hand and pour. In the clinic, I always end up back-pedaling when I see them approach this test.

Now, the stimulation is turned on. The patient can perform this task. As a physician taking care of some of these patients, the most gratifying thing has been for patients to say how their quality of life has been increased and how they have even used terms like being reborn, that they can now do these very simple activities that we take for granted.

[Slide.]

I would now like to go on and review with you the results from both the U.S. and the European tremor study. I will first talk about study methods and design. The University of Kansas had many patients in the U.S. tremor study. The study was designed to prospectively enter patients into the trial.

We attempted to randomize and blind the study as best we could for our surgical procedure. We decided that,

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at three months, we would have a blinded evaluation so the patient wouldn't know if the device was turned on or off, and the evaluating physician wouldn't know if the device was turned on or off.

Then they would be scored that was as an attempt to at least blind the evaluations. Patients were seen at one month, three months and then every three months. In the U.S. study, only the blinded evaluation occurred at three months and the rest of the evaluations were open follow up.

For the Parkinson patients, when they were evaluated, they were off drugs at the time of the blinded evaluation. For essential-tremor patients, they were off drug for the whole study. So, one month before the trial, any medicines were stopped and they remained off medicines, certainly, through the three-month blinded evaluation.

For the Parkinson patients, of course, they need their medicine for their other symptoms and they were kept constant for three months. The patient was off medicine from the evening before at the time of the three-month blinded evaluation.

[Slide.]

Patient selection; for Parkinson's disease, we chose patients who had severe tremor, weren't responding to medication, that caused significant disability. So these

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would be patients with, basically, tremor-predominant Parkinson's disease so other symptoms weren't as disabling.

Essential-tremor patients, also, were patients with severe tremor that was disabling causing functional disability and not responding to medication. Patients, in general, had about a ten-month follow up.

[Slide.]

Just to say a couple of comments on the primary outcome measure variable. The tremor for Parkinson's disease, we use the Unified Parkinson's Disease Rating Scale. This is a clinical scale that has been developed for evaluation of Parkinson's disease. For all drug trials, now, this is the scale we use to assess efficacy. It is the clinical rating scale used in Parkinson's disease.

We use the tremor component for that. For essential tremor, for determining primary outcome variable, we use the tremor rating scale. It is, again, a very widely used scale.

[Slide.]

I would like to briefly show you these scales because this is the primary outcome variable. Tremor is measured both at rest during posture and during movement and the scale is shown here, from 0 to 4, 0 being absent. Then we go from slight to moderate to marked to severe.

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[Slide.]

Similarly, the Tremor Rating Scale, which we use for essential tremor, uses a similar scale. We look at tremor in the three positions, various body parts, and then we use a scale from 0 to 4, 0 being absent 4 being very severe.

These are scales that the clinicians involved in these trials use quite frequently and this is just a standard way we evaluate tremor in the clinic.

[Slide.]

Now, I would like to show you some of the results and first talk about Parkinson's disease and then later talk about essential tremor.

[Slide.]

These are the demographics for the U.S. tremor study for Parkinson's. There were 39 patients, mainly males. The average age was 65 years. Patients had about a ten-year disease duration. Symptoms were bilateral in the majority of patients. When surgery was done, most patients chose the right side to be done, mainly because, for most patients, they were right-hand dominant.

Both the physician and the surgeon and the patient decided on what tremor would be the target tremor, what side and whether the rest, postural or action tremor would be the

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target. For most patients with Parkinson's disease, the rest tremor was the target symptom.

[Slide.]

This slide shows some of the data. This is data from the three-month blinded evaluation for the Parkinson patients and the clinical rating scale. You can see, at baseline, patients have around a 3 which is a very severe tremor with stim off, a mild reduction, but nothing much. But with stimulation turned on, there is a marked reduction going from about a 3 on the scale to a 1. That is a change of, obviously, statistically significant but it is really a robust change.

It is going from a very severe marked tremor to, in fact, a very mild tremor. So it is certainly a change of a really dramatic magnitude. I think, just looking at the lines, one may not appreciate that. You can probably see, at this point, the whole cohort, at least in the U.S. study, of both the Parkinson patients and the essential-tremor patients, about half the patients had total tremor abolition.

It was gone, a 0, which was really quite dramatic. I think we saw in the video some of those where the tremor is basically not there anymore. That is simply something we can't achieve with drugs.

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In the studies we have done in the past, and I have certainly been involved in a lot of these studies of propranolol and primidone, we never saw efficacy of this magnitude.

[Slide.]

To look at the long-term data, this is one-year data, open label. Certainly, I think it is important that the procedure not only have three-month efficacy but has efficacy longer than that. When we submitted this paper to Annals of Neurology with the three-month data, they rightly asked for one-year data which is shown here. We provided that in the paper and that paper is now accepted and in press in Annals of Neurology.

It shows that with stim off, there is really no change from baseline for the Parkinson tremor but the efficacy over the year period remains with really no change in efficacy for the one year. So, clearly, there is no loss of efficacy during the one-year period.

Professor Benabid, in Grenoble, France, has data going out to seven or eight years which he has recently published in the Journal of Neurosurgery last year showing that efficacy can be maintained much longer than just the one-year period. This is what our data shows.

[Slide.]

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We also looked at a variety of activities of daily living. These are part of the UPDRS scale. This one is for tremor and we asked the patient, how does tremor affect your life, does it disrupt your life at all. The scales are from 0, it doesn't affect me at all, to, it is a really big problem most of the time.

[Slide.]

Here is the data. I will show it on the next slide a little more blown up. There is a marked decrease in the patients' disability related to tremor on this particular question of the UPDRS. This is statistically significant and it holds from 1 through 12 months without much change. So the patients report that the reduction of the tremor with deep-brain stimulation has resulted in increased ability for them to do things.

[Slide.]

We also asked on the UPDRS other activities of daily living. These are shown here; handwriting, drinking, cutting food, et cetera. With deep-brain stimulation, these weren't changed. They were statistically not significant.

I would make a couple of comments here. One is that the patients we chose to be included in this form of therapy were patients who had more tremor and less bradykinesia. Bradykinesia is probably more related the

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these types of disability as measured by the UPDRS.

This form of therapy, as you realize, is effective for tremor but not effective for other Parkinson's symptoms. So we wouldn't expect, say, disability related to bradykinesia to be reduced by deep-brain stimulation, only that related to tremor.

[Slide.]

We also looked at global disability assessment. This is done both by the physician and by the patient. These results are shown here for the one-year period, again, really, a marked reduction with DBS stimulation turned on. These are done in quartiles so we asked the patient to estimate the disability in quartiles.

This is statistically significant in dropping of about one quartile. So these are actually a little more than one quartile. Their improvement just on their global disability is certainly in the range of 25 percent.

[Slide.]

Now I would like to present some data from the European study. The first graph shows blinded data. In the European study, it is different in this instance. The patients, particularly in those slides I am going to show you, they were taking their anti-Parkinson drugs at the time of evaluation.

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So we actually get to look at it both ways, the U.S. studies without the time evaluation, without Parkinson drugs being taken, and in the European study when the drugs were on board.

[Slide.]

This is blinded data. These are patients that were evaluated at around two years after therapy in a blinded fashion using the same protocol we used in the United States, a study at the three-month blinded evaluation. You can see really marked change once again. They even dropped from around 3 to less than 1, so it is really an incredible reduction in their tremor shown at the two-year period.

[Slide.]

I would like to show some more of the European data in the open label, long-term. This is for the rest component of Parkinson's disease. Again, this is meds on, going up to one year. There is, again, really a dramatic reduction in tremor and, over the 12-month period, there is not loss of efficacy.

The European study also looked at tremor in patients who had bilateral implantation. This is bilateral stimulation on, rest tremor, meds on, looking at long-term efficacy. Once again, with stim off, not much change from

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baseline, marked reduction with stimulation on and this reduction in tremor in maintained through 12 months.

[Slide.]

In the European study, they also looked at the effect of--this is bilateral stimulation on activity of daily living related to tremor, the same question that we asked in the U.S. study. The results are quite similar, in fact, even a little more robust here. There is a marked reduction of disability related to tremor from baseline and it is seen at each evaluation and there is no change at each evaluation.

[Slide.]

The European study also looked at the Schwab and England activities of daily living. It is part of the UPDRS, a very common global measure of disability. For the Schwab and England, the lowest scores are worse, so at 100 you are not disabled at all and at 0 you would be totally disabled.

It is around 60 at baseline. It improves with deep-brain stimulation. This is consistent over time reaching almost 80 percent. So a 20 percent increase in disability would really be quite dramatic. These patients were obviously doing better with the DBS.

[Slide.]

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Now I would like to talk about the results from the essential-tremor study, talk both about the U.S. study and the European study of essential tremor.

[Slide.]

This study shows the demographics. 45 patients were enrolled. The mean age was 67. Once again, there is a male predominance. Patients had the disease for some 30 years, and that is quite common. The disease may be not much of a problem initially. As time goes on, there is more and more disability.

The right side, again, was the side most often chosen. The kinetic tremor was the target tremor in the majority of cases and the overall mean follow up of these patients is about ten months.

[Slide.]

This study shows that the three-month blinded evaluation data from the U.S. study of unilateral stimulation for the treatment of essential tremor. Baseline; we have around a 3 severity. It doesn't change much with stim off. Stim on, there is really a marked reduction dropping two points.

Of course, this is statistically significant. But half the patients I mentioned before, their tremor was really gone. It is really quite remarkable. I think for

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essential tremor, this degree of change, say, dropping from a 3 to a 1, is like pushing the disease back 20 years to when it was just beginning and mild and not that big a problem.

[Slide.]

Of course, it is important that the procedure have long-term efficacy. This is from the U.S. trial, one-year data, showing, again, marked reduction. This is maintained through the 12-month follow up without loss of efficacy and not much change with the stimulation turned off.

[Slide.]

We also, in the trial, looked at a variety of activities of daily living for the essential-tremor patients. I would like to show the next four slides just showing these data.

This is baseline. These are scaled 0 to 4, 4 being the worst. This is just for drawing, for data from one through the 12 months, marked reduction, statistically significant.

[Slide.]

The next slide shows similar data for writing. Again, the similar thing is seen; marked reduction in disability, and improvement. As you heard from the patient, these are the things that they are really interested in.

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This is what improves the quality of their life and allows them to go on and live life in a more normal manner with a higher quality.

[Slide.]

Similar data from drinking liquids, marked reduction. It is sustained at 12 months and is, of course, statistically significant.

[Slide.]

Similarly for pouring. Patients have a marked reduction in this disability and remains constant over 12 months.

[Slide.]

This is the global disability where we asked patients and physicians to make some comment on global disability. Like the other measures, it is markedly reduced compared to baseline and this marked reduction is sustained throughout the 12-month interval.

[Slide.]

I would like next to talk about the European study. This is a European study. It looks at the blinded evaluation, at patients out 20 months. As can be shown, similar to the other data, there is a marked reduction with stimulation turned on dropping from about a 3 to around a 1 on the scale. Of course, this is statistically significant.

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[Slide.]

I would like to show just some other data from the European trial. This is unilateral stimulation for patients with postural tremor. Again, really, a gigantic and dramatic reduction of their tremors even below the 1 level. That is sustained even out to 12 months.

Looking at the kinetic component of the tremor, that data is again quite similar. This is getting redundant; marked reduction of tremor stays constant throughout the 12 months.

[Slide.]

I would also like to show you some data from the European study with bilateral stimulation. This is for the postural tremor, for both the right and left hand. As you suspect, if it works on one side of the body, it should work on the other side of the body. There has been marked reduction, this time of the postural component, and that is sustained over 12 months.

[Slide.]

If you look at the data for action tremor, or kinetic tremor, it is quite similar; a marked reduction of tremor to the mild level and it is sustained throughout the trial. We also looked at a variety of activities of daily living. This is quite similar to the U.S. data. I can go

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through these quickly. Drawing; marked reduction of disability. Patients can do it much better.

[Slide.]

Similarly, if you look at the patients for writing, now they can do it much better. They have dropped from a marked to a mild disability and that is sustained over time.

[Slide.]

Similarly, for drinking liquids, bringing liquids to the mouth; a marked reduction. Certainly, the disability is markedly reduced in these patients.

[Slide.]

This is their global disability, again marked reduction and it is sustained over time.

[Slide.]

The last part of the data I would like to present is the safety data or adverse reactions. I would like to divide these into the three general categories; adverse reactions related to the procedure, itself; adverse reactions related to stimulation and, lastly, talk about the implanted device as a source of potential complications.

[Slide.]

This slide lists so-called procedure-related complications. Of course, the one that is one top and the

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one that we worry about most is intracerebral hemorrhage, around 3 percent. At least in the U.S. trial, the majority of these--all our patients who had hemorrhages returned to function back to normal.

Other complications are listed here, a variety of complications. Most of them are transient and went away. Seizures; one of our patients had several seizures post op. They haven't returned. She is now off anticonvulsants a year later.

For the most part, these complications were transient and patients improved.

[Slide.]

This slide shows the complications related to stimulation and is shown both for the U.S. site and the European site. By far the most common complication that was reported--and this was reported in open-ended fashion; the patients could just tell us if anything was changed--was paresthesias. The majority of patients in the U.S. trials said that when the stimulation is turned on, they experience a transient paresthesia, numbness in the target hand, that would last 3 to 4 seconds.

That was really not much of a problem. In fact, all the stimulation-related complications are mild and easily adjustable. Dysarthria was probably the next most

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common and also the patients--if it was a problem, we could reduce the stimulation and that would no longer be a problem or, if there was some loss of efficacy when we reduced the stimulation, many patients would say, "Well, I can put up with that side effect because I want to have a greater degree of tremor control."

[Slide.]

Lastly, the complications related to device were infrequent, usually less than 2 percent. The ones that did occur were erosion of the lead, infection which could be treated. And then there were some failures, very infrequently, of the impulse generator. But, in general, the adverse reactions were mild, all of them, and they could be treated appropriately.

[Slide.]

I would like to end just by making a general statement. I believe that deep-brain stimulation is clearly a safe and effective mode of therapy. For many of our patients, we really have nothing else to offer them so to have this form of therapy to offer patients opens up a whole new avenue of treatment.

I believe the studies have been well done, prospective, a large number, using the appropriate measures. I think this procedure will find, hopefully, widespread use

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and help many patients with both Parkinson's disease and essential tremor.

Thank you for your attention.

DR. WILKINSON: Could you stay there for just a minute, Dr. Koller.

I had questions, I know, for Dr. Koller. Are there any others from the panel?

DR. CANADY: I was struck, at least in the slide you mentioned relative to Parkinsonism, the relatively non-significant effect, statistically at least on handwriting and other facts, as compared to essential tremor where there was such as statistical difference.

DR. KOLLER: I think that is easy to explain. In essential tremor, the only symptom is tremor and we get, obviously, a really great effect on the tremor. That results in those patients being able to do all their activities now because all their activities were disturbed by tremor.

In Parkinson's disease, their disability relates not only to tremor but other Parkinson symptoms, bradykinesia, rigidity, et cetera. And the deep-brain stimulation, while effectively treating tremor and the disability particularly to tremor, does not treat bradykinesia, rigidity and those resultant disabilities.

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DR. GONZALES: Dr. Koller, I know what you mean with your first statement, but the statement that you made, "We haven't destroyed part of the brain," is not correct; that is to say, the implantation of the lead, in fact, does go through the brain and obviously the complications are associated, oftentimes, with that fact.

DR. KOLLER: Maybe I could just clarify that because I think it is an important point. Certainly, when the lead is implanted, there can be a problem or can be some destruction. I certainly wouldn't deny that and maybe I misspoke in that regard.

But there is some data, both published and unpublished, that have looked at people who have died with the lead in place. The lesion of the electrode is incredibly small, maybe the width of the electrode. The only difference I was making is it is not certainly the same volume of tissue destruction we do with thalamotomy.

But thank you for correcting me. Maybe I wasn't clear enough.

DR. GONZALES: A question about your selection. Since you have 31 males and 8 females in one study, and similar type numbers, why the sex discrepancy since the gender issue is not that big?

DR. KOLLER: In essential tremor, it is an

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autosomal dominance, so there shouldn't be a gender difference. In Parkinson's disease, there is probably a slight male predominance but not enough, as you point out, to account for this.

In all our drug trials, we had mainly males for Parkinson's disease as well so I don't know, really, why that is. We didn't try to go by gender. It just turned out the way it does with many drug trials, we end up with more males.

DR. HALLETT: If you could say some more about lead dislodgement and migration. There were problems that you said that you had seen. What sorts of problems are they, actually, and what do they lead to?

DR. KOLLER: Maybe it is more appropriate to have one of the neurosurgeons answer that. I could give my answer but maybe one of the neurosurgeons wants to answer that, or maybe you want to have that question answered later.

The one lead dislodgement in the one study was actually--I can tell you because it happened at our site--at the end of the surgical procedure, the resident bumped into the apparatus and it got dislodged. I think I see the resident working in the cafeteria now. He seems to be happy down there.

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DR. HALLETT: What did that lead to or--

DR. KOLLER: Actually, the lead had to be replaced.

DR. HALLETT: Here comes your neurosurgeon.

DR. S. WILKINSON: I am Steven Wilkinson. I am a neurosurgeon and I am a consultant for Medtronics. When implanting the lead, the lead is placed into the brain to the target and then the stylet is removed from it so that it becomes flexible. Then it is placed into the burr-hole ring and cap.

So the lead has to be held at the site of the burr hole while the stylet is removed. So then you can see it in the burr-hole ring and in the cap. And so that is one time when you can have dislodgement or migration of the lead, is not securing the lead correctly at the burr-hole site.

DR. HALLETT: Did that lead to any sort of clinical problem? It was sort of listed as one of the problems, so I just want to understand what it actually means to have that happen.

DR. S. WILKINSON: In some instances, it lead to having to replace the lead a second time.

DR. HALLETT: But there wasn't any clinically adverse effect that happened to the patient at that moment.

DR. S. WILKINSON: Deleterious effect from a

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neurologic standpoint?

DR. HALLETT: Yes.

DR. S. WILKINSON: No.

DR. KOLLER: There were no neurological sequelae.

DR. HALLETT: The second question I have perhaps you could answer best as well. When you had infection, which, apparently, happened rarely but did happen, how was that managed? Did the lead have to be taken out at that time or what was the--how did it present and how did you manage it?

DR. S. WILKINSON: The only infection that we had had was at the site of the IPG. That was treated by moving that to a different site and treating that area locally. We have not had any infections that involved the DBS lead.

DR. HALLETT: Has there been any at the lead?

DR. HARKNESS: No, Dr. Hallett; there haven't been any actually involving the lead. All the infections involved other components of the device.

DR. WILKINSON: Maybe you should say there have been no infections yet, being realists.

DR. HARKNESS: That is a good point.

DR. WILKINSON: And I might say, at this point, that Dr. Wilkinson and I both share the last name and the same profession, but we are not related, to my knowledge.

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DR. GATSONIS: Actually I have two questions on the selection of the population, the patient population, and the other one is about the analysis.

One question, just to follow up on the issue about the gender imbalance, I noticed that, too. I wonder if you could comment on whether it is important about the generalizability of the findings.

DR. KOLLER: I can certainly do that. There were certainly females in the study and they responded as well. We actually looked at the response of the females and the males and they were similar. Plus, I don't think there is any biological reason for either of these diseases to think that there would be some gender-specific reasons why they would be different. So I think it is generalizable.

DR. GATSONIS: The other question about the description of the patient population. How reliable is the assessment of the tremor? In other words, how reproducible is it for the same assessor and across assessors?

DR. KOLLER: That has been studied for the UPDRS and it is pretty reproducible. There are certainly some minor differences and I think it is important that the same evaluator does the same patient because there is some intervariability in assessments. But the studies that have been done, it is pretty close.

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I think the changes we have seen in this study make it easier because you have such a magnitude that it is quite easy to see the efficacy. But, if there was a very small, change, there may be difficulty in sensitivity between some drug trials.

DR. WILKINSON: Along that line, could you comment about the other scales, the ADL scale and the disability scale, since the European versus the American study in Parkinson's patients seem to show a significant discrepancy.

DR. KOLLER: I think there is a problem and maybe some of the other people may want to speak to this as well. I think the disability scales and the quality-of-life scales are much more problematic. We really don't have, for Parkinson's disease, a good disease-specific quality-of-life scale.

A lot of these scales are how it is presented to the patient. Those scales are more difficult. But, fortunately, for this study, a lot of the changes were of, really, a tremendous magnitude as we saw on the video. They went from unable to pour liquids to be able to do it. I think, if we are looking at those magnitudes of change, those scales are probably useful.

DR. CANADY: Has there been any neurophysiologic monitoring rather than just clinical assessment?

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DR. KOLLER: One way of assessing tremor is through tremorgrams. This has been done for some drug trials. We have gotten away from doing that because it is just not as reliable. Tremor does change from second to second. Tremorgram just doesn't seem to be the best way of doing it.

People do like objective measures. Most of our studies of tremor now, we don't do tremorgraphic recordings.

DR. GATSONIS: In terms of the long-term study, the long-term efficacy study, what was the exact time frame? At some point, I read something about 12 months. You mentioned, I think, 24 months. What is the exact time frame?

DR. KOLLER: In the U.S. study, we did 12 months and that is the data that we have presented. In the European study, they went back and randomized and did a blind evaluation for both Parkinson essential tremor--I think one was 24 months and one was 20 months, if I remember correctly.

DR. WILKINSON: Since both of these diseases progress, is 12 months an adequate time period? I am asking Dr. Koller's professional opinion at this point.

DR. KOLLER: Actually, I think there are two answers. One, for these people, I think if you gave them

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one--if you only had one year of efficacy and that was it, I think mostly people would say they want it and they are very happy with the one year of efficacy.

DR. WILKINSON: I think that should be listed by the manufacturer as part of its marketing.

DR. KOLLER: But if you look at the data--we have now, just anecdotally, patients out over two years and there doesn't appear to be any loss of efficacy. And there is published data from Benabid, et al, in the Journal of Neurosurgery, 1996. They have efficacy out to seven or eight years.

DR. HARKNESS: Dr. Gatsonis, I wanted to address the issue you raised regarding the time frame. The patients that were in the cohort, in the randomized, double-blind, trial had finished the 12-month follow up for the European trial so they were done after the European trial had been completed or after they had been completed in the European trial.

Their range of follow up on those patients was generally from about 12 months out to about 33 months.

DR. GATSONIS: Why did you select Sweden for the study of the long-term efficacy. The companion question to that is were there intercenter differences or intercountry differences in both the European study and in the U.S.

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study?

DR. HARKNESS: First, the reason that we chose Sweden was that, number one, there were four centers there that had all done a relatively equal number of patients. We were also able to secure the services of a movement-disorders neurologist who could assess all of those patients. He was willing to travel to each of the centers and see the patients.

So it was partially a matter of ease as well as just being able to have those patients where we needed them.

I'm sorry, would you repeat your other question.

DR. GATSONIS: Were there differences in the efficacy observed across centers, for instance?

DR. HARKNESS: In Europe, there were not differences among centers. When we compared centers and their results, there were not. In the United States, we also did a similar analysis where we took Dr. Koller's center and the center in Toronto and then pooled all other centers and, basically, particularly, did an intercenter variability analysis. There was not any difference between centers.

DR. GATSONIS: One last question. How did you handle the dropout on these studies? I noticed in several of the longitudinal data that were presented there was some

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degree of dropout. What did you do about that--in the sense that dropout can do various kinds of biases. The bad patients can drop out and then the curves may look just fine.

DR. S. WILKINSON: I think that is an important point to clarify. They really weren't dropouts. They were patients who hadn't reached the 12-month evaluation. So I think the mean of the follow up was about ten months but not all the patients had reached 12 months. So they really weren't dropouts. They just hadn't gotten to the 12-month assessment yet.

DR. GATSONIS: So you did not have any dropouts in the study? In other words, you did not have patients that were just not evaluated after--

DR. HARKNESS: In the U.S. study, no; there were not dropouts. Again, the difference in n's that you are seeing there is the fact that they have not reached the 12-month follow up. In the European study, there were dropouts. To control for that, we didn't really do anything special.

DR. GATSONIS: Thank you.

DR. SCHMIDT: In terms of your leads, you are using a quadripolar lead. I assume you are only stimulating from one side on the lead; is that correct?

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DR. HARKNESS: One site of the lead is generally negative and then another site on the lead is positive. You can also set the case as positive. You can also set more than one electrode as negative or more than one electrode as positive, but, generally, that is not done.

DR. SCHMIDT: Over the long-term follow up, then, were the selections of the leads changed or were you using the same set of leads that were used to set up the initial parameters?

DR. HUBBLE: My name is Jean Hubble. I am a neurologist and today I am serving as a consultant to Medtronics. I specialize in Parkinson's disease and other movement disorders.

In terms of the conduct of the clinical trial in the United States, yes, the parameter settings include electrode selections that were periodically changed during the course of the study. That was one, in each instance, to either achieve optimal tremor control or to minimize or even totally alleviate any side effects.

Almost all of those parameter-setting changes, those readjustments, were made during the initial several weeks in each subject's case. We believe those changes are just kind of a shifting target, if you will, and are because of changes that occur in the brain post-operatively, or

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intraoperatively; that is, unquestionably, there must be some swelling, some edema, attendant to the insertion of the device intraoperatively.

So, usually, after three months, little or no additional parameter readjustments were made.

DR. SCHMIDT: So it is the long-term effect, after the initial parameters and sites were selected, how stable was the system, because you could change the site you were using or the way you are stimulating and--

DR. HUBBLE: Absolutely.

DR. SCHMIDT: You could change where you are stimulating in the brain.

DR. HUBBLE: In fact, I think, perhaps, you have data on the actual parameter settings. I think you see, after about three months, all the parameter settings including voltage frequency, electrode setting, et cetera, tend to stabilize at that point. Most adjustments were made in all of the parameter settings in those first few months.

DR. SCHMIDT: I don't think there was anything given on the actual stimulation, electrode, selection.

DR. HUBBLE: I'm sorry; there probably is not--

DR. SCHMIDT: I wasn't even sure what was done on the--how you were stimulating?

DR. HUBBLE: But we could change all those

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variables, electrode selection, frequency and actual intensity and pulse width.

DR. AMINOFF: I wanted to follow up on some of Dr. Hallett's comments, if I might, for Dr. Koller, really. In the situation where there was a lead displacement, first of all, did this require reoperation and what was actually done and where there instances--I can't remember, now, from your slide--where you couldn't actually place the electrode at all? There was, if I remember correctly. Why was that?

DR. KOLLER: In the cohort that we put in the Annals of Neurology paper there were 59 subjects. Of three of those, we couldn't find any operating room, the right targets to suppress tremor. So those patients weren't implanted. That cohort I am familiar with just having written the paper.

Maybe Dr. Wilkinson can answer the question that is more neurosurgical.

DR. S. WILKINSON: For the patients that had lead dislodgement, yes, they did require another operation, or another positioning of the electrode.

DR. AMINOFF: And that was successful and there was no further problem.

DR. S. WILKINSON: In most instances, yes.

DR. WILKINSON: And this included late

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dislodgements?

DR. S. WILKINSON: For dislodgements, those were ones that were considered from actually securing the electrode that seemed to be at the time. So we would get tremor control in the operating room but, post-operatively, the patient wouldn't--and it was felt that the lead had been moved in securing it to the cap.

DR. WILKINSON: So were there no late dislodgements, then?

DR. HARKNESS: There have been what have been termed as late dislodgements. Something that I think is important to keep in mind is that when we are talking about displacement, dislodgement, migration of the lead, this is an investigator report. Many times, it wasn't confirmed that that is actually what had happened but there had been, perhaps, some loss of effect or there was no stimulation.

In many instances, indeed, the lead was repositioned or was replaced.

DR. AMINOFF: One follow-up question for Dr. Koller, then. In the instances where you couldn't, in fact, find a correct placement, do you think that you were actually in the right sort of area but it simply didn't work or that you weren't in the right area? It is almost a metaphysical question, I suspect.

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DR. KOLLER: We thought we were in the right area. Why it didn't work, I am unclear. I don't know if Steve has any additional comments.

DR. AMINOFF: Because it really boils down to is there a subset of patients in whom stimulation in the correct site doesn't work.

DR. S. WILKINSON: I think that that is the case because, even with thalamotomy, there are certain patients that you cannot control their tremor. I think that is a small subset of the whole.

DR. GWINN: I have a question, or just a clarification, really. The data that you presented in the graphs had a slope line from the first time of assessment to the end, for example, from preimplant to 12-month follow up, with, I suspect, from what you have said that, within the first three months, that became stable and did not change thereafter. In other words, there was not a slope suggesting ongoing change but rather a stabilization.

DR. HARKNESS: That's true. That slope is not meant to represent an ongoing change. That slope was more connect-the-dots, if you will, on those particular graphs. The tremor suppression, despite the fact that it was often necessary to change parameters, to change electrode selections during that first post-operative period, tremor

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suppression was often at a very good level during that period, so it was something that actually happened in the operating room.

DR. GWINN: That raises two points. One is the point that Dr. Hubble addressed which is that within the first three months, most of the manipulations and changes that you would have to make would be completed and the parameters would be relatively stable thereafter. Is that a true remark or do you not know?

DR. HARKNESS: Yes; I believe that is a true remark in our parameter data when we have looked at it. It does tend to stabilize it.

DR. GWINN: Then if the data is presented on a slope line, that implies that if we extrapolate it beyond 12 months, there would be continued improvement and yet your data doesn't actually suggest that as far as I can tell.

DR. HARKNESS: You are asking me if it--

DR. GWINN: If there is a sloped line from beginning to end, you would think that slope may extrapolate if you continued on. You don't have data to suggest that.

DR. HARKNESS: That's right. That would not be a fair interpretation of the data. I agree.

DR. EDMONDSON: Dr. Koller and Dr. Wilkinson, I was wondering if we could revisit the slide on adverse

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effects and really compare the profile in the study to what one would observe typically with thalamotomy, and particularly since most of these patients ultimately would need bilateral implantational. I was wondering if we could stratify the serious side effects and those that were transient and minor and give a global sense of what the total morbidity and mortality incidence would be for thalamotomy versus deep-brain stimulation.

[Slide.]

DR. KOLLER: I could specifically talk to the 59 patients in the Annals paper because that is what I am most familiar with. For those patients, we had no persistent morbidity and no mortality at all. Even the hemorrhages, they resolved and the people were left with really no discernable deficit. So the persistent morbidity, out, like, at three and six months in these patients, was not present.

Maybe Steve wants to expand on that, but those are the 59 patients that I know best. I know that data very well.

DR. S. WILKINSON: I think if you looked at a series of thalamotomies, there would certainly be a higher incidence on permanent, neurologic problems such as paresis or sensory loss that you don't see with the DBS procedure.

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So I think that that is the difference. The intracranial hemorrhage rate is probably similar, the rate of seizures. All that is probably similar.

DR. EDMONDSON: Do you have any gestalt of what that number would be for thalamotomy, just grossly, if you summate all the morbidity incidences that would be vis-a-vis DBS.

DR. KOLLER: If I may make one comment. Looking at the old thalamotomy literature which really predates clinical assessment--and I don't think that data probably accurate reflects what really happened. I think the old data is probably pretty hard to compare to more recent data because our methods of reporting, our efficacy measures, are really quite different now than it was 25 years ago.

DR. HARKNESS: Dr. Lozano, would you like to address that question? One comment that I wanted to make so that we are very clear; there has been one death in the clinical trial that we have reported in the PMA, although that patient was not included in the efficacy data because that patient was enrolled in the trial after we had made our final submission.

That death was, indeed, related to the procedure and did involve an intracranial hemorrhage. Just so that you understand; we want to make sure that picture is

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complete.

DR. LOZANO: My name is Andres Lozano. I am a neurosurgeon at the University of Toronto and I am a consultant for Medtronic.

If one looks at the literature on thalamotomy, by far the most common complication is that is speech disturbance which involves predominantly dysarthria but also some instances of dysphasia. The incidence of this complication can be as high as 45 percent in the thalamotomy series and it is more common with left-sided thalamotomy procedures and is much more common when the procedures are done bilaterally.

So the main advantage of the stimulation is, of course, that you can adjust the parameters and, in fact, reduce the intensity, to reduce the incidence of this disabling complication.

DR. NUWER: I wanted more information about the hemorrhages, the size and site of the hemorrhages and what clinical response there was to the patients who had the hemorrhages. I guess there were about 13 of them. Were the electrodes then left in place and they continued on in the study after that?

DR. HARKNESS: No. As a matter of fact, many of the hemorrhages occurred before the device was ever opened

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in the operating room. For example, there would be a subdural hemorrhage at the time of drilling the burr hole and then the device was never implanted.

In the U.S. study, we saw, I believe, two patients in whom the device had been implanted and the hemorrhage occurred after that, including the death.

DR. NUWER: Were they intracerebral hemorrhages or subdural?

DR. HARKNESS: Most of the hemorrhages were intracerebral. There was one subdural hemorrhage.

DR. WILKINSON: But, in the European study, I think it was the other way around.

DR. OLANOW: I am Warren Olanow. I am a neurologist and serving as a consultant to Medtronic. Most of the hemorrhages that were seen were subcortical. They weren't at the target site, for the type of hemorrhage that you typically see in a stereotactic procedure. About half of them were asymptomatic so that frequently they were recognized on post-operative scans.

From what I gather, none of them had long-standing clinical disability or residual even if they did have some symptomatic effects when they occurred.

But it is important to realize that in the majority of instances, it wasn't at the target site. It was

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subcortical probably related to passing through a sulcus.

DR. NUWER: What is the size of this?

DR. HARKNESS: We didn't collect that information.
We don't know.

DR. NUWER: Are you talking about a centimeter?

DR. HARKNESS: Again, we don't have that
information. We didn't require MRs or CTs. We do have,
obviously, the autopsy report from one patient.

DR. CANADY: As a neurosurgeon, I have never had
an intraoperative subdural. I have had a few post-operative
subdurals, but you can usually identify the bleeding at the
time of the operation, stop it and proceed.

DR. S. WILKINSON: This was a patient that, when I
drilled the burr hole, they happened to have a large
collection of veins right underneath where the dura was.

DR. CANADY: So you really stopped because the
veins were in the way.

DR. S. WILKINSON: Yes.

DR. KU: I noticed that there were episodes where
there was an inadvertent stimulation due to either magnetic
or electrical interference. Since the device has been used
in other forms for pain control, has there been a problem
seen in that area?

I would assume, based on the design of your units,

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that they are probably not MRI-compatible.

DR. HARKNESS: That's true. They are not MRI compatible and, indeed, we label against or label for that incompatibility, if you will. There have been, at least within the tremor clinical trials, no reports of increased stimulation or those sorts of things due to magnetic fields.

Anecdotally, for some DBS for pain patients and their devices, there have been, involving a very old, deep-brain stimulation study, two anecdotal reports in which walking through a theft detector, seem to increase the stimulation and had adverse effects in regards to that.

With those same old devices, there has also been the report and, obviously, this is one of the reasons we label against using in the MR. There was also a report of two of these patients who had, indeed, been put in an MR scanner and they complained of nauseousness, kind of a general ill feeling.

DR. WILKINSON: But I have recently encountered a patient with a new Medtronic spinal-cord stimulator who did report this due to ambient activity, I guess, electromagnetic activity. So it is a concern.

DR. HARKNESS: It is a concern and we label for that concern in both spinal-cord stimulation and in DBS for tremor.

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DR. WILKINSON: Anyone else on the other side with questions? I had one question. Dr. Koller, the studies seem to address tremor only in the upper extremity, yet the slide that Dr. Harkness showed of indications simply said for control of tremor. Are you suggesting that this is valuable for tremor in upper and lower extremity, or will it be marketed only for upper extremity?

DR. KU: I don't know about the marketing. I am just a clinician. But, for essential tremor, the tremor of the lower extremity, it is not usually clinically significant. If the patient holds up their leg, you can see it, but that is never a complaint.

In Parkinson's disease, of course, you can see tremor of the lower extremity and it can be problematic. We just measure the target symptom with the data that we showed which was always the upper extremity.

My own clinical experience with the DBS is that, particularly in Parkinson's, it will often control leg tremor as well as hand tremor. We just finished a study looking at both unilateral and bilateral effect of DBS on voice tremor. There are some patients in a blinded evaluation that it clearly gets better with their voice tremor.

DR. AMINOFF: To follow up on your comment, Dr.

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Wilkinson, how about head tremor in essential tremor.

DR. KOLLER: In our study, we didn't have enough patients with head tremor to make an assessment, a blinded assessment, so I think that still remains an unknown.

DR. HARKNESS: I was going to say that, in some discussions with FDA over the past couple of weeks, they have suggested an indication for upper-extremity tremor, and the company certainly wouldn't object to that.

DR. WILKINSON: One last question, Dr. Nuwer.

DR. NUWER: Is there a sensitivity to cell phone use? Does it need to be labeling with regard to not using cell phones?

DR. HARKNESS: There has not been a sensitivity to cell-phone use reported. The cell-phone use in regards to implantable pulse generators generally relates to the devices that have a sensing component to the device. For example, in cardiac pacemakers, when it is sensing that the heart needs to increase the rate due to activity or whatever, that seems to be what the cell phone interferes with.

We have not had any reports of-our device does not have that sensing capability and we have not had any reports of problems with cell phone use.

DR. WILKINSON: We better let you get back on

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track with your presentation, Dr. Harkness. Who follows Dr. Koller?

DR. HARKNESS: I do, thank you. Really, that pretty much concludes our presentation. Again, we would like to request that the panel make a recommendation of approving this device in this therapy for the treatment of tremor due to Parkinson's tremor and due to essential tremor. Certainly, as other questions come up during the rest of the morning and the afternoon, we would be happy to address those questions as well.

Thank you.

DR. WILKINSON: A mercifully brief presentation.

Can we proceed with the FDA presentations? Is that feasible?

Unless it is too disruptive to the presentation, we were talking about the timing. Since we did not take a break in the morning session, I had envisioned running until approximately noon, perhaps the first presenter, and then picking up again after lunch, if that is agreeable to the presenters.

FDA Presentations

MR. MacFARLAND: Good morning.

[Slide.]

My name is Bill MacFarland. In a few moments, I

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will be introducing you to Victor Krauthamer and Ann Costello. We are the team involved interactively with the sponsor in review of their PMA for the deep-brain stimulation system. I will first give you an engineering summary.

[Slide.]

In this summary, I will first describe the components of the system, briefly, relying on the sponsor's description. I will go over the safety concerns for this system, discuss the bench testing that was provided by the sponsor and I will go over the outstanding engineering issues.

Let's first look at the DBS system. It has an implantable pulse generator, implanted subcutaneously beneath the clavicle. An extension is attached to that stimulator. It is also implanted subcutaneously, tunneled up over the clavicle along the neck, and that connects to the lead which is secured in place by the burr-hole ring and cap.

That lead is implanted stereotactically into the thalamus. This system's hardware is either the same or identical to that used in spinal-cord stimulation but the sponsor has addressed some safety concerns in their submission.

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In our assessment of the safety concerns of the system, not only do we address the risks posed by the device in the event of failure, but we also address those introduced to the patient during normal operation of the device.

[Slide.]

So let's look at those safety concerns during normal operation, first, for the IPG, implantable pulse generator. There is the concern of charge balance, that if the stimulator provides an imbalance of charge, it could change the pH level or inject metal ions at the electrode site.

The sponsor has addressed this through some testing where they connected the stimulator to a resistor and they looked at the wave form to address the issue of charge balance.

Another issue is of stimulation parameters which Victor Krauthamer will get to in a few minutes, but the concern here is that the stimulator can provide a higher output than that which was investigated in the clinical trial and that which was studied in animal testing, or that where, historically, there is a safe level of stimulation, let me say.

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There is the concern of mechanical and electrical reliability, that the device once implanted will operate as intended. The sponsor has addressed this first through electrical reliability of the hybrid circuit which is part of the IPG and they have looked at mechanical reliability through tests such as header shear-force testing, permeticity testing, drop testing and vibration testing.

There is the concern of softwear that it operate reliably. The sponsor has provided validation and verification testing. For the extension, this extension is being placed in a new location when compared to spinal-cord stimulation. So there are reliability concerns there with the shear, tensile and compression forces.

The sponsor has provided animal testing and bench testing and analyzed that to address this issue.

[Slide.]

There are concerns for the burr-hole ring and cap. First of all, the concern of lead stability and the sponsor addressed this through some in vitro testing. There is the issue of biocompatability.

For the deep-brain stimulation lead, again, the issue of mechanical liability where there are different shear forces and tensile forces imposed on the device when compared to spinal-cord stimulation. The sponsor has

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performed some testing and provided the results of that.

There are polymers involved with this lead and the issue of sterility and pyrogenicity. There are some biocompatibility issues there as well that the sponsor has addressed.

[Slide.]

Let's look at the issues associated with potential failure, in the event of a failure; for the implantable pulse generator, that it does not provide a D.C. current in the event of a component failure in the stimulator. The sponsor has provided a hazard analysis to address this issue.

There is a concern with respect to the DBS lead with withdrawal in event of a failure. We had asked the sponsor to address that.

[Slide.]

There are some engineering issues which need to be resolved. In the package that was handed out to you prior to your coming here, the details of this have been provided, but let me go over this briefly.

For the implantable pulse generator, the stimulation parameters. The stimulator can provide a higher output than that which was investigated. Charge-balance testing; how does the testing which they performed emulate

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clinical use of the device. D.C. current blocking; some more information on their hazard analysis.

The reliability of the device. We need a little bit more specific information on the path-cell criteria and things like the sample-size justification.

Battery information; the sponsor provided us a piece of labeling which they intend to convey to the physician and patient, the expected battery life given certain stimulus parameters. But that labeling refers to parameters which were not investigated in the clinical study. So those issues need to be resolved.

[Slide.]

There are also outstanding issues associated with the extension, the reliability and its being placed on the clavicle. With respect to the DBS lead, mechanical reliability testing issues, path-cell criteria, the specifics on this testing. They have performed it and we need some more detail--the issue of biocompatibility.

Finally, the microrecorded electrode which is used during the implantation of this device, we feel some information needs to be put in the labeling to provide this information to the physician.

That is an engineering summary of the sponsor's submission. I would like to introduce you to Dr. Victor

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Krauthamer who will go over the preclinical animal testing.

Preclinical Animal Testing

DR. KRAUTHAMER: Good morning. I am a neurophysiologist with the FDA. I reviewed, primarily, the safety of the preclinical animal and related studies.

[Slide.]

This device we paid particular attention to because it goes into the brain and stimulates in neurologically impaired patients.

[Slide.]

There are basically two reasons why we had particular concern. First of all, since it goes into the brain--the brain doesn't feel pain. There are no receptors in the brain so that if there are any adverse events going on due to the electrical stimulation, the patient may be unaware of such events without the ability to feel the pain.

The other reason is that these patients already have neurological impairments. Therefore, any damage that may occur from electrical stimulation could be difficult to recognize over background neurological deficits.

Of course, with any animal study, it is possible to stimulate a high levels and also to do histological sectioning which isn't normal for most patients.

[Slide.]

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I want to take a couple of minutes to show how we analyze the safety of electrical stimulation. A lot of this work was based on the work of Douglas McCreery and his colleagues at the Huntington Research Institute in California. I just want to explain the basis by which we look at stimulus parameters.

There are two things here that can affect neurological damage and that is the size of the electrode or the electrode surface area and the amount of charge carried in each stimulation pulse. The reason charge is important is that charge tends to be a very robust factor in terms of electrical stimulation.

Whether you get stimulation or not depends very much on the level of charge, and charge remains relatively robust whereas other factors, such as voltage or current, can vary with stimulation. With charge as this most robust factor for stimulation, it also is related to electrically produced damage because damage, most often, is produced by excessive stimulation. So this is the rationale for using charges as one factor.

The other factor, of course, is electrode surface area. You can imagine if the same amount of charge is distributed from a very small electrode, there is a very high charge density and fairly intense stimulation. So

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there is more likelihood of electrical damage for small electrodes than there is for high electrodes where the charge is more diffusely distributed.

The way this plot was constructed, it was based on the work of McCreery and his colleagues, where they stimulated--and this happened to be cat cerebral cortex--in a rather standard way with different size electrodes and with different amounts of charge. They did histological sectioning after the stimulation and looked for histopathic damage.

The open filled symbols represent animals, the charge and the electrode size that did not produce any histological change.

The closed figures represent histological sections where the combination of electrode surface area and charge did produce a histological change. They use these data to draw a line, sort of a damage threshold. Again, this isn't the most exhaustive study but it is the best way we have now of comparing what a device does to what is known from the physiology.

The first thing to look at is the maximum output of the device. We see that it is in a zone where the combination of charge and electrode size would probably cause some histological changes. That is the maximum. But

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if we look at what is actually used by the patients in the clinical trial, we have a mean that is in the area where there are no histopathic changes occurring in other animal studies.

If we look at the entire range, we selected three months which is actually the worst-case situation, stimulation parameters were actually highest at three months. If we look at the range, we see that the range extends up until about the border where the animal studies showed some histopathic damage--not damage, really, but histopathic changes.

Actually, in this study, there was only one patient who actually exceeded the line and that patient, in further follow ups, had his stimulation levels adjusted and he actually fell below the line. So the device maximum is quite different from what was actually used in the study.

If we look at the animal studies, and I will go over that in more detail in a minute, there were two animal studies done, one in which an animal was stimulated at the maximum level for a short period of time, and those animals were stimulated at the maximum over there, and a chronic animal study in which animals were stimulated at their maximal level they would comfortably tolerate for a period of six months. That level is close to the patient maximum

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level, there in green.

Before going into the details of the animal study, I just want to mention one other case. There was one report in the literature by Ceparros, Lefebvre and his colleagues, of a post-mortem study of a deep-brain stimulator--this happened to have a different electrode, so the electrode size is different.

[Slide.]

I want to discuss now what their study found. By the way, I was unaware of the unpublished reports that Dr. Koller mentioned. We would be interested in learning what other autopsy reports have shown for this device.

First, they concluded that there were small lesions--they found small lesions near the electrode site. They concluded that these lesions were produced by electrical stimulation. They used the terms "lesions," but they were actually what we would call microlesions. These lesions were under 100 microns and they were all within 2 millimeters of the electrode.

They noted that the lesions were smaller than those that would ordinarily be produced by microthalamotomy. The patient, from this autopsy, didn't seem to have effects from the device and did continue to use the device.

[Slide.]

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Going into the animal study, as I mentioned, there was an acute animal study with maximum stimulation. In this animal study, the histology showed that there were no large lesions produced. There was a fair amount of insertion trauma which would be expected when the histological sections are taken immediately after insertion.

But it didn't let us see the kinds of lesions that Ceparros LeFebvre reported within 2 millimeters of the electrode site because of the underlying mechanical damage from the lead insertion.

I mentioned the chronic study. Here, the study again didn't show any large lesions. There were small lesions within 1.6 millimeters of the lead track and those included ratification of the neurophil, gliosis, occasional axonal spheroids and mild macrophage infiltration.

There were a number of issues and Medtronic has since gone back and realized some of the histological data. One of the issues is the small number of animals. As I mentioned, mechanical damage from the lead in the acute study. Difficulty in lead placement in the thalamus; actually, in the chronic study, half of the thalamic leads actually missed the thalamus. Seven of the 14 thalamic leads actually were not in the thalamus.

The important one is difficulty in electrode site

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location. It is difficult to look for histopathic changes from electrical stimulation if you can't exactly locate where that electrode was placed. This is something that is a difficult problem for anyone to overcome during histology.

But, on the encouraging part, there is a good chance that they did see some electrode sites and there were no lesions found in any section examined.

[Slide.]

So, in conclusion, the evidence from the literature is that there is the chance of the development of small lesions near the electrode site. That is mainly from the Ceparros LeFebvre study. These lesions are very small, under 100 microns, and they are very localized.

The animal studies indicate that the device does not appear to produce large or the more classic lesions, the kind you would get from a thalamotomy. So it is definitely not a lesioning device. In the strict, scientific sense, the animals studied did not locate specific electrode sites. Therefore, subtle histopathic changes from stimulation could not be examined in this study.

I should note that, more than electrical stimulation, the major problem was surgical, that more of the animals suffered from surgical complications than from complications due to stimulation.

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[Slide.]

I just want to emphasize that point now with a cartoon, that the surgeon is very important in this. That is not Bill Clinton sitting there. I also want to use this--and we are going to break for lunch now--to introduce, after lunch, Dr. Ann Costello who is the lead clinical reviewer for this and also happens to be a surgeon.

DR. WILKINSON: Before you sit down, Dr. Krauthamer, could you clarify for the clinicians especially that slide that you showed about the charge density for a given electrode surface area. Does this slope hold fairly true depending on variations in pulse amplitude and frequency, pulse width, the other parameters?

DR. KRAUTHAMER: That is an excellent question. Charge involves current and pulse duration. So pulse width and amplitude are taken care of in charge. It doesn't involve frequency effects. You would expect that damage would increase, or histopathic changes would more likely occur, with higher frequencies of stimulation.

The data from McCreery were done with stimulation at 50 pulses per second and the data for the--well, the Medtronic device can, I believe, go up to 130 pulses per second. But that is unknown ground, a little bit, so we can't evaluate it retrospectively with this type of

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analysis. But we do look at the histology of the animal study where the animals were challenged with the highest frequency possible from the device.

DR. WILKINSON: So that was looked at. Certainly, as a surgeon, I can use a device in the operating room that either coagulates tissue or cuts tissue depending on the frequency of the parameters. So you feel that was adequately addressed?

DR. KRAUTHAMER: In the animal study, because the animals were pulsed at the maximum rate.

DR. WILKINSON: The maximum likely to be damaging electrical parameters.

DR. KRAUTHAMER: Well, in the acute study, everything was turned up to the absolute maximum that the device would do. In the chronic study, the pulse rate and pulse duration were at the maximum and the pulse amplitude was adjusted to the maximum that the animal would tolerate, which was well above what is used by people.

DR. WILKINSON: Other questions from the panel? Since we have heard a lot about human values this morning, I think we need to break for lunch. Be back in an hour, please.

[Whereupon, at 12 o'clock p.m., the proceedings were recessed to be resumed at 1 o'clock p.m.]

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A F T E R N O O N P R O C E E D I N G S

[1 o'clock p.m.]

DR. WILKINSON: I would like to resume the session for the afternoon. Let's proceed with the FDA presentations. I understand there are still some questions regarding earlier FDA presenters, but let's finish the FDA presentation with Dr. Costello and then we can have the panel ask questions of all three FDA presenters if questions still remain.

DR. COSTELLO: Good afternoon, Dr. Wilkinson and members of the panel. This afternoon I will be discussing issues from three clinical studies.

[Slide.]

These are the U.S. tremor study, the European tremor study and the safety study which includes both the DBS pain study and the European basic safety study. I will focus mainly on the U.S. tremor study and the European tremor study which the sponsor has submitted to support the claim that deep-brain stimulation is safe and effective for unilateral and bilateral tremor suppression in subjects with essential tremor and Parkinson's disease.

[Slide.]

FDA believes that each of the four indications for the deep-brain stimulation system should be addressed

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separately. These indications are summarized briefly on this slide; unilateral stimulation for the treatment of essential tremor, bilateral stimulation for the treatment of essential tremor, unilateral stimulation for the treatment of Parkinson's disease and bilateral stimulation for the treatment of Parkinson's disease.

[Slide.]

FDA proposes the following indication for the deep-brain stimulation system and is asking for panel consideration to expand this indication. The indication reads, unilateral thalamic stimulation by the Medtronic Model 3382 DBS lead and the Medtronic ITREL II Stimulation System is indicated for suppression of essential tremor in the upper extremity.

The system is intended for use in patients who are diagnosed with essential tremor not adequately controlled by medications and where the tremor constitutes significant functional disability.

[Slide.]

The concerns which FDA has regarding the other indications for the device are briefly summarized on this slide. FDA hopes that the panel will advise FDA on the clinical impact of these issues. The first three issues regard the Parkinson's disease indication. There are

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medication adjustments. There was a lack of improvement in the activities of daily living except for the tremor-specific activity of daily living.

And, in some patients, 7 out of 39, there was a worsening of tremor and/or other symptoms of Parkinson's disease. The two issues related to bilateral stimulation concerned a small number of patients that had been studied, and adverse event reporting, a difference between adverse event reporting in the U.S. and the European studies.

[Slide.]

The next several slides will summarize the U.S. tremor study and the European tremor study which I will be focussing on. The U.S. tremor study was designed as a randomized, double-blind clinical trial of unilateral stimulation for the treatment of tremor suppression associated with essential tremor or Parkinson's disease.

The U.S. tremor study was done without medication. The assessment was done without medication.

[Slide.]

The European tremor study, on the other hand, was a multicenter, prospective clinical trial. It assessed the ability of unilateral and bilateral stimulation to suppress tremor with essential tremor or Parkinson's disease. The patients, in this study, when they were assessed, were on

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their usual medications.

[Slide.]

The following is a flow chart of essential tremor patients enrolled and their follow up. 45 patients were enrolled. Four of the patients were not internalized. One patient was not internalized because he had tremor suppression from the presence of the lead and, therefore, did not need the stimulator to cause tremor suppression.

The other three patients were followed out to six months for safety data. The 41 patients were internalized and were followed at 1, 3, 6, 9 and 12 months. Not all the patients have reached these follow-up visits and that is one of the reasons that the numbers vary.

It is important to realize that the tremor assessment at 1, 6, 9 and 12 months are done with optimized stimulation parameters. However, the stimulation parameters at the 3 months, the design of the study which was the primary outcome of the sponsor's study, was a randomized, double-blind control where 20 patients received stimulation on and 17 patients were randomized to stimulation off.

A question arose this morning, also, regarding the number of dropouts. In fact, at the three-month time, there was one dropout. At four months, an additional patient dropped out and, following the 12-month visit, there was an

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additional dropout patient. All these dropouts were explanted.

[Slide.]

The sponsor has determined success as a tremor score of 0 or 1, or if a patient went from a score of 4 to 2. Some patients did have a thalamotomy effect which meant that, with stimulation off, their tremor was suppressed. In addition, there was some clinical variation so a tremor score from a 2 to a 1 or from a 1 to a 0 may be clinical variation and not real tremor reduction.

Therefore, FDA decided to determine success based on a two-point reduction in tremor. As you can see, the patients in the U.S. tremor study, at all time points, roughly 50 percent or more of the patients did obtain a two-point reduction in tremor. Again, this success is based on an assessment without medications.

[Slide.]

The sponsor has shown you this morning the results of the randomized, double-blind controlled trial at three months. As you can see, there was a statistically significant decrease in tremor score at the three-month study point. The primary objective of the study when control, stimulation off, was compared to stimulation on, the treatment group.

Again, patients were off medications overnight. In other words, they had foregone their morning dose of medication and, in addition, they were told to turn their stimulators off the evening before the assessment.

[Slide.]

The primary medications used by essential tremor patients are primidone and propranolol. Patients in the IDE which was the investigational study, the U.S. tremor study, were considered refractory the medications as medications had not adequately controlled the tremor for at least three months prior to implant as determined by the neurologist.

As can be seen, only 11 of the essential tremor patients were on primidone at pre-implant. Of these 11 patients, two of them increased their dose of primidone and seven of them decreased. The two refers to the one patient who resumed as well as the patient who had the dose increase.

Four patients were on propranolol at preimplant. The three of them which have reached follow-up visits all had their dose decreased so there were no increases, and three patients decreased their dose of propranolol.

[Slide.]

This slide shows the activities of daily living

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for the essential tremor patients. This is liquids to mouth, pouring, drawing and feeding solids, writing. As you can see, we are plotting here the follow-up visits and the change in the activity of daily living at each of the follow-up visits compared to pre-implant.

As you can see from this slide, at each of the time points for each of the activities for daily living measured, there was a statistically significant improvement of the activities of daily living.

[Slide.]

This is a flow chart of the essential tremor patients who were in the European tremor trial. In this case, 38 patients enrolled. 28 of them were treated with unilateral stimulation and, in the European tremor study, they were followed and assessed at 3, 6 and 12 months. Ten of the patients received bilateral stimulation and, again, they were followed at 3, 6 and 12 months.

[Slide.]

These are the European patients that were on primidone and propranolol. Four of the patients were on primidone, pre-implant. None of the patients increased their dose of primidone. Three of the patients decreased the dose of primidone. In the case of propranolol, there were six patients on the drug pre-implant, two of which

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increased the dose and four of which decreased the dose of the medication.

[Slide.]

This shows the identical data for patients treated with bilateral stimulation. In this case, three patients were on primidone at pre-implant. One of the patients did increase the dose. At follow up, one patient did increase the dose of primidone, three patients decreased their dose.

In the case of propranolol, there were five patients on the drug at pre-implant. None of these patients increased their dose. Four of them, in fact, decreased their doses.

[Slide.]

This is a summary slide of the results of the essential tremor study. In the first column, we have the U.S. tremor study. In the second column is the European tremor study. As you can see, the number of subjects in the U.S. tremor study, for essential tremor patients, there were 45. In the European, there were 28 patients treated unilaterally and ten patients treated bilaterally.

The number of sites in which the investigation was done was eight in the United States and nine in the European tremor study. There was a difference in the hypothesis that was being tested between these two studies. The hypothesis

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that was tested in the U.S. tremor study was that the tremor score with stimulation on would be the same as the tremor score with stimulation off.

In the case of the European study, to reject the null hypothesis, there had to be a two-point decrease in the tremor score. The designs of the study were different again. To remind you, the patients were off their medications in the U.S. tremor study for assessment but were on medications for the assessment in the European study.

As far as stimulation was concerned, they stopped stimulation the night before.

The largest number of sites was Dr. Koller's site, the University of Kansas, which had 31 patients. The next largest site was Toronto Hospital which had six patients. In the case of the European study, the largest site had ten patients. The next largest site had six patients.

In terms of whether or not there was a difference between the means of stimulation on and stimulation off, in fact, there was a significant difference between the stimulation on and stimulation off scores for each of the three categories. In the case of a two-point decrease, at 12 months, 57.7 percent of the patients in the U.S. had a two-point decrease.

In the European trial, again a difference is that

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they assessed postural versus action tremor. In both cases, they were able to reject the null hypothesis; in other words, there was at least a two-point decrease stimulation on and stimulation off.

The ADL, which is an objective measurement of improvement, was statistically significantly improved in all three categories. Similarly, the disability score which is more of a subjective score, was also improved in all categories.

Just to remind you again, in the case of the U.S. tremor study, two people increased primidone, seven people decreased primidone. For the unilaterals, zero people increased their primidone, three decreased the primidone. In the final category, bilateral, one patient increased primidone dosage and three patients decreased.

Similar results were found for the propranolol. The majority of the patients, in fact, did decrease their dose of propranolol. The mean follow-up time is ten months in the U.S. tremor study and the European study was taken out to 12 months. So that is the data that is available in terms of the assessment periods.

[Slide.]

This is a flow chart of the Parkinson's disease patients that were enrolled in the U.S. tremor study. There

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were 39 patients enrolled, three of which were not internalized, and were followed out to the six-month safety follow-up visit. There were 36 patients that were internalized. They were followed at 1, 3, 6, 9 and 12 months. Again, the randomized, double-blind, primary outcome variable, the three-month variable, was done on 15 patients randomized to stimulation on and stimulation off.

Again, the 1, 6, 9 and 12 month assessments are done with stimulation off compared to optimized stimulation parameters.

[Slide.]

As I said before, the sample size for the Parkinson's disease patients was 39. The mean age at implant was 65.3. The mean age at disease diagnosis was 55.6 and the mean age of definitive diagnosis was 57.3 years.

I would like to make the point here that there were roughly eight years between the time of definitive disability and the time of implant.

[Slide.]

When success is measured on a two-point reduction in tremor, in the U.S. tremor study, without medications and stimulation off overnight, as you can see, essentially 60 percent or greater of the patients had at least a two-point

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reduction in tremor score at each of the follow-up visits.

[Slide.]

This, again, is the three-month randomized trial. Between the control group, stimulation off and stimulation on, there was a statistically significant difference. As the sponsor has discussed previously, the results were similar on the cohort of patients that were done for long-term efficacy, the cohort of patients from the Swedish sites that were involved in the European tremor study.

[Slide.]

Parkinson's disease patients suffer from other symptoms such as rigidity, bradykinesia, and postural instability. The motor examination section of the Unified Parkinson's Disease Rating Scale evaluates these other clinical symptoms in Parkinson's disease.

When these patients were evaluated without medications, stimulation did result in a marginally significant improvement in rigidity at 3 and 12 months and in bradykinesia at 12 months. The purpose of this slide, though, is to show you that, in all cases, the other symptoms of Parkinson's disease were relatively mild.

[Slide.]

This is a flow chart of the Parkinson's disease patients that participated in the European tremor trial.

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There were 75 patients enrolled. Two were not internalized. Of the 73 internalized, 17 received bilateral stimulation and 56 received unilateral stimulation.

In this case, 12-month follow up was reached in 45 of the patients in the unilateral arm of the study.

[Slide.]

The issue which I will be discussing now is the medication adjustments.

[Slide.]

L-dopa is the standard drug therapy for Parkinson's disease and does control all the symptoms of Parkinson's disease such as bradykinesia, rigidity, postural instability as well as tremor. It is important to remember, though, that the other symptoms of Parkinson's disease had to be mild to be included in the study and that the average patient had been diagnosed eight years prior to implant.

During the U.S. tremor study, of the 18 patients that were on L-dopa at preimplant, 17 of these patients increased their dose and eight of the patients decreased their dose. In the case of the anticholinergics, eight of the patients were on anticholinergic drugs at preimplant. None of the patients increased their doses and six of the patients decreased the dose.

It is important also to realize that we do not

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have data on medication use in a number of the patients that were involved in the U.S. tremor study. At preimplant, as I say, there were only 19 that were stated to be on L-dopa and nine on anticholinergics.

In addition to the medications L-dopa and anticholinergic, patients were also being treated with dopamine agonists, benzodiazepams and tricyclic antidepressants which may affect tremor although they also affect other disease processes in addition.

[Slide.]

This is a summary of the Parkinson's disease medications for the patients that received unilateral stimulation. 33 of the patients were on L-dopa or Sinimet at preimplant. 17 of these patients increased their dose of L-dopa, 11 of them decreased their dose.

In the case of the anticholinergic Artane, there were two patients on in preimplant. None of the patients increased the dose and two of the patients decreased the dose.

[Slide.]

Similar data for the bilateral indication. Bilaterally stimulated patients from the European tremor trial showed that there were 15 patients on L-dopa at preimplant. Seven of the patients increased their dosage.

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Three of the patients decreased their dose.

No patients were on Artane. However, again, these patients in the European tremor study were being treated with dopamine agonists, benzodiazepams and tricyclic antidepressants.

[Slide.]

This is a listing of the patients who had increased tremor. Although these patients were supposed to be drug refractory, several of the patients did have increased tremor and were treated with variations in their medications. As you can see, the first patient started L-dopa. The second patient changed from selegiline to pegolide. L-dopa was the same, in this case. In fact, patients in this particular case, did drop some of their medications. In this case, patients added dopa, and so on and so forth for the other four patients.

[Slide.]

A very important aspect of deep-brain stimulation is the issue regarding the activities of daily living and the impact that the device would have on the patient's life. I would like now to discuss the lack of improvements in the activities of daily living.

[Slide.]

These are handwriting, tremor, dressing, cutting

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food and hygiene. This slide shows the patients--this is actually ADL impairment. As you can see, there was basically no change in the amount of impairment from preimplant over the 12-month follow-up visit in all of these categories except for the tremor-specific ADL.

[Slide.]

This is shown on the next slide as an ADL improvement. Again, here, we are measuring the difference between preimplant and the follow-up score. In this case, as you can see, tremor was statistically significantly improved. Handwriting was not affected. Cutting food was not affected. Dressing and hygiene was not statistically significantly improved in this patient population, which was assessed without medications.

[Slide.]

The next issue which I would like to discuss is the worsening of tremor in seven of the 39 patients. Seven of the patients had increased tremor or worsening of symptoms. Also, as can be seen, the Hoehn and Yahr staging system is a staging system for the Parkinson's disease patients.

As you can see, over a 12-month period, in this group of patients, there was a statistically significant change. These patients were going from, essentially, a

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stage 2 to a stage 2.5 Hoehn-Yahr staging score.

Stage 2 is bilateral disease without impairment of balance. Stage 2.5 would be mild bilateral disease with recovery on the pull test.

[Slide.]

This is a summary similar to the ET summary for the Parkinson's disease patients. Again, there is the U.S. tremor study and the European tremor study. There were 39 patients in the U.S. study and these were at eight sites. In the case of the unilateral patients, there were 57 patients. 17 had bilateral implants.

In the European case, 12 sites were involved. Again, the hypothesis for the U.S. tremor study was that the stimulation on tremor score would be equivalent off tremor score. In order to reject the null hypothesis in the European tremor study, there had to be a two-point decrease in tremor score with stimulation on versus stimulation off.

The design of the study; the medications were off for the assessments in the U.S. study and the patients had taken their morning dose of medication in the European study.

The largest number of sites is, again, the University of Kansas where there are 16 patients. The next largest was also Toronto Hospital where there were nine

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patients. The largest site in the European study had 23 patients and the next largest had 12.

In terms of a mean difference--in other words, was the tremor score statistically significantly different with stimulation on versus stimulation off. In all cases, there was a statistically significant difference.

There was a two-point reduction in tremor score in 66.7 percent of the patients in the U.S. tremor study at the 12-month follow up. In the European tremor study, they analyzed rest tremor and action tremor. In the case of unilateral patients in rest tremor, there was, in fact, a two-point reduction in tremor score between stimulation on and stimulation off.

Thus, they could reject the null hypothesis. However, for bilaterally stimulated patients, there was not a two-point reduction in tremor score between stimulation on and stimulation off. In the case of action tremor, for both the unilaterally and bilaterally implanted patients, there was not a two-point decrease between stimulation off and stimulation on.

In terms of the activities of daily living, the objectives measure, the activities of daily living, in the U.S. tremor study, were not improved except for the tremor-specific activity of daily living. In the case of

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the European study, both groups, the unilateral and a bilateral, did improve their ADLs.

In the case of the relatively subjective measure, the disability score, they were improved in all three categories. To summarize very briefly, again, the change in medications, most of the patients in these studies did increase their dose of L-dopa. However, some of them did, in fact, decrease their dose of L-dopa. I did not do the calculations for the dopamine agonists and benzodiazepams and tricyclic antidepressants. There was no simple way of presenting that data.

The mean follow up was 11 months in the U.S. study and reached 12 months which was the final assessment point for the European study.

One other issue which I would like to raise now came up this morning regarding stimulation parameters. In fact, there was a difference between the Parkinson's disease patients and the essential tremor patients. In the case of the Parkinson's disease patients, the amplitude did continue to increase from discharge through 12 months.

The frequency that is used for stimulation is approximately 185 Hertz. I do have a transparency of this if you would like to see it afterwards. The sponsor, however, did do a calculation to show that the change in

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amplitude at nine months and 12 months was not statistically significantly different from the amplitude that was measured at the six-month assessment point although, at all points, they were different from discharge.

[Slide.]

The next issue which I would like to discuss is the small number of patients studied.

[Slide.]

In terms of bilateral stimulation, there is a total of 27 patients, ten essential tremor patients and 17 Parkinson's disease patients.

[Slide.]

77, or 92 percent, of 84 patients who participated in the U.S. tremor study were, in fact, implanted and completed follow up. Seven of these patients were not implanted. In the first patient, as you can see, he had a lead in place and continued with tremor suppression so did not require placement of a stimulator.

The other six patients did not have either the lead or the stimulator placed. UST 15 was not implanted due to an intracranial hemorrhage. This was the cause of not implanting the device also in UST 39. UST 27 had an intracranial hemorrhage at one day post op. The final two patients, UST 41 and 75, had insufficient tremor suppression

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during the trial stimulation period with this device.

On patient, in addition, was not able to cooperate with the procedure. During the trial stimulation period, the patient is awake and the physician needs to assess the degree of tremor suppression and this patient could not cooperate with the procedure.

[Slide.]

Rebound is a phenomenon in which the patient's tremor appears clinically exaggerated compared to baseline after turning the stimulation off. As you can see, for the essential tremor patients, approximately 25 percent of the patients did experience rebound. It ranged from approximately ten minute up to about 40 minutes. In the case with the patients with Parkinson's disease, about 20 percent of the patients experienced rebound and it lasted anywhere from about 15 minutes to 35 minutes.

[Slide.]

Here is listed the events that, in the U.S. tremor study, were related to disease progression. You have much greater detail on the adverse events in the handouts that were given to you regarding the labeling. There are several safety issues, though, which I would like to bring to your attention at this time.

Four patients were reported by physicians to have

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an adverse event of worsening of Parkinson's disease and four of the investigators reported that increasing tremor was a symptom. Two patients also complained of depression. The reason that depression is on the slide is that it has been found in some patients who were being treated with deep-brain stimulation, especially in the pain population, that deep-brain stimulation does cause suicide ideation and, if the parameters are decreased, the depression reverses.

[Slide.]

These are the adverse events reported in the U.S. tremor study. As you can see, at 84 patients, there were a total of 599 adverse events reported. As you can see, most of them were a transient paresthesia which occurred upon beginning of stimulation. The other adverse events which are reported in a large number would be dysarthria; there were ten patients.

Eight investigators reported paresis. Seven reported disequilibrium and five reported dystonia.

[Slide.]

Here are listed the major complications related to the surgical procedure from the U.S. tremor study. Five patients had intracranial hemorrhages. Three of the investigators considered the paresis to be a complication rather than an adverse event. In two cases, there was

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disequilibrium. And there was one patient who did have a seizure. Dr. Koller mentioned that patient this morning. After 12 months, the patient is free of all anticonvulsant medications.

[Slide.]

This slide shows the adverse-event frequency. In terms of the unilateral patients. Out of 85 patients, ten reported adverse events for a frequency of 12 percent. In the bilateral population, you can see that it is a very similar number of patients. There were four events listed in a total of 22 patients.

[Slide.]

On this slide, we have listed patient deaths. In the U.S. tremor study, there were two patients who died. One died of an intracranial hemorrhage which occurred post operatively. Another patient's death certificate stated that the patient had Parkinson's disease. The investigator, however, did not feel that the DBS system was the cause of the death.

In the European tremor study, one patient committed suicide. One patient had cancer and one patient had ileus. In the combined safety studies, two patients had suicides. Two patients had myocardial infarcts. And one patient died of old age.

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[Slide.]

The other comment which I would like to just make is that in none of those patients who died, which are listed on that slide, did we have any autopsy reports on. The only autopsy report that FDA is aware of is the article that was referred to by Dr. Krauthamer this morning which did show that the patient had a neural lesion.

In this slide is a summary of the complications for all--well, it is basically four studies. This combines the pain and the basic safety studies. In total, there are 416 patients. There were nine deaths. It is important that you realize, too, that in the safety study, these patients had various diagnoses. They were not implanted only for movement disorders.

In the case of intracerebral hemorrhage, overall, there were 13. Two patients had strokes. Five patients had seizures. And, in the case of DBS system explant, or, in other words, patient dropout, in the U.S. tremor study, there would have been four patients. One patient in the European trial was reported.

[Slide.]

The final issue which I would like the panel to address is the reporting of adverse events.

[Slide.]

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This is a summary slide of all the issues which FDA would like panel recommendations for. At the very end, I will discuss that adverse event reporting for which we would like a recommendation.

The issues were broken up to these issues; U.S. tremor study, European tremor study, unilateral and bilateral. The main drug of interest in this population is L-dopa. So, in terms of medication adjustments, we focussed only on the L-dopa drug. As you can see, in all cases, more patients did increase the drug than decreased the drug.

In the case of the activities of daily living, they were not improved in the U.S. tremor study but were improved in the European tremor study. Again, the U.S. tremor study, however, did show improvement in the tremor-specific ADL. Tremor was reported as increasing in seven patients out of 39 and was not reported in the European studies.

Issues regarding bilateral stimulation; the sample size. As you can see, in the essential tremor, patients, there were only 10 implanted bilaterally, and 17 Parkinson's disease patients.

Finally, we see the difference in the recording of adverse effects between that U.S. data and the European data. In the U.S. collection of data, there were 599

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adverse events reported where there were only 90 adverse events reported in the European tremor study. This was in 61 patients in the U.S. study and 113 patients in the European tremor study over eight months versus 22 months.

This may reflect a difference in the number of follow-up visits. In addition, since the device is marketed in Europe, some physicians do not feel that the paresthesia would be considered an adverse event. That is what is responsible for at least two thirds, and maybe even three-fourths, of the adverse events.

This concludes my discussion. I will ask Dr. Wilkinson to proceed with panel review of the device unless any of the panel members have questions for Mr. MacFarland, Dr. Krauthamer or myself.

DR. AMINOFF: It would not be surprising to me as a neurologist if patients who have a progressive disease like Parkinson's disease get worse over the course of the study. So it does not surprise me that their Heohn and Yahr scales have deteriorated as the study went on.

It does also not surprise me that their Sinimet medication may have had to be increased because Sinimet, as you know, is less helpful for the treatment of tremor. Of more importance and relevance, perhaps, is the fact that the anticholinergic medication could often be reduced. That is

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particularly helpful usually for the treatment of tremor.

So the fact that it was reduced, then, following this use of stimulation is probably highly relevant and appropriate.

DR. CANADY: I am just curious about the patient who was improved merely by the placement of the lead. Did that patient have a small hemorrhage?

DR. COSTELLO: I don't believe so.

Don, do you want to address that?

Is that appropriate to ask the firm to respond to that?

DR. WILKINSON: Sure. Absolutely.

DR. HARKNESS: That was Dr. Lozano's patient. I will let him answer that.

DR. LOZANO: Yes; that was my patient. He did not have a hemorrhage. In fact, he had a CT scan done immediately after the surgery as we do in all our patients. Just the mere introduction of the electrode in his case was sufficient to arrest his tremor. This has now been three years and he still has no tremor.

DR. HALLETT: Were the patients who worsened with the tremor over time, could you see that any of that was related to actual stimulation or was that just a matter of

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time. In other words, could it be seen that if you turned up the stimulator, the tremor worsened?

DR. COSTELLO: No.

DR. HALLETT: Was that just merely a matter of time?

DR. COSTELLO: Exactly. Again, Don may want to correct me if I speak wrongly, but I believe that, in all seven cases, stimulation did, in fact, still suppress the tremor.

DR. HARKNESS: One comment that Ann and I have discussed previously. With all due respect to Ann, I believe that those seven patients--actually, worsening of tremor was not their complaint but, in many of them, it was disease progression; that is, a symptom had manifested itself and the physician related that to disease progression, not to the stimulation, itself.

DR. HALLETT: Another question. Were the patients who were bilaterally implanted worse in terms of their Parkinson's disease than those who were unilaterally implanted?

DR. COSTELLO: Again, I believe you should ask the firm that.

DR. HARKNESS: I'm sorry, Dr. Hallett. Would you repeat your question.

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DR. HALLETT: Were the patients who were bilaterally implanted clinically worse than those who were unilaterally implanted.

DR. COSTELLO: You mean besides the fact that they have unilateral versus bilateral, obviously.

DR. HALLETT: Not necessarily.

DR. COSTELLO: In terms of Parkinson's disease progression, it would be longer.

DR. HALLETT: Yes; did they have worse disease.

DR. HARKNESS: The one thing that I would comment on as far as worse disease in those patients is that in the European study, bilaterally implanted patients were fluctuating quite severely. Almost all of those patients were, indeed, fluctuating. So, from that standpoint, yes.

DR. HALLETT: One more question. Was the dysarthria always controllable when it was seen in the setting of DBS? In other words, could it always be changed so that there was no dysarthria but there was a tremor effect?

DR. COSTELLO: I am not sure about all this.

DR. HARKNESS: I have to admit I am not sure about it always, either. But, indeed, for most dysarthria patients, changing the stimulation parameters did change the side effect.

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DR. HALLETT: Right. I understand that it made dysarthria better, but when it was reduced so that dysarthria was better, was the tremor still controlled. I guess that was the question.

DR. COSTELLO: Stimulation on did still cause tremor suppression.

DR. GATSONIS: Did the sponsors submit to you the protocols of the studies that you showed us the data?

DR. COSTELLO: The sponsor submitted the protocol for the U.S. tremor study for the long-term efficacy study which was the subcohort of the Swedish patients from the European tremor study.

DR. GATSONIS: Do these protocols specify planned sample size and planned observation time and were these sample size and planned-observation time adhered to?

DR. COSTELLO: No. Because of the dramatic effect, FDA considered looking at the data with a much smaller sample size number than was originally projected for the study. I don't know offhand. I cannot remember offhand. In addition, we did require that they had the U.S. tremor study go out to 12 months. Again, because of the dramatic suppression, the company came in with a proposal to do this long-term efficacy study in the European subgroup.

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DR. GATSONIS: So, if it would be fair to summarize, then, that they were planning a study with many more patients and a longer observation interval and this was curtailed because they got good results.

DR. COSTELLO: Exactly. Some of the patients did reach 12 months. Not all of the patients reached 12 months.

DR. HARKNESS: May I respond to that? I want to make sure that we are clear. A prospective sample size was determined in the U.S. study for the three-month follow up. A prospective sample size was determined in the Swedish protocol or the European long-term protocol. There was not a sample-size justification for the European long-term study or for the safety study.

DR. GATSONIS: What were the two sample sizes, if you remember.

DR. HARKNESS: I'm sorry; I don't remember right off the top of my head. Actually, in the European long-term study, the figures you saw were very close to what that sample size had been justified at. For the U.S. three-month study, the sample sizes were actually a little smaller. The determinant sample sizes were actually a little smaller than what you saw submitted. We didn't analyze any data, though, until the patients you saw were analyzed.

DR. GATSONIS: So you had determined that sample

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size in 1993 or whenever you started the study.

DR. HARKNESS: Right.

DR. GATSONIS: For the three months.

DR. HARKNESS: That's right.

DR. GATSONIS: So you were expecting, up front, that you would see a homerun kind of an effect.

DR. HARKNESS: Yes; frankly, based on the literature and what had been published before that time, we did expect to see a homerun kind of effect. I think that is a fair statement.

DR. COSTELLO: May I make just one other comment. FDA did propose to the sponsor that we would like a randomized, double-blind controlled study of these patients so that we could, in fact, determine whether stimulation caused progression, whether medications were having an effect in both arms.

What we proposed to the sponsor was that they use a low stimulation group and a high stimulation group, optimal stimulation group. However, the sponsor stated that this was not ethical because there was so much literature and, in addition, the patients would be unblinded, unmasked, just because of their dramatic tremor suppression.

In some cases, they are, in fact, able to feel that the stimulator is on by these paresthesias. So, again,

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it would break the blind.

DR. GATSONIS: I have one more question. Do the protocols specify how were the patients selected for these studies and did the sponsor give you information as to, for instance, how many patients came along in a consecutive series in any of these sites, participating sites, and were rejected, and so on. In other words, my concern is that there may have been patient selection for a particular number of reasons that are not represented in the database.

Depending on what kind of selection it is, as you know, this could give you this type of result or another type of result. Were these consecutive series of patients in every site?

DR. COSTELLO: The patients had to meet certain inclusion, exclusion criteria. The inclusion, exclusion criteria required that they had a tremor score of at least 3 or 4, that the functional disability that the patient had was due to the tremor, not due to the other symptoms of Parkinson's disease, that the patients were drug refractory as determined by a neurologist for at least three months.

In the case of the essential tremor patients, I believe they had to be off all medications at implant time. In the case of the Parkinson's disease patients, they had to have constant medications for at least one month prior to

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implant.

In addition, the patients could not have any supraspinal or any other type of CNS disease besides essential tremor or diagnosed Parkinson's disease.

DR. GATSONIS: I understand the visual inclusion, exclusion criteria, but my question is like this. Let's say the University of Kansas or any of the participating sites, consecutive patients came in. Somebody checked whether they met the inclusion, exclusion criteria or not, or whether they hit off on one of the exclusion criteria. If they did meet the inclusion criteria, they were given the implantation.

Was there any other selection beyond that. That is what I am saying.

DR. COSTELLO: Maybe Dr. Koller could address that.

DR. GATSONIS: And do you have patient logs to address that question?

DR. HARKNESS: Just in response to Dr. Koller, Dr. Koller had to leave rather unexpectedly, but Dr. Olanow, would you please address that.

DR. OLANOW: Yes. I think that the criteria are fairly stringent. The number of people that have tremor-dominant Parkinson's disease is relatively small.

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That, perhaps, reflects the fact that you are looking at a somewhat select subgroup. Usually, they have a somewhat more benign course which is why they have this long latency of eight to ten years.

Every patient that met the criteria of having a 3 to 4 tremor and was drug resistant, could not be controlled for drug, was offered the procedure. A substantial number did not accept the procedure but that was the primary reason for turning them down. There were no competing studies for which they were otherwise being randomized and failure to be controlled by medication was an entry criteria.

DR. GATSONIS: Do you have a lot that shows essentially how many patients were not included in the study?

DR. OLANOW: We do at our site. We keep a record of all patients who are screened and why patients are not screened for every trial we do.

DR. COSTELLO: Could I just make one additional comment. I am not sure either the firm or I adequately addressed that there is a trial-stimulation, either intraoperatively--that the neurosurgeon does see the suppression. If an investigator did not see the tremor suppression immediately--he would watch the patients to three to seven days.

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In some cases, they would go back a second time to see if they could provide lead placement that would, in fact, suppress tremor.

DR. HARKNESS: Actually, the protocol requirement required that there be tremor suppression in the operating room. Otherwise, the lead was not to be implanted. There were no requirements for long-term screening of these patients as has often been the case for stimulation for pain applications. Either you saw tremor suppression in the operating room or, if not, the patient was not implanted.

DR. GATSONIS: Can you give us a sense of in how many patients you did not see the tremor suppression?

DR. HARKNESS: In the U.S., that was three patients, I believe, who had basically--they were unable to find the site in the operating room.

DR. GATSONIS: So it is a very small number compared to the total number that you considered.

DR. HARKNESS: It is a very small number; yes.

DR. COSTELLO: I presented a slide which may directly address that, that, out of 84 patients, only seven were not implanted. In fact, just to clarify, again, one patient did have a first attempt during the procedure, through consent. And the neurosurgeon came back a second time and tried to place the lead and the patient did not

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cooperate.

DR. CANADY: I was just curious, in the place where they kept the logs, did you have the same kind of sex discrepancy? Is it reflected in the exclusion criteria, a reflection of tremor-dominant--I mean, there is such a disparity of sex--

DR. HARKNESS: I will ask Dr. Olanow to respond to that for his log. I want to make clear that Medtronic did not require such logs to be kept.

DR. OLANOW: One of the peculiar things about Parkinson's disease in trials is you see the same kind of imbalance in almost every trial. I don't know why it is but, invariably, we seem to have more male patients than female patients. There was no attempt to include or exclude any patient based on sex.

DR. WILKINSON: I had a question for Mr. MacFarland. In the engineering concerns that were given to the panel prior to this meeting, a number of questions were raised and the comment was made several times, that the manufacturer was asked for additional data. One of the questions, for instance, is is the extension lead safe as it runs over the clavicle and the constant movement across the clavicle.

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From your presentation, I had the impression that FDA received the information that was requested and deemed that it was satisfactory; is that correct?

MR. MacFARLAND: This is an interactive review so we will work directly over the phone or through fax. So, due to its interactive nature, there are quite a few submissions of information and review.

On that particular issue, they did provide somewhat of an analysis on the issue of the clavicle and that extension in that the tissue ingrowth somewhat protects the lead. In their analyses, they took some of their leads that were implanted in animals and they tested them on the bench for their fatigue properties afterwards.

So, yes, they responded. I expect to ask them how did that bench testing mimic what you would see clinically, in the clinical environment. We will get a response to that as we continue the interactive review.

DR. WILKINSON: That leaves me still a bit uneasy because the panel is being asked today to vote on a recommendation. And now we are being told that there are lots of loose ends.

MR. MacFARLAND: I think the issues that I have raised--we feel that the sponsor definitely has the ability to investigate these issues. They have done quite a bit of

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testing. I feel it is a clarification of results, a little follow up to make it clear to us what their testing was, how they determined the path-cell criteria.

I don't think the issues we brought up point out testing that is going to take years and years. I think it is something that has been in the works and we just need to follow up with it.

DR. CANADY: Some of the answers to that question, I think, are already in the papers. Speaking like an old shunter, the prospect of bringing in tubing over the clavicle sounds like it is more difficult. But, in fact, we technically have more difficulty with fracture of lumbar catheters coming around the abdomen.

I think if you look at the safety study which was the spinal implantation, you actually saw a higher incidence of that cable fracture there than you did coming across the clavicle which would have been what I would have expected from my experiences with shunting for hydrocephalus.

It is something that sounds like it should be more of a problem but, technically, you actually see the opposite.

MR. MacFARLAND: That is why we posed the question and allowed them to answer it. That is the way this process

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has been going.

DR. HALLETT: In terms of long-term, say there is a patient who gets a lead put in and, for five years, things go well or for six or seven years, things go well. And then, at that point, it no longer works. Do we have any sense about how difficult it might be to take the lead out at that point?

We have heard that there were leads that have been taken out at about one year, I guess. Is that what you had mentioned? But do we have any sense that it might be more difficult at a longer period of time? As we get into clinical practice, it might be that leads might be changed at five years down the road or ten years down the road, or something of that sort.

Is there any difficulty with that, perhaps?

DR. COSTELLO: Basically, we are asking you for a recommendation upon that in terms of the labeling of the device. That is in one of the questions that we are going to ask specifically of the panel after this discussion.

Two patients were explanted, one at three and four, and one at 12 months. I believe, in all cases, the whole system was removed. However, in most of the informed consents that we have that sponsors submit to us for brain stimulation, we do request that they inform the patient that

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the lead may have to be left in place because it may cause more damage trying to, in fact, explant it.

In this case, there were no patients. I do not believe there were any patients who had multiple leads in place; in other words, they had one and it broke and it migrated and they put in a second one without removing the first.

And there were no patients, I do not believe, who had two leads implanted.

DR. HARKNESS: There were no patients who had more than two leads implanted at the same time. As far as explant, I would actually like Dr. Wilkinson to respond to that.

One other comment I have, though, is that, in watching Mr. MacFarland's presentation, Medtronic believes that, indeed, we have already responded to those issues. Some of those responses, as he indicated, are via interactive review and some of them have occurred within the past, say, two to three months and may not have been entirely resolved at this point.

But we believe that we have fully and completely responded to those outstanding issues.

DR. WILKINSON: Without finding problems.

DR. HARKNESS: No; we don't believe we have found

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any problems.

DR. S. WILKINSON: In terms of explanting the DBS lead, the only experience I have had is up to one year. There was no problem with removing the lead at that time. I don't think that pathologically, or physiologically, an extra amount of time would make any difference. We certainly have experience with other things similar in devices for epilepsy that were removed without difficulties.

DR. WILKINSON: One other point that I saw raised in the FDA literature prior to this meeting was a question about the polyurethane material that would be left in contact with brain tissue. I have not heard any discussion of that, really, today.

DR. COSTELLO: I believe that Ms. Morris did the review of that. She could address that issue, please.

MS. MORRIS: The firm has provided a substantial amount of test data on biocompatibility issues. I just haven't completed my review of it. There are a few outstanding issues that I want to discuss with the firm, but I think that we can come to a resolution with the data or maybe request some additional testing.

But, for the most part, I think they have adequately addressed it.

DR. WILKINSON: So, again, the panel is being

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asked to vote today but do we have sufficient information in the eyes of the FDA.

DR. COSTELLO: I think FDA agreed to bring this PMA to panel because we believed there was sufficient safety and efficacy information especially for one indication. We are asking you for recommendations regarding the other. FDA would not have brought the PMA to panel if there were what we consider major deficiencies.

In other words, if Ms. Morris felt that there was a major problem with the polyurethane, we would not have brought it to you at this point. Similar issues regarding Mr. MacFarland's engineering review; if there were things that we did not feel we could resolve through interactive faxes and submissions, we would not have brought the PMA device to you today.

MS. MORRIS: I would be happy to go through some of the details of the biocompatibility based on my recollection of what I have reviewed so far. We focussed most of the presentation on the clinical section and minimized the amount of engineering and biocompatibility summary because of the limit of time in addressing all the issues.

But I can touch on the highlights if that would be helpful.

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DR. WILKINSON: I assume the inference is, then, that if the clinical data proved that the device was safe, then biocompatibility was proven also?

MS. MORRIS: Biocompatibility was kind of an illusive topic to address in great detail. Of course, in the review of a premarket approval application, we are considering risk/benefit. With respect to polyurethane, it has been used widely with a long historical use in other medical devices.

The issue I raised was the fact that it was implanted in brain tissue in contact with CSF. That is a different issue that we have to look at different endpoints. The standard biocompatibility tests do not address the potential physiological effects of the material.

The data that has been provided by the firm discusses and approaches the histopathological effects, so the local effects in the tissue. But whether there could potentially be long-term neurotoxic effects, we still don't know, at this point.

The best estimate I have been able, or the approach that I have tried to take, is to look at the material characterization and to see if there would be any constituents that would show, based on our knowledge of neurotoxicity of various compounds, whether or not there

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would be any kind of predictor of some neurotoxic effects.

As far as I know, there aren't. So, based on the information we have, we think that it is a fairly safe and biocompatible material. But we never have a complete assessment of biocompatibility for all products in all target tissue areas. It is more of an assessment.

Does that answer your question?

DR. EDMONDSON: I was wondering if we could make some reasonable extrapolations with regard to devices used outside of the brain. Polyurethane is really a controversial issue, of course, with breast implants and the sole issue of--

MS. MORRIS: The controversy is more with the silicone materials.

DR. EDMONDSON: Right; but the query has been raised with regard to its carcinogen it could be. I was just wondering, by sheer volume, the hardware that has been implanted elsewhere that might have been polyurethane coated, if there is any post-marketing data to support biocompatibility in those areas.

MS. MORRIS: I am not aware of any documented literature to suggest that it would be carcinogenic. I am not aware of any prospective studies to actually look at it. I would have to look into some of the other device areas to

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see when we address biocompatibility if they actually performed actual tests for carcinogenicity.

DR. EDMONDSON: This whole issue of silicone, for example. The brain is immunologically a privileged organ. There are no lymphatics and so on and so forth. So, in large part, brain tissue may have greater tolerance for certain types of foreign bodies.

So the whole issue of polyurethane, again, at least to make a comparison context--I mean, what else is out there that is polyurethane coated that, device-wise, is put into the body elsewhere? How safe are these things?

MS. MORRIS: Is your question what other medical devices in other parts of the body where it has been implanted?

DR. EDMONDSON: Right.

MS. MORRIS: Well, you have pacing leads. You have various other catheters. Does anyone have any other recollection? There is a large use of polyurethane. But the unique thing about polyurethane is that there are numerous polyurethanes. There are differences between one polyurethane versus another, so one polyurethane can't be compared to another in various cases.

So you are going to have a different biological response potentially.

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DR. EDMONDSON: But, even with the query of controversy, is it related to a specific class of polyurethane, or is this just a general--

MS. MORRIS: You can say that silicones can be a part of a class of silicones. But I am not aware--I think that the polyurethanes are a slightly different animal. I am not an expert on polyurethane, but it was my understanding that you would have classes but there are numerous classes.

The polyurethane that I am aware of that is used for this device is Polythane ADA. The various delineations of the different materials have a lot to do with what material properties you want, whether or not you want a different durometer, the ductility of the material. So that is why there is such a wide variation.

DR. EDMONDSON: So, at least, is there precedence? I guess that would be the--

MS. MORRIS: There is a precedence. Pelethane, ADA, I believe is also used in pacing leads.

DR. KRAUTHAMER: May I just add something to that? In the histology, we have very good samples of lead tracks, millimeters and millimeters of lead tracks. Typically, there is a very thin connective tissue sheath that forms around the lead track and a very, very mild tissue reaction

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outside that sheath, all within several hundred microns of the lead track.

So the brain is a privileged area, as you mentioned, and there isn't much of an inflammatory response.

Panel Discussion

Primary Panel Reviewers' Comments

DR. WILKINSON: Now, the panel has to actually go to work. We have to earn our keep. The next part of this process is really going to be in three phases. We have three primary panel reviewers, Dr. Gonzales, Dr. Hallett and Dr. Gatsonis. We will hear from each of them.

Then we will go around the table and ask each panel member to comment, keeping in mind the specific questions that were raised by the FDA. When we get to that part of the procedure, I will try to summarize those questions.

Then the third part of this panel activity, intrinsic panel activity, is actually coming to a vote where we can vote to approve, to approve with conditions but specifying what conditions, to disapprove and on what grounds. Disapproval doesn't mean stop the research, of course, but it just means disapprove for now.

So that will be the third part of the activities

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still ahead of us. The first reviewer is Dr. Gonzales.

DR. GONZALES: I have sent my own review to all the panelists regarding the information that was sent to us so I am not going to reiterate any of the review. I think that has been done extremely well. What I will do is I am going to be passing out--I have passed out to nearly everyone except for the last two people at the table over there and Medtronic. If you wouldn't mind passing those out to people who have not received them.

I have written out my issues, questions and comments because, after reviewing the material, because of the number of issues, comments and questions that I have, 29, in fact, I really felt that to follow along, it would be important to have this written out so that you can see what the question is or my issue or the comment.

A lot of that has been modified through these presentations and what the sponsor has mentioned already. So it won't be quite as painful as it sounds here with the numbers. But I would like to go ahead and ask or pose these issues and comments.

I have broken them down into--again, this is based on the information that was provided prior to this meeting. I have broken down my issues, comments, questions into three areas; first, what I feel are safety issues alone; efficacy,

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and efficacy alone; and then, finally, where it is really hard to distinguish between both safety and efficacy or where it really involves both, in terms of the issues, comments or questions.

The first that I would like to pose, on the first page, is, as it states, if a charged density in excess of 20 microcoulombs/cm² is potentially neural damaging, can the amplitude, pulse and combinations that produce a charged density of greater than 20 microcoulombs/cm² be locked out?

In other words, is it possible to lock out any harmful or potentially harmful settings with this device? I think that accidents are going to happen and the potential for creating an overcharge or a charged density that is potentially neural toxic based on what we have seen already is there.

Is that something that can potentially be done by the company?

DR. S. WILKINSON: May I respond? We have done something in regards to that. The manner in which we have locked out is by cautioning in the labeling that there are certain parameters into which you should not go, or that if you go into that area, you, as a physician, need to understand the risk involved in going into that area.

The particular charged density issue that you are

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talking about here is, again, at least from a clinical standpoint, nothing that we have seen specifically in regards to adverse events or anything of that nature.

DR. WILKINSON: The controller device does allow you to set those parameters for any given individual anytime they come in to be readjusted; is that correct?

DR. S. WILKINSON: That's correct.

DR. GONZALES: But there is no lockout, per se; that is to say that you can never exceed a certain combination that is potentially neural damaging.

DR. HARKNESS: There is not lockout per se. I think that is true if you are referring to hardware, software, types of issues.

DR. GONZALES: The next two questions, really, I think have been answered but, also, with the third question about the helical coil and induction of electromotive forces that occur because it is a coiled, deep-brain stimulator lead. I think that you have probably answered some of the questions there.

I do have a question, though. What will happen if a patient has a pacemaker or requires a pacemaker--not that you have already excluded that. You have indicated that people should not go into an MRI machine or have pacemakers placed, but is there any information--I couldn't find any

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regarding the deep-brain stimulation and for pain in terms of whether that has ever been reported and what might happen in that situation.

DR. HARKNESS: I am not aware of any information that has been reported. What I can say is that I know Dr. Lozano has, indeed, had cause to place one of these patients in an MR system. If you would like, he can certainly comment on that.

DR. LOZANO: With respect to the implantation of the leads in the brain, we do our surgery in two stages. The first stage involves implanting the lead. On the second day, another day, we put in the pacemaker. We routinely obtain post-operative MRIs on our patients to confirm the position of the lead

What we don't do and what we have no experience with is doing the MRI after the pacemaker is in place. But I do know of other centers that have, indeed, done this. They turn off the device and patients have had their MRIs with the IPG in place and they have not reported any adverse effects.

So it seems to be safe to do that if it is necessary.

DR. GONZALES: There is some information on deep-brain stimulation following thalamotomy. One of those

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reports was the Portenoy article in 1986. What was interesting in that article is that he also brought up many issues cognitively that can occur to patients who have bilateral thalamotomies or deep-brain stimulation including issues of short-term recall, verbal visual-spatial information loss, the fact that some patients, as you mentioned, can become aphasic, a unilateral neglect and a number of other issues that I have listed here including generalized arousal and endocrine effects.

Since these were not really looked for and, in the design of the study, you are going to find basically things that you are looking for. Unless that side effect slaps you in the face or is quite profound, you may not find subtle effects like the neurological changes.

I am wondering if, in the design of the study, since this is such a major issue, at least with the European study where bilateral placement and, since you are asking for approval for bilateral placement of these leads, it seems to me that the neurocognitive aspects or results of doing bilateral lead placements are incredibly important.

That has really not been looked at. You have done the MiniMental Status testing but, as far as cognitive impairment, what happens to these people long term, or even short term. Unless you ask the right questions cognitively,

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with some of the subtleties that can occur with these patients, you are just not going to see that.

We are a little concerned that these studies have not been done especially with the bilateral. That is really more of a comment than a question.

Do you have anything to say regarding the kinds of study that the Europeans may have already done?

DR. HARKNESS: Sure. In the published literature, there has not been any concern such as you are talking about elicited and there have been some of the neuropsychological testing done and reported in some of the articles. But, to my knowledge, this has certainly not been an issue in Europe where they do a number of bilateral patients.

I will let Dr. Hubble and Dr. Wilkinson speak to that as well.

DR. S. WILKINSON: In our group of Parkinson's patients, we have ten that we study with neuropsychological testing before and after the surgery. There has been no statistical change in any of the tests, no significant change in standard deviation in any of the testing parameters with DBS.

DR. GONZALES: That was with formal neuropsychological testing?

DR. S. WILKINSON: Yes.

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DR. HUBBLE: Similarly, although I can't quote you the actual tests that were implemented, Benabid's group in their summary report of 100 deep-brain stimulation for tremor patients--I think it is in the supporting materials, maybe a copy of that manuscript, Journal of Neurosurgery, 1996--they did, in fact, formal neuropsych testing on all their bilateral stems and report no significant changes.

Again, I apologize. Neuropsych is not my area and I can't tell you exactly the test procedures used but it was formal full neuropsychological testing.

DR. WILKINSON: Is that also true for dysarthria, dysphasia?

DR. HUBBLE: That becomes a more complicated issue. If we are talking about unilateral stimulation, I think we have already addressed that to some extent. In our hands, the U.S. tremor study, we had no patients with persistent dysarthria as an ongoing limitation following parameter readjustments.

I have never been actively involved with bilateral stimulation for tremor here in the United States. So here I am going to quote you chapter and verse from the European studies. But my understanding is, in fact, as you probably would expect, anatomically, you do have a higher occurrence of dysarthria with bilateral stimulation.

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The number I am going to quote you, and I think this is right, is about 20 percent. Again, that was in their bilateral stimulation, the European experience, for tremor control.

Also, my understanding is that again that would remit. None of that was permanent dysarthria. It always remitted with either discontinuation of one side stimulation--that is, the patient could turn off their device--or readjust the parameters.

It is, I think, noteworthy in that European experience, they do have patients with a thalamotomy on one side and a stimulator device implanted on the other. Now, dysarthria rates start running 40 percent plus, some of which did not remit well, is my understanding from that report.

DR. LOZANO: I have a comment about this issue of memory and visual-spatial side effects. The thalamus is segregated into 60 subnuclei. You have to be in VIM to get an effect on tremor. We don't anticipate any cognitive effects based on the cognitivity of VIM with the motor cortex.

On the other hand, the pulvinar, for example, which you have mentioned, is a visual-spatial-association thalamic relay. So we would expect side effects related to

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visual-spatial disorientation if we place our electrodes in the pulvinar.

Similarly, if we place electrodes in other nuclei in the thalamus that have connections to the limbic system, we would expect cognitive and memory disturbances. So the disturbances and the side effects are very much a function of which site on the thalamus is chosen.

I think that, based on the anatomy and physiology of VIM, we would not anticipate any cognitive dysfunction with stimulation VIM.

DR. GONZALES: Something that has come up during the discussions here, and on page 2, the first question that I pose here, in the three safety and efficacy studies, patients were to be drug resistant as part of the selection process for entering these patients into the study.

Yet, the essential tremor patients did not come off their medication in the European study. The second question on that list, and it shows the location of the statement, "Though patients were asked to discontinue the medication the night before the evaluation, many of them refused to discontinue stimulation for that period of time due to logistics and travel."

What does that mean; they refused to turn off their stimulators and remained on the medication and they

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did this due to logistics and travel?

DR. HARKNESS: I will answer your second question first. In the European long-term tremor study, this was a concession to the patients who complained that they did not want to come in. Indeed, they were off medications the night before. They felt, though, they had to have their stimulation in order to travel.

When those patients did come in to the center, the stimulation was turned off and then not turned on again for at least four hours after that.

In regards to the first question, with the ET patients, the European trial did not require that patients come off of their essential tremor medications. Indeed, it required that they, basically, not change their medication regimen as they were enrolled in the trial at the beginning of the trial.

Obviously, a number of patients did come off during the clinical trial.

DR. GONZALES: Although it was put earlier in a positive light that here we have an opportunity to see patients remaining on their medication, and so you could see the end result of stimulation not only without medication but with medication. By remaining on medication, it would suggest to me that the essential tremor patients were, in

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fact, not drug resistant, that they remained on the medication because it was helping.

Yet, by exclusion, they were supposed to be off medication because they were refractory.

DR. HUBBLE: I guess I would offer the following. I would not use the term "drug resistant" for either of these patient groups, either in the European experience or our own. I would say, instead, these were individuals who persisted in having disabling tremor refractory; in other words, the medications could not afford a sufficient degree of relief of their disability referable to tremor.

To me, as a clinician, that is very important distinction to drug resistance. In fact, and in a way of clarifying the information presented a moment ago by the FDA in terms of ET patients, essential tremor patients, and their medicines, all of our patients were actually withdrawn prior to their baseline visit and they were off drug for 30 days.

My understanding is that then, subsequently, two protocol violations, I believe--that is two patients who were placed back on primidone. I think both of those were placed back on primidone following that three-month blinded efficacy visit.

But, again, I would not consider these people to

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be drug resistant in the sense of no effect at all of medication but, rather, that attempt was made to optimize conventional medication and they still had severe disabling tremor.

DR. GONZALES: Regarding one of the statements in one of the summaries--well, actually, the summary by the sponsor, page 113, 83, was this a mistake in terms of the numbers, 83.3 percent of patients in the U.S. tremor study had headaches?

DR. HARKNESS: That is a misprint.

DR. GONZALES: Because I did see it in the context of the information that it was a different number. But when it was stated on the table, it did say 83.3 percent. I am assuming that that is incorrect, that that is the incorrect number. I don't remember what the correct number was.

DR. HARKNESS: That is incorrect.

DR. GONZALES: There is a question I have regarding the issue of lead migration. Because of the potential for obviously long-term serious complications, in the European basic safety study, what is the difference between lead migration, 5 out of 178 patients and lead dislodgment, 2 out of 178 patients. There may be a neurosurgical term or something to make that distinction.

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DR. HARKNESS: Generally, with lead migration, we were thinking that the lead, itself, will actually move within the brain--that is, actually move out of position. Lead dislodgment was generally to be taken as some physical act moving the lead, for example, a blow to the head or, as Dr. Koller indicated, a problem in surgery earlier.

Something that I think is important to keep in mind; this was a report from the physician and, to my knowledge, these were not verified, for example, using neuroimaging technique and comparing implant time to post-implant.

DR. GONZALES: The next several questions on page 2, from the Benabid study, I think you have answered already regarding bilateral thalamotomies and the review that he did on that plus the patients that he actually bilaterally implanted and the neurocognitive aspects.

But, in the Benabid study, he states that Parkinson's patients have suppression of tremor for up to eight years. Is that correct, and is that the only study that shows--for efficacy, that becomes really, in my mind, a major issue in terms of how long. Since we have information indicating 12 months or less on some patients, and the fact that, in presenting evidence that is efficacious for that

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period of time, I would like to also know, or feel comfortable, that this is going to extend beyond a one-year period. The only information that I am aware of is that Benabid study.

Are you aware of any other information that indicates that there is a longer period of time of efficacy of bilateral stimulation?

DR. HARKNESS: No; I am not aware of a longer time point. Keep in mind that Professor Benabid implanted his first patient only about ten years ago. So, going out, there is not a lot of data and he is the one who has, by far and away, the most experience. So eight years probably is the longest he has out for efficacy.

DR. OLANOW: If I could just add on his data. One of the things that is noteworthy is eight years down the road, the magnitude of benefit remains the same. And when he turns the stimulator off, the benefit continues to disappear back toward a baseline level so that the kinds of effects that are being described at 12 months, he has continued to see through eight years.

DR. GONZALES: In regards to that, on Page 3, the third question down, in the Benabid study, he showed that there were microthalamotomy effects in 23 patients. Yet, except for the U.S. tremor study, patient 007, there were no

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microthalamotomy effects at all.

I think it is best expressed by one of the slides that shows that, in fact, the patient really remained on the off position of the lead, that the baseline never changed so that, initially, after surgery and certainly delayed downstream in time, the patient never declined further.

But I am wondering why, what led to no microthalamotomy effects in your study as opposed to the Benabid study where 23 patients, in fact, had that benefit.

DR. HARKNESS: We didn't list microthalamotomy effect as one of the adverse events. It wasn't considered an adverse event. Certainly, I can ask Dr. Wilkinson and Dr. Lozano to discuss their experience with this effect.

DR. OLANOW: Let me also mention that he used a slightly different technique. He uses a holder that puts five electrodes down more or less at the same time so that he is doing microelectric recordings with five electrodes simultaneously whereas others of us, in our group, used single microelectrodes all at one time.

If we are comfortable where we are, we try to minimize the number of passes through the brain. So I think he used a greater number of passes through the target region and that may have accounted for why he had more of a thalamotomy effect.

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DR. GONZALES: That is interesting because the way he describes it in the paper is multiple passes but he doesn't describe multiple passes simultaneously.

DR. OLANOW: He does do it simultaneously. It is a ring that holds five electrodes and he puts all five in through that ring all at the same time.

DR. GONZALES: He is doing that now, but did he do that eight years ago?

DR. OLANOW: I can't remember if he did it eight years ago.

DR. S. WILKINSON: I think that was the case. I think it depends on how you want to define the term "microthalamotomy" because it is not uncommon at all for our patients to have suppression and tremor the next day up to two to three weeks after the surgery.

By that time, almost all the time, it comes back completely. There is, I think, one patient who presented who had a persistent thalamotomy from the lead placement that Andres talked about earlier. But it was not uncommon in our series to see that as a temporary thing.

Those people, as they were followed on, continued to have tremor at either the 3 or the 4 level, whatever they had initially.

DR. GONZALES: One other question on this page and

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that is, in the FDA summary, there is a statement that says no failures on the bench but six failures clinically. My question would be is the bench testing prior to clinical trials rigorous enough. That was on page 5, section 4, book 1 of the FDA summary.

DR. HARKNESS: Do you recall exactly what it was in reference to?

DR. GONZALES: This is a preclinical testing of the device, itself, the leads and the extension.

DR. HARKNESS: But six failures clinically?

DR. GONZALES: Right.

DR. HARKNESS: Do you recall what the failures were or anything?

DR. GONZALES: It was a variety of failures in terms of either the IPG, the extension or the lead, itself. If you add all those together, there was a total of six failures. Yet, in the preclinical trials regarding testing, looking at all three segments of the device, there were no failures.

DR. HARKNESS: One thing that, I guess, needs to be clarified; the term "failure" is often used, perhaps, a little more liberally than it should be. Physicians will, for example, tell us they have a failure.

When we actually get the device and analyze the

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device, indeed, there was no failure. Something else was going on and it may be in reference to that sort of thing.

DR. GONZALES: Just a comment regarding--since the sponsor is using deep-brain stimulation for pain as a comparison to justify thalamic stimulation, looking at the literature, and some of the literature that I am familiar with with deep-brain stimulation, and if you gather all the information of the six major studies in deep-brain stimulation for pain, the malfunction rates of the systems, even 15 years ago, are very similar to--this is just a comment. This is not necessarily a question that you need to answer--were very similar to the failure rate of the present study; that is, the U.S. tremor study, 7.2 percent and other studies ranging, again, from about 8 to 15 percent.

So there really isn't a great deal of difference even though there have been a large number of changes in terms of a stimulator. I think this is kind of leading to the fact that you have not changed the lead from the spinal-cord stimulator. You are using that same lead presently.

DR. HARKNESS: Indeed, that is not the same lead. This is a different lead from our spinal-cord stimulation leads. It is based on the same technology but it is not

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exactly the same lead by any means.

DR. GONZALES: I think I am going to stop right there and we will have some other questions or comments once everybody else has spoken.

DR. HALLETT: Most of my comments, I guess, are relatively simple. Much of the stuff which I wanted to talk about has already been said but I would like to emphasize it from a clinical point of view. The questions that I have had in terms of what I picked up during the reading, I have already asked, by and large, during the course of the presentations.

ET is a monosymptomatic illness characterized by tremor in action which can be functionally disabling. Oral medications are useful but there is a large population of patients who cannot find relief with the current therapies and new treatments are certainly welcome.

Thalamotomy is already an accepted treatment approach and, to a certain extent, I think that we have to compare DBS to thalamotomy. PD, on the other hand, has multiple aspects of which tremor is only one.

Tremor is characteristically present at rest in that circumstance where it can be a cosmetic problem. That isn't to say that that isn't bad. Cosmetic problems can be bad, also, but the tremor can be present in action also in

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Parkinson's disease and, in that circumstance, interfere with function.

However, it is clear that the most important problems with Parkinson's disease are bradykinesia, postural instability, and freezing. In the life span of patients with Parkinson's disease, tremor may be the chief problem at one time but it would seem likely that other problems would become significant over time to the patients.

On the other hand, as has already been pointed out here a couple of times, Parkinson's disease has several different clinical presentations one of which is a tremor-predominant form. Bradykinesia is, in fact, less important and perhaps many of the patients that have been studied and have been presented here have been the tremor-predominant form.

In any event, in terms of the possibility for treatment of Parkinson's disease, there are many of them. But I don't think, at the moment, any are really optimal and none have been demonstrated to be long lasting. The only long-lasting treatment at the moment which I think has been out there is, once again, thalamotomy which has been used for a long time for tremor in relation to Parkinson's disease.

So I think that, to a certain extent, the benefits

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of DBS need to be judged with respect to thalamotomy which is an alternative treatment directed to the same anatomy and the same physiology. It is just in a different mechanism. But it is relatively directed in the same way.

With regard to thalamotomy, I think that we have heard that there is an increased incidence of dysarthria in that circumstance. We have talked quite a bit about how, with DBS, dysarthria would be less of a problem.

Additionally, thalamotomy probably can't be used bilaterally whereas DBS can be used bilaterally. That may be a substantial benefit of DBS over thalamotomy in that regard.

In relation to the clinical data that has been presented, I don't want to go over that in any detail. It has been gone over quite a bit. I think that, to me, one of the important things just to note is that, while the studies have been said to be randomized, double-blind studies, the randomization and double-blindedness referred only to the assessment part of it.

It wasn't a randomized, double-blind trial in the sense of randomized, double-blind trials as we ordinarily think about them. There really was no population of patients that was not, in fact, treated. So I think that that is just part of what we have to deal with in this

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particular situation in terms of understanding the data.

In terms of ET, I think the evidence for efficacy seems to be very, very strong. It is a dramatic effect. The word "home run" was used earlier and it seems to be very clear. There is clear improvement in functional scales.

There are a number of points back and forth that we have debated details, but it seems to me that it would be hard to argue against efficacy in the matter of tremor.

I guess that is all I would want to say about that.

In terms of Parkinson's disease, the evidence for tremor is also reasonably strong, but I think it is equally clear that there is no good evidence for benefit in any of the other aspects of Parkinson's disease and functional improvement for the patient is not really major.

Tremor relief for some of the patients is valuable, nonetheless. Patients must continue anti-Parkinson medication and needs for medication might still increase. The long-term question for me is whether alternate surgical intervention might be needed sometime in the future and whether, therefore, alternate sites for surgery might be better.

That is an interesting issue that hasn't really be discussed here today.

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Concerning bilateral stimulation, it is clearly possible for both ET and Parkinson's disease. The data are not extensive as we have already heard although I think that it does seem clear that benefit is better bilaterally for patients if they, in fact, need bilateral treatment. Complications don't seem to be too much increased.

In relation to explanting leads, which we have talked about somewhat, this has been done largely for lack of efficacy. It appears to be done without complications. I was concerned about explanation after long periods of time but it sounds like that isn't a real important problem.

I guess those are the most important things I wanted to say.

DR. WILKINSON: Thank you.

Dr. Gatsonis, you were our third primary reviewer.

DR. GATSONIS: Since I was high on the list of those who have the most questions, I will make my comments very, very short. I will give an overall evaluation of the studies in order to place them a bit in a context and sort of address somewhat the generalizability of the findings of these studies because this generalizability, I think, is what is relevant to the questions that the FDA is asking.

The way I see it, the two randomized studies that were presented involved a relatively small number of

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patients. They were fairly straightforward in terms of the basic design, the basic endpoint. The statistical analysis for the basic endpoint was straightforward. I don't think anybody would argue with that sort of presentation about the two small, randomized studies that were presented.

I say small because with the number of patients and with the scope of these studies, you really don't have the leeway of looking at subclasses of patients to answer various other questions that may be relevant for FDA types or purposes.

You also cannot assess, really, any effects of, say, differences between centers. If you have three patients here and two patients here and six patients here, you cannot really do that sort of thing very well. You really don't have the power to go through the ramifications of what it might mean that such a device gets approved and it gets used in every hospital in the country where there is a neurosurgeon.

The evidence that we have at this point says that in a small, select number of institutions that were probably involved in developing the lead, there was an effect in terms of tremor, in the short run, and at least the bulk of the evidence is for the unilateral implantations.

If you wanted to go beyond that now and look at

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efficacy as to what would happen in the long run or what would happen if this procedure gets done across lots of institutions without major expertise in this, and so on, it is difficult to know what exactly will happen.

Without this kind of analysis, it is difficult to know, for instance, whether the safety issues that we see are really as a result of having high-class neurosurgeons who are working on this particular study or whether there is something inherent about the device.

Any sort of confounding is difficult to address using studies with 20 or 30 patients. I think that is fair to say and it is also something important for our understanding of how far the results of these studies would be generalizable.

Just to end. Issues about informality of the experimental design and so on were addressed, I think, at least questions that I had were addressed by the sponsors. One issue that we didn't get into is the issue of several instances of multiple comparisons without accounting for it.

For instance, there are probably more p values in the reports than there were patients. I am exaggerating a bit but this is a common mistake. You don't want to see it in the final analysis. At least for the numbers on which you will base a decision, you have to make an attempt to

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control for it.

I think for some of the main findings, the p values that were reported of testing every time, for instance, are so extreme that anything you did to control for multiple comparisons would probably not invalidate the results.

But there was one case, for instance, in the slide that Dr. Costello showed, where there was a series of p values--I think it was for the long term. Then, lo and behold, by month 12, there was a p value of 0.02. Now, there were at least five p values on that line. If you did anything simple to control for the multiple comparison, this was a non-significant p value at the 0.05 level, just to be sticklers about it.

Generally speaking, the analysis for the longitudinal studies, I think, should have been done using longitudinal methods. In the last 15 years, there are a lot of those that have been developed in the statistical literature. I think they would have helped in terms of getting a better handle on the data.

That is all I am going to say.

DR. WILKINSON: Thank you.

Review of FDA Questions

DR. WILKINSON: We will go around the table and

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ask each panel member for a discussion. I believe the FDA questions can be put on the screen. To the panel members, please don't feel you need to run down question 1 through 10 and answer the questions but keep in mind what these questions reflect.

We are asked to advise the FDA of our impressions regarding safety and effectiveness of the device under several different conditions; for Parkinson's disease, for essential tremor and for unilateral versus bilateral implantation.

We are asked to advise the FDA regarding labeling, what are proper indications for the label, precautions, warnings for the labeling. So that is basically what we are asked to do for the FDA. I think all of you recognized that as you came.

The questions are detailed, but the answers don't need to be that precise.

Dr. Canady, would you be our lead-off hitter.

DR. CANADY: I think the surgical issues are not really particularly bothersome to me. I think we have talked about pallidotomy. We have talked about thalamotomy, all of which, I think, are technically more difficult procedures than this represents.

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We have been implanting and explanting various types of small tubes in the brain for a long time. I don't think that represents a major problem. In fact, one thing in my experience that you have more difficulty with is the pocket for the generator than anything else, which is certainly the easiest technical part but the most difficult management part.

So I think the surgical issues are not, to me, really problematic here at all. I think that, relative to essential tremor, I would agree that unilateral disease, there is a strong argument to be made that it is effective.

In Parkinsonism, I would share the issues, again, with unilaterality, that, clearly, there is benefit. It is important to the patients but less clearly makes a dramatic change in their lives, themselves, in terms of life activities.

I think it still would be very interesting to look at, in the population of patients to whom we offer the procedure and those that refuse, I think there is an interesting study to be done in terms of analyzing who refuses and why.

I think it is important for us, if we are going to use this kind of data in the future, to generalize to the population that we understand what those factors might be.

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In terms of the bilaterality, I think the numbers are not there. I think that is more problematic. They are just so small compared to the unilateral numbers that one still has to have concerns about what type of complications there may or may not be.

The final issue I would make is that since hemorrhage seems to be one of the significant potential complications, I would think that there should be labeling specifically referable to coagulopathy and contraindications in patients who have coagulopathy.

That's all.

DR. WILKINSON: Thank you.

Dr. Gonzales, any additional comments as part of your regular discussion?

DR. GONZALES: My feelings, based on the data that has been presented, is that the efficacy is less of an issue to me than the safety issues. I do have a concern about the number of patients that are being used to justify the bilateral stimulation.

When you compare--and the sponsor has made an issue of comparing the thalamotomy versus VIM stimulation, that there is a tradeoff. Obviously, with the lesion, the thalamotomy, this is the permanency, the static nature of what you do is what you get and that is what the patient

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remains with.

But there is a tradeoff also in terms of safety with stimulation and that is the issues that we have talked about with lead migration, device failure, the possibility, still, of delayed injury with these cumulative effect. I am not sure that that has been adequately addressed in terms of the continuous stimulation over a long period of time.

What if a patient requires a pacemaker. Even if it is safe to put a pacemaker, even if it is safe to do an MRI, I think the warning is going to keep that from happening. I think that most physicians are going to be cautious about doing that.

The deterioration, effect, of course, that all patients go through with these degenerative diseases like Parkinson's disease, I have already stated my concerns about the neurobehavioral aspects.

But regarding the safety issue, the one thing that still stands out and I am not sure that we have received the answer yet, is really, if it comes down to if FDA is not able to say that polyurethane is safe outwardly to us, I don't feel I am in the position to say that it is okay or vote for going towards an implantation of a device or a product into someone without that data first.

So I would still like to hear--I realize we are

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now at the point of nearly voting, but to hear from FDA a resolution to that issue of the safety of the polyurethane. If there is no answer to that, then I would have to kind of lean towards waiting for an answer to come up before going in that direction.

Again, that is a safety issue. I think it is an important safety issue. It may be that the answer is there, but I haven't heard it quite yet.

So those are the things that I would like to say right now. I think that is all.

DR. HALLETT: I am not sure I have anything further to say beyond what I said before. I think that the benefit is clear. The issue that we have to face is risk/benefit ratio. I think that it would be my sense that the risks are clearly smaller than the benefit in this case so that the benefit outweighs the risk.

That would be my view in terms of weighing what we have seen. I guess that would be all I would add to what I said before.

DR. GATSONIS: I agree mostly with the summary that Dr. Canady gave. I would add to that that the issue about the evidence on the bilaterality is not just the numbers. It is also the experimental design. I didn't detect a design study for that sort of thing.

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I would rather, if the FDA wants to make an issue of this and, if they want a special indication for it, then it would have to be addressed as a study.

The other issue I think, when we talk about efficacy, somehow, the sense of this panel ought to be, I think, that efficacy, in the long run, data on the efficacy has not been presented. By long run, I mean beyond a year.

DR. SCHMIDT: I guess my only concerns are on the implantable stimulator. One, I don't see anything mentioned about battery life of the device. I think that this, with all pacemakers, battery life is given and at least the patient knows how long this device will be useful to him before they would have to go in and replace it.

So I think that should be addressed.

DR. HARKNESS: May I address that? Indeed, we have labeling that gives indications for various parameters what the battery life will be for those parameters.

DR. SCHMIDT: Okay; so that is now incorporated.

DR. WILKINSON: What is that labeling, for the record?

DR. HARKNESS: I'm sorry; it is a manual that has listed the various parameters, how long the device is used and, based on those parameters, how long you would expect the battery to last.

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DR. WILKINSON: But for the average Joe Engineer who says, "I want the device put in me," what do you tell him? One year? Five years? 20 years?

DR. HARKNESS: Three to five years.

DR. SCHMIDT: In terms of the stimulation parameters, you said that they were going to be specified to the person that was going to set up this stimulator in terms of what the limits were. My concern is that, even though you specify these limits to someone, there are always chances of making mistakes. The stimulator is definitely capable of producing lesions operated in certain modes.

It seems to me that your softwear in your programmer could be set up to check parameters before they are sent out to program the stimulator and actually lock out and give an error message to the programmer saying, "This is not a reasonable set of parameters you have entered. Please verify these."

DR. WILKINSON: Dr. Schmidt, would you accept an alarm instead of a lockout?

DR. SCHMIDT: I don't want the parameter sent to *stimulator.

DR. WILKINSON: As long as the clinician is willing to accept a little brain damage to create a good benefit. It is nice to have the device just give an alarm.

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DR. SCHMIDT: I am not as concerned with giving small lesions, microthalamotomies, as if you happen to just make a mistake when you went in and programmed it and you set the stimulator to its maximum value in one of the parameters which could produce a very large lesion.

To give an alarm after you have done it is after the fact. You have already made your lesion.

DR. WILKINSON: You could have a lockout with an alarm and an override. How would that be? If the clinician wanted to--clinicians are a pretty ornery bunch. We like to do what we damn well like to do. We had having a machine telling us, just because it is safe or not safe.

DR. HARKNESS: Can I ask Dr. Hubble to address this issue of lockout and dosing parameters.

DR. HUBBLE: I will offer a response in terms of a clinical perspective, not necessarily the bioengineering perspective, if you will. First of all, as the data that was very nicely demonstrated on the part of the FDA, actually the parameters that we ended up using in the clinical trials in the U.S., of course, fell underneath that magic bar that was demonstrated.

How we arrived at those--well, we knew going in approximately what the most optimal settings would be primarily because of the European experience. But, in

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addition, those optimal settings were defined based on clinical experience; that is, when you set the device too high, you get intolerable side effects.

So, in fact, that is why our ranges, really, when you look at the settings, while they vary from individual to individual, and change somewhat over time, particularly the first few weeks postoperatively, we are not talking about a huge range in parameter settings in the clinical trials conducted to date.

In terms of what that represents to risk, either to the liability to the treater or risk to the patient, I would make the analogy to drug therapy. I write prescriptions every day for medications for this exact same group of people, that, if they were improperly used or overdosed could represent significant morbidity and even mortality, depending on the medication given.

Yet, I accept that potential responsibility and liability and ask the patient to also share in that by educating the patient as well. So I think that this issue we deal with every day in clinical medicine, and that is how most appropriately, how best, to use a therapy that, in overdoses, could be harmful and even cause death.

So I think we all handle that every day in the treatment of these very same individuals. In fact, to me,

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these actual parameters of safety and efficacy, these kinds of margins of safety and efficacy, weighing these risk/benefits when applying a therapy like deep-brain stimulation are actually clearer than the use of medications in this very same group of patients.

I spend most of my time as a Parkinson's disease specialist actually attempting to juggle side effects versus benefits from all the medicines that I currently have. Yet, at least with this therapy, I have not only guidelines in terms of the actual parameter settings but I can tell what represents a true adverse event and I can tell what represents true efficacy in the individual.

So I would say that actually these kinds of clinical issues, in terms of overdosage, in terms of overstimulation, is one that all clinicians are very competent in handling on a day-to-day basis with that patient group.

DR. WILKINSON: Dr. Schmidt, further comments?

DR. SCHMIDT: Are there a series of capacitors in the output of the stimulator, one, to balance charge and, two, to protect the electrode and brain from failures in the stimulator?

DR. RICE: Mark Rice from Medtronic. The answer

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is no, there is no capacitor in series with the output lead.

DR. SCHMIDT: So if you have an outward transistor failure, you could apply the full-supply voltage to the lead.

DR. RISE: Potentially. This device is the same device, the ITREL II is the same product, that has been on the market for six or seven years. The reliability of the device is quite high.

DR. SCHMIDT: What is the failure rate there?

DR. RISE: I think it is--I don't have the number. My colleague has the number.

MS. OTTEN: My name is Lynn Otten. I am a principle design engineer for Medtronic. We took a database of 20,000 units. These are the ITREL IIs. We are looking at a 0.001 percent failure rate.

DR. WILKINSON: Mr. Spyker, do you have comments?

MR. SPYKER: Since you asked, I will respond to the questions about the polyurethane and other engineering issues. I guess I have got three quick points to make. Number one, our mission, the agency's mission, is to get treatments to patients. As you have heard, a lot of the development review and labeling really involves many parallel paths.

If we waited for each path to be completed to

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everyone's satisfaction before starting the next path, we would not be this close on this project or any other.

The second is that absolute safety is not what we are about here. In fact, the definition in the regs for safety is, simply stated, the benefits must outweigh the risks when the device is used as intended. There is no such use as safety in the absence of efficacy. We don't even think that way.

The third thing is, although this panel has very broad responsibilities, our focus, and I presume your focus, is on the clinical issues. We are not coming to you for a lot of help with engineering issues. It is certainly appropriate for you to raise these questions, but that is not what we have been focussed on in our presentation.

So we are ready to proceed.

Dr. Gooray is no longer here? Ms. Maher?

MS. MAHER: I have nothing further to add since the FDA clarified the issue on the biocompatibility issues.

DR. GWINN: I agree with many of the other statements, one of the benefits of getting to speak towards the end. I agree that the benefits outweigh the risks. I feel that that is true for both essential tremor and Parkinson's disease. As a clinician and clinical researcher, both, I see a lot of patients with both of these

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disorders and I can certainly think of patients with Parkinson's disease in whom treatment of the unilateral tremor would benefit the patient.

I think patient selection is the key when it comes to actually both of those disorders.

A couple of comments. Earlier, the statement was made that stimulation in the VIM, or the VM, is the only region in which tremor suppression occurs. Perhaps, I am misquoting the person who said that. I believe it was Dr. Lozano. But that is actually not necessarily true. Stimulation is done in pallidotomy and thalamotomy all the time to localize the internal globus pallidus.

Stimulation in both of those regions do suppress tremor and I do think that the cognitive problems are real and that cognitive dysfunction presurgically should be a contraindication. I am also wondering if hallucinosis or a history of hallucinosis should be considered as a potential problem.

We are dealing with a population which is elderly and at risk for other kinds of problems including stroke and cardiac disease and anticoagulation may be an issue.

I am wondering if that is a contraindication in the future if the person should have a stroke and need TPA or heparin or something like that, if that is going to

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increase the risk for intracranial hemorrhage and one of the serious adverse events that we talked about. That is just a question.

I think that is pretty much all of my questions. We talked a little bit about battery lifetime and it was suggested that patients should turn the device off at night. But many patients will have tremor when they wake up a little bit, especially Parkinson's disease patients, and it will keep them awake the rest of the night. So that is not necessarily always possible.

Those are really just all of my comments. Anyone who wants to address any of those, feel free to do so.

DR. OLANOW: If I could just briefly mention, most of the hemorrhage occurs with the passage of the needle through the brain. Once that procedure is done and the electrode is in place, I think the risks of anticoagulants in any other group of patients.

I think you are correct that other sites such as subthalamic nucleus or GPI can provide inhibition of tremor. These are areas that we are currently investigating. I think the point Dr. Lozano was making is that within the thalamus, this is the area that provides the best area for tremor resolution and that this is a different area than those which are connected to known cognitive areas.

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DR. GWINN: Some people do thalamotomies historically speaking.

DR. OLANOW: I can't comment on that but I think one of the great advantages of this procedure is that you manage to get comparable, if not superior, levels of benefit without the need to make a lesion.

DR. LOZANO: There are many targets that have been chosen historically. But I was specifically addressing the thalamic target. I was not speaking of extrathalamic targets for treating of tremor. Specifically, with regard to within the thalamus, this has been looked at.

The top 16 neurosurgeons were polled by Dr. Laitenen. This was published in the Journal of Neurosurgery in 1985 and, by far, the most common site within the thalamus was VIM. The other sites involved lesions in the zona inserta which are the thalamic afferent fibers.

So either VIM or its afferents are the best target according to the top functional neurosurgeons in the world.

DR. GWINN: The best target and only target was the one I was raising an issue with.

DR. EDMONDSON: I would have to say that the benefits really outweigh the risk. From my standpoint, there are a couple of issues that I would like to briefly comment on. I think the human experience and the human

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value of an intervention, vis-a-vis, disability is really important.

Joan Samuelson's recitation underscored some of the issues. Given the numbers of the various studies that were presented here today, from a statistical standpoint--and I am not a statistician--but, indeed, some of those numbers were small, for example, in the bilateral stem category.

But I think, even so, there is a preponderance of indication that the benefits outweigh the risk. If, indeed, it is acceptable to perform thalamotomy in a Parkinsonian patient, even though the disability values don't seem to be demonstrably improved in the data that was presented to us, then, indeed, I think that there is some categorical benefit here that, perhaps, can be discerned postmarketingwise, in terms of post-marketing surveillance and study.

So I would be in favor, should this go through, to definitely emphasize that we will need some post-marketing study and some longitudinal, long-term data over time. But the human issue, I think I would put to the forefront here, given the fact that the benefits do outweigh the risk.

I would like to ask one question of Dr. Wilkinson and that is, basically, before we vote, and because of the fatigue factor as we go around the table and present our

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comments, whether or not the panel could have a brief break before voting. I am just making that appeal.

DR. WILKINSON: I assume you are referring to this Dr. Wilkinson.

DR. EDMONDSON: Right. With regard to labeling concerns. One of the concerns that I think should be brought to the floor is that, should this go through, that clinicians don't really implant this willy-nilly out there for a number of motives, or I'm sure that there are patients who will have a strong--will try to be very cogent in their arguments for why they need this high-tech device.

So, in the indication in labeling, I think some category of disability should be addressed as a criterion even though we don't want to be so rigid and stringent that it excludes folks who would definitely benefit.

DR. NUWER: I would agree that the devices seem to have a good track record on safety and efficacy, both for Parkinson's and essential tremor, both unilaterally and bilaterally. On the polyurethane issue, I think that the risks you are looking at there are much smaller than the risks we already know about like intracranial bleeding. I would say, in the face of that, I would not worry about the polyurethane issue enough so to influence how I vote.

On the MRI compatibility, I think the labeling

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should say what the experience actually is; that is, in a series of x number of patients, with the unit turned off, MRIs were conducted and there were no significant side effects noted, or whatever the specifics were of the experiment that was stated earlier today.

On the bilaterality, I think that although the risks seem like they are greater than that for unilaterality, they still seem well within the acceptable range.

On the issue of an alarm, I think the worst-case scenario still is that if you overstimulate and do cause some local tissue destruction, you are going to cause a lot less destruction than the neurosurgeon would if you put a deliberate thalamotomy in the same place. To me, I don't think that that risk is so great as to prevent the use of this device.

I think the risk, again, is also much less than the known risks such as intracranial bleeding.

That is all I would have to say.

DR. KU: I think all the other panel members have reviewed most of the questions. The one remaining question that I had was with the bilateral lead placements. I assume from what I saw in the time frame that they were not

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bilateral simultaneous lead placements but rather bilateral lead placements with one done at a separate time following placement of another.

Is that correct?

DR. HARKNESS: Not entirely. Some of them were, indeed, simultaneous. Others were staged.

DR. AMINOFF: Let me just make several very brief points. First of all, I agree that the benefits, quite clearly, outweigh the considerations about safety here. I think that the data presented are fairly impressive--in some cases, very impressive. I do believe, therefore, that this should be available for the treatment of essential tremor both unilaterally and bilaterally even though the bilateral data is more restricted in number.

Similarly, I think that this should be available for the treatment of Parkinsonian tremor. As I indicated before, the fact that there was no major change in disability scores is hardly surprising. It is what you actually might expect. The fact that medication was increased in some cases is what you might expect.

I do not think it would be appropriate, therefore, to try and restrict patients with Parkinson's disease to whom this is given on the basis of their disability scores but disability scores reflect more than simply tremor.

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So I would not try and make any such restriction as, I think Dr. Edmondson, suggested. I would make it available for both essential tremor and Parkinsonian tremor, either unilaterally or bilaterally. I do not feel that there is any further note that needs to be added to the adverse events or precautions that are mentioned in the attached document.

Except that I agree with Dr. Nuwer that some comment about MRI and the safety of doing MRI is, perhaps, appropriate and that some comment should be made based upon the available, although somewhat limited, experience.

Somebody raised a question of an alarm. Personally, I do not feel that that is necessary and will simply complicate matters further. I agree with the comments made by Drs. Hubble and Nuwer that that, perhaps, is best left to the physician.

Thank you.

DR. WILKINSON: The chair has a right to be heard on this as well as on everything you have heard me say earlier. I am acutely aware, of course, of the human values in this disease. But I think we also have an obligation, under that general rubric, of not allowing the public to be disappointed by going through a risky procedure and a costly procedure that might be more damaging than helpful.

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So I am pleased that the panel has kept human values in perspective in both aspects of the significance of that consideration.

I, too, am not worried about the polyurethane question. Certainly, there has been presented animal and one human histologic data. There has been at least one-year data showing no change in functional significance or no major change in parameters. That seems to support the safety of the polyurethane. It doesn't seem to produce any problems.

The MRI language certainly needs to be strengthened. The idea of putting in a recommendation that the device at least be turned off, I think is minimum language. I think there should be language, also, specifying not simply that this is intended for the use of treatment of tremor but that it is not intended for the treatment of rigidity or bradykinesia, a negative statement more than simply a limited positive statement, and a negative statement that activities of daily living may not be significantly altered to the extent that they are impacted by the remainder of the disease.

Postmarket surveillance is clearly going to be important in a technology as new as this, and I would encourage that, as part of the postmarket surveillance,

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something be put in about post-mortem evaluations. I think it is discouraging that even though there have been a number of deaths, there have been no post mortems on the patients who died with these devices in place.

That should certainly be encouraged. If you are going to sign up for this device, you sign up for a post mortem, also.

We will follow through with the human values part of it now as far as Dr. Edmondson's suggestion. If we can limit the break to ten minutes and then we will come back for a vote.

[Break.]

DR. WILKINSON: We will wrap this session up. I have been asked if Dr. Olanow from Mt. Sinai could make one comment before we go to the vote.

DR. OLANOW: I just wanted to make one final comment that I hoped I could get you to consider, and that is that Parkinson's disease and essential tremor are both diseases that are bilateral, affect both sides of the body, that the kinds of patients we are talking about for these procedures are patients who cannot be satisfactorily managed with the best of available medical therapies.

One of the great advantages of deep-brain stimulation is that, in a relatively safer way, it permits

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us to affect both sides of the body and, thereby, correct the problem for a patient who is bilaterally disabled.

So I just wanted to encourage you to strongly consider the bilateral issue because of the tremendous importance that that has for our patients and the relative advantage that this procedure has with respect to bilaterality over all other existing therapies.

DR. WILKINSON: Thank you.

Committee Vote

DR. WILKINSON: As we move to the voting section, I will remind everyone that the voting members are the core members of the panel and the deputized voting members; myself, Drs. Gonzales, Ku, Nuwer, Canady, Edmondson, Gatsonis and Hallett.

I would ask, as you consider your vote, that you make two assumptions. The first is that we do want to expedite delivery of effective and safe treatment to the American public but that a delay of approval would not prevent continuous studies. It wouldn't be the end of the world or the end of this device.

The other assumption I would like for you to make is that changes will be made in many of the details that have now been called to the attention of the FDA and the manufacturer. So I think we can safely make those

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assumptions, that labeling will be changed, that engineering concerns will be answered.

So that should not be used as an impediment to your vote.

As for the vote, the voting members of panel, you have three choices in your vote. You can vote to approve the device for all indications that we have heard today, essential tremor and Parkinson's, unilateral and bilateral.

You can vote to approve the device but with conditions. The condition can be that it is restricted to unilateral use, that it would be approved only if such and such data was presented, only if there is 36 months of follow up, whatever concern you feel is important enough to delay approval.

But if you ask for conditions, I would ask that you specify what those conditions are. Then, your third option is to vote to disapprove the device. There, again, I will ask that you specify the reasons for disapproval. If you feel that there are sufficient concerns about either safety or efficacy, to warrant a vote of disapproval, tell us why. We would like to be helpful here.

If we are not going to approve the device, let's make sure that when it comes back, all of the questions have been answered. So I would like to see us have a very

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positive approach to this.

DR. NUWER: Can I ask a question about the instructions?

DR. WILKINSON: Sure.

DR. NUWER: When you earlier mentioned the issue of having a negative statement on the list of indications, a statement that is negative about its lack of usefulness in treatment of, and you listed several specifics, like bradykinesia. Is that one of the conditions that we are now talking about?

DR. WILKINSON: If you feel that that is a strong enough concern that you would like to say that it be approved only for tremor and with a specific disclaimer against other uses, then that should be stated as part of the disclaimer.

As it now stands, the literature that we were given is that the manufacturer is asking approval for the treatment of tremor. I am not sure we actually need a motion. Our technical chairman here is saying do we actually need a motion. He is more than the technical chairman. He is the boss.

I would propose that the vote, then, is for approval of this device for both essential tremor and for Parkinson's disease for both unilateral and bilateral

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application. Does anyone wish to--as a motion. You can obviously vote to restrict the motion or deny it.

[So moved.]

DR. WILKINSON: Did we do it? Let's go around the table, then, in the same order, the voting members, of course, only, and ask for your vote.

DR. CANADY: I guess I have to vote against that motion. I believe that the device is useful, should be approved for unilateral, both Parkinsonism and essential tremor. That offers those patients who have bilateral tremor to have the opportunity to have their dominant hand done in all cases and I think we have to have more than ten patients to approve the bilateral indication. So I have to vote no.

I would support unilateral for both.

DR. WILKINSON: So you are voting no only on the segment of--

DR. CANADY: The bilaterality.

DR. GONZALES: I am voting no. That is to say, I am voting no for the bilaterality of the use of the deep-brain stimulator, much like already has been stated by Dr. Canady. So, with the same conditions.

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DR. HALLETT: I would vote yes for the motion, but I would say that it should have negative comments with respect to bradykinesia, as you had mentioned earlier. I would also speak in favor of some sort of warning with regard to excessive stimulation on the device.

DR. WILKINSON: So voting yes with two conditions.

DR. GATSONIS: I would vote yes with modifications. I do not think there is enough evidence about the bilateral issue. I think that we should specify that effectiveness has been demonstrated for a period up to a year. And I agree with specifying that effectiveness has not been demonstrated with respect to other conditions such as bradykinesia, et cetera, that was just mentioned.

DR. WILKINSON: So you are suggesting the first two objections as labeling issues.

DR. GATSONIS: Well, I think that, for the bilaterality, I don't think it should be approved for bilaterality.

DR. WILKINSON: And the labeling, that the effectiveness is shown for one year only.

DR. GATSONIS: Yes. And also add the issues of bradykinesia, et cetera.

DR. EDMONDSON: I would have to vote yes for the unilateral indication for tremor in both groups, essential

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tremor and Parkinson's disease. My query in pondering with regard to bilateral treatment, recognizing that most of these patients do have bilateral presentation, is that if that is approved as well, which is the crux of this, then certain commitments are still hanging.

So I would really suggest that is* having bilateral implantations should really be study referral patients and that all the criteria raised, the very salient criteria that were raised, queries that were raised here, that that is addressed in a study with a larger number of patients.

DR. NUWER: I would vote to approve for both unilateral and bilateral. I think that the worries people have about bilateral use are, for the most part, a fear of the unknown and that the problems that have come up with what bilateral stimulation has been run so far have not been serious, at least the risks seem to be much smaller than the benefits of the bilateral use.

So I would definitely support the bilateral use based even on the smaller number of patients that were presented.

I would draw the analogy to the issue of it works well on one side. It works well on the other side. The only problem we are looking at is the interaction between

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the two sides. There is not a great problem with the bilaterality in the data that has been provided. I don't see why we should not just go ahead and approve bilaterally and request that postmarketing surveillance of the bilateral be done in the way, I'm sure, that it is going to be done.

DR. KU: I would vote yes for bilateral indication for treatment of tremor. I think there needs to be postmarket surveillance of this. I also think that the one area that I am concerned about, the bilateral implantation for tremor, is that if it is done simultaneously because of the potential for a bilateral thalamic injury.

If it is done sequentially, then I would have no reservations. I would vote yes for single, unilateral, individual for Parkinson's and that we need additional studies before bilateral placement is approved for Parkinson's. Also, the additional warning on MRI compatibility or incompatibility needs to be strongly worded.

DR. WILKINSON: So you are supporting unilateral or bilateral for essential tremor, unilateral only for Parkinson's.

DR. KU: Right. I am not convinced that the

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benefit is that great for Parkinson's as was demonstrated for essential tremor.

DR. WILKINSON: I am voting in favor of the entire motion. I believe that bilateral implantation certainly does not have enough data yet but I think data will come. I think a bilateral device is probably safe to put in and if it is not working well, it can be turned off on one or the other side.

So I don't see bilaterality as a much greater risk factor to the patient. The efficacy, I agree, more data is needed. The postmarketing surveillance, I think, is going to be extremely important and, as I said earlier, including post mortem data.

MR. KEELY: May I have a clarification on Dr. Canady and Dr. Gonzales. I believe they both voted to disapprove and the reason was because of the bilateral; is that it? Am I right in saying that you approve for ET and PT, but you would not agree with the bilateral? I just need to have that confirmed.

DR. CANADY: Right. I think that we do have data that bilaterality in other thalamic procedures is substantively different. And we don't have the positive data that it is not here.

DR. GONZALES: I am voting for unilaterality of

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the stimulation for ET and Parkinson's disease but against the bilateral deep-brain stimulation for both because, again, the data, I feel, is lacking and the concern primarily is the safety issue of what is becoming of these patients long term. I don't think there is enough data to support the bilateral yet.

MR. SPYKER: Could I also get a clarification from Dr. Edmondson on the bilateral issues.

DR. EDMONDSON: Basically, in accordance with Dr. Gonzales, I am in favor of the unilateral use of it both essential tremor and Parkinson's disease and basically would refer patients who have had unilateral implants who desire the opposite side done, that they enter a study.

I think that is probably the most effective way of really answering these lingering issues.

DR. WILKINSON: I want to remind the audience that this panel's deliberations are advisory. The panel, itself, does not have regulatory powers. So I hope that we have been helpful not only to the FDA and the company but, even more important, to all of the Parkinson's and essential tremor patients in the United States, and to the general public of the United States, as well.

I certainly, personally, appreciate the presentations that the company has made. They were very

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precise, scientific, thorough. For the deliberations of the panel, it is really a privilege to be in a room with such experts on both sides of the aisle.

Are we finished now, Mr. Bossman?

MR KEELY: I just wanted to make one last comment. This will complete the end of the open session. We will break for five minutes. Everybody in the general public is expected to leave. Please take your materials with you and take your trash with you.

[Whereupon, at 4 o'clock p.m., the proceedings were adjourned.]