have an adverse event over the course of one year trial is something we routinely see in any studies, including pharmaceutical agents.

The adverse events were divided into three groups to help us try and understand them better. One's that were associated with the surgical procedure, those that were associated with the device and those that were associated with the stimulation itself when you turned on or turned off the stimulator. Next, please. So with respect to those that were associated or attributed to the surgical procedure, the most frequently reported events were confusion, intracranial hemorrhage and infection. The events resolved in most patients.

I can tell you and I'll show you a slide in a moment, but I believe there were five or six patients that ended up with residual neurologic disability. And I'll show you those and describe them in a moment. I will also show you that these event rates are consistent with other stereotactic procedures in this type of patient. So here you can see the results of what was seen from our point of

view. We considered the intracranial hemorrhage to be the most important. It occurred in 11 patients.

I point out there were 159 patients who were in the study, but that they had 301 procedures, so one could consider it from that point of view as well. We've shown the percentages as related to patients, but in the literature much of the data relates to procedure, with people having just unilateral events. Other problems were infection, dysarthria, thinking abnormal, headache and convulsions.

Most of the convulsions really were in the group that had the intracranial hemorrhage and as indicated most of those have resolved. Next, please. I just want to spend a moment on hemorrhage because we consider that to be an important issue. Hemorrhage was reported in 11 patients, 6.9 percent. But as I indicated, only in 3.7 percent of procedures. It was reported as a serious adverse event in only seven of the 11 patients, and interestingly it occurred at only a small number of Centers.

Three of 105 or 2.9 percent were in the

group that had subthalamic nucleus and four or 7.4 percent were in the group that had GPI. We did not see any evidence that implanting STN was associated with increased risk in comparison to GPI as has been alleged by a previous correspondent. The hemorrhages were seen in six, of the serious ones, six bilateral and one unilateral procedure. And interestingly, two of the patients were taking lisuride, which is a dopamine agonist that has anti-coagulant properties that had not been appreciated at the time, and may have played a role in their development of hemorrhage.

We now recommend that patients not use lisuride in the future. And lisuride, by the way, is a drug that's not available in the United States, so these were European samples. Of these 11 hemorrhages, of which seven were serious, four ended up with patients having persistent neurologic deficits. So all of the others cleared. Five of the serious seven were subcortical in location.

One was within the subthalamic nucleus and one was subarachnoid. So those were the locations. And this is just some data from Ron Tasker, who looked

at this thalamotomy data and thalamotomy studies and pointed out that 1.5 to six percent of procedures had hemorrhage in the thalamotomy group. So not a lot different than what we saw. And in the Activa Tremor Control Therapy study in which we do DBS of the VIM nucleus, which is currently approved, four percent have hemorrhage. So again, not too much different from what we saw in this study. Next, please.

With respect to adverse events that were attributed to the device, you can see them listed here. Intermittent continuity is a classification term and it refers to the fact that a lead that was working stopped working or it then started again or stopped working and didn't start again. And in two cases that was reported to be serious. There was lead migration that was considered serious in six cases.

Other problems included infection which was considered to be serious in four. I think that these results were considered to be consistent with what had been seen with the Activa Tremor System or DBS VIM. And I think on the next slide you can see that because of these problems, eight patients had to

undergo device revisions of one sort or another. With respect to infection, you can see that of the entire 159 patients, 15 had infection. This was slightly higher rate than what was seen with the DBS Tremor System and may reflect the fact that these are longer procedures and that some people left the device explanted for as long as weeks before they implanted the IPG.

In the majority of instances, these resolved and here are some data from other surgical techniques showing what their infection rate was. Five percent with spinal cord stimulation, 5.7 percent is sacral nerve stimulation and 1.5 to six percent in CSF shunts. So infection rate is more or less in the same range as what's been seen with other procedures that are currently available. Next, please.

With respect to stimulation, it's difficult to gather information and a lot depends on how the evaluators judge it. The reason is that when you're trying to tune up the stimulator, what many of us will do is deliberately try to induce some kind of side effect, like paresthesia or muscle twitching in

order to know how high we can go. And then we'll adjust at each electrode configuration. So there was variability, I suspect, in how people reported whether that was an adverse event or not.

I think the important thing from our point of view is that these are all typically mild and well tolerated by the patient, for the most part, and what characterizes the Activa System is that by adjusting the stimulation parameters one is able to control these in virtually all instances. So the ones that were reported in more than five are listed here and include dysarthria, dyskinesia, dystonia, paresthesia, etcetera. But again, I want to emphasize that you can make any patient have an adverse event as you stimulate, what matters is how many persisted and were problematic. And the answer there was virtually none. Next, please.

During the course of the study, three of the 159 patients died. None of these were attributed to study participation. One died with what was reported to be worsening Parkinson's. One of a suspected myocardial infarction. And one with cancer

of the esophagus. Persistent neurologic disability occurred in eight patients. Five of these reported hemiplegia, four of these were from the hemorrhage group I described, and one patient had an independent hemiplegia.

Two patients were thought to have had cognitive decline over the course of the study and one had persistent dysarthria. Those were the patients in the study that had persistent neurologic deficits. Next, please. So we conclude that the adverse experiences that occurred in the course of this investigation are of a type and of a frequency that can be seen with other stereotactic neurosurgical procedures. And a summary of a number of different articles is provided here. You can see that in our study about 8.2 percent have confusion, whereas in ablative procedures it's four to ten percent of the studies are recorded.

Hemorrhage was seen in 6.9 percent, four percent serious, and again with ablative procedures as reported in 1.5 to 12 percent. Infection, as I mentioned, was a little higher than what's been seen

in other procedures for the reasons I've given you. Dysarthria was about five percent. Most of the ablative procedures are unilateral. With bilateral it's typically much higher. Cognitive deficits, seizures and mortality are all more or less in the same range as what's been seen with other surgical procedures of this type. Next, please.

In contrast, the kinds of benefits that we've seen in this study and that I've shown you include the fact that deep brain stimulation of the subthalamic nucleus and GPI improve motor features, they reduce the motor complications resulting from levodopa, the increase on-time without dyskinesia and they decrease off-time. They allow patients to regain independence in performing activities of daily living. They allow most STN patients to reduce the dose.

They reduce disability as determined by both physician and patient, and the treatment has the advantage that it's reversible and any stimulation-related side affects can be eliminated by adjusting stimulation to meet the individual needs of the patient. I just want to show you this more or less

final slide, because I think it is important to put what I've described for you into context. These patients that we've entered into the study are typically patients who have failed on medical therapy.

These are patients who have advanced Parkinson's Disease and cannot be further improved with the best of medical therapies that we currently have available. Now in comparable studies in advancing Parkinson patients, but not nearly of this level of severity, drugs that are currently approved offer the falling level of improvement in on-time in the case of Entacapone or Comtan, 0.6 to 1.4 hours per day in the studies that were pivotal for FDA approval. In the case of Tolcapone, 1.7 to 2.9 hours per day and in the case of Mirapex or Pramipexole, approximately two hours per day.

What I want to emphasize is this is increase in on-time, but with no adjustment for whether that on-time was complicated by dyskinesia. And I can tell you that in any Parkinson patient I can give them more on-time by just increasing the dose of levodopa, but then they'd have dyskinesia. Here you

see the magnitude of improvement that was obtained with GPI and STN stimulation, 5.5 to 7.7 hours and 6.8 to 7.3 hours, between three and five times higher than other approved agents in a population that can no longer be improved with these agents and in a population where this improvement is not just in on-time, but in on-time without dyskinesia. Next, please.

So at this point I think we want to just show the video one more time so that you could get another look at what we've been describing in this study.

(Video is showing.)

DR. OLANOW: Here then is that first patient. This would be the patient in medication-off, stimulation-off, unable to move, hardly able to turn, markedly compromised by his Parkinson's. And now medication-off, stimulation-on state, the stimulator is turned on. And the kind of benefit he experiences. Note that his on state is not complicated by dyskinesia. And here the second patient you saw in the medication-on, stimulation-off state.

Experiencing the benefits of the drug, he is able to move. But the movement is at a price, the corresponding involuntary movements.

And now medication-on, stimulation-on showing that his motor functions are more or less the same, but his dyskinesia has been very dramatically reduced. Can we go on to the next slide, please. So I would like to conclude this presentation and thank you for your patience in letting me give you such a lot of information. By telling you that in our opinion the Activa System deep brain stimulation has been clearly demonstrated to improve the feature of Parkinson's Disease in patients who cannot be satisfactorily controlled with medical therapy.

I want to emphasize to you, not being satisfactorily controlled was one of the criteria for being entered into this study and that in these patients, no drug that I have ever seen before has ever been able to provide these patients with the level of improvement that we see here, without the complicating complications that we've shown you. We believe that the therapy has an acceptable safety

profile given that it is an intracranial surgical procedure.

And that the level and magnitude of improvement that is potentially available to these patients warrants this level of risk. And finally, conclude that at least with respect to stimulation, there is the additional advantage that the therapy is reversible.

CHAIRPERSON CANADY: Thank you very much.

DR. OLANOW: Thank you.

CHAIRPERSON CANADY: Ms. Pritchard, rather than present the lists of the people you have available for questions, why don't we ask the panel for questions and then as your people speak have them identified. I think that might be more useful to the panel. Questions from the panel?

DR. NUWER: One of the things that we really haven't covered is with the surgical implantation itself. Obviously the implantation has to be done very carefully by the right people with the right equipment and the right expertise. Could you comment further on how you would be able to assure

that the right people with the right experience and the right equipment and the right monitoring are chosen to be able to do this? How can we protect that the patients are given implantations by the right people with the right equipment and the right help?

MS. PRITCHARD: Certainly as with the other devices that Medtronic has available and specifically the Activa Tremor Control Therapy, Medtronic does target only the Neurosurgeons who are experienced in the stereotactic procedures for implantation of this device, as well as Medtronic puts on many training sessions for the physicians. There is very comprehensive labeling and educational materials for the physicians, as well as all of the surgical staff that are involved in the surgeries to ensure that only the patients who have received appropriate training are implanting the systems.

DR. NUWER: Are you saying you would restrict the sale of these devices to the situations where the surgeons pass a certain criteria of training?

MS. PRITCHARD: Medtronic really doesn't,

we don't certify a patient, or a physicians for implantation, but when the physician expresses an interest in the product then we will provide the training that we have available.

DR. NUWER: So you're saying you provide the training. What would stop the surgeon from deciding he wants to go ahead and set up a program for doing this without having sufficient training?

MS. PRITCHARD: I can't say that there's anything that would stop them, but we discourage it.

DR. NUWER: How much experience with stereotactic surgery is needed before a surgeon really is ready to do this? How do you judge that?

MS. PRITCHARD: Okay, I guess I would like to have Dr. Andres Lozano, who is one of the Neurosurgeons involved in the study, answer that question.

DR. LOZANO: I'm Andres Lozano, I'm a Neurosurgeon at the University of Toronto and I specialize in stereotactic and functional neurosurgery. And Medtronic has paid my way to come here today and I'm a Consultant for Medtronic. There

are currently 400 Neurosurgeons in the North America that are members of our professional society called the Society for Stereotactic and Functional Neurosurgery, the American Society. Of those, approximately 140 are involved in doing this type of functional neurosurgical procedure on patients with Parkinson's Disease.

And there have been already approximately 140 Centers that have implanted DBS electrodes for tremor therapy. And so I think these are the Centers which will be first in line to offer this type of surgery. And I would hope that through the efforts of Medtronic and through the professional associations that the Centers with the most experience could then be used as resource centers to help train those Neurosurgeons that require some extra training in this field.

CHAIRPERSON CANADY: Is the society, the Stereotactic Society, a self-designated or are there admission criteria?

DR. LOZANO: The only admission criteria for the Society are you must be a Neurosurgeon with an

interest in stereotactic and functional neurosurgery.

DR. NUWER: I guess my concern is not so much with those surgeons who are obviously well trained and have experience. The issue is with new people trying to enter the field and who might want to take advantage of being able to offer the service, and how does one assure that as new people enter the field that they have had the experience that's necessary to be able to do this safely?

MS. PRITCHARD: I guess, once again, I would just state that whenever a physician comes to Medtronic and requests a device or expresses interest in the therapy, then we will go through the different training opportunities that we do have available and we suggest that either they attend one of the Medtronic-sponsored training programs or visit with another physician that has experience in the procedures.

We also have videos available for the physicians that instruct on the surgical procedures.

CHAIRPERSON CANADY: Dr. Zamorano.

DR. ZAMORANO: Yes, I would like to, maybe

would Dr. Lozano could comment on this. I'm a Neurosurgeon too and I perform many stereotactic and neurosurgical procedures. Now there are many people performing thalamotomies and we have the Activa Tremor approved for placement on the VIM. My opinion is that that is a relatively easy procedure to get into the VIM and do they give complication or do they give training to do that so a general neurosurgeon with a general training in stereotactics would be able to do that?

I have some concerns about subthalamic nucleus and GPI, globus pallidus, more concern actually with the subthalamic nucleus where I think you need a degree of expertise to get to that nucleus, I think to be very, very high. And I have concern that, you know, many people will have training to get to those nucleus. Could you comment on that, what is your opinion?

DR. LOZANO: This is in deed a novel therapy, a novel target, treatment, so there is a need to, for training, to learn how to do the techniques. The more training experience the surgeons have, I

think the better the results and the better it will be for patients. As it stands now, the surgeons that are best poised, I think, to enter in this are exactly those that you mentioned. Those that have experience in doing certain type of functional neurosurgical procedures.

If they have experience in doing thalamic stimulation procedures then there is, it's not a very large step to embark on the globus pallidus and subthalamic nucleus. There is some training required, some acquisition of knowledge required, but I feel that this is within the realm of any well-trained neurosurgeon who has already some experience in doing functional neurosurgery.

CHAIRPERSON CANADY: Yes, Dr. Piantadosi.

DR. PIANTADOSI: Thank you. I have a few questions about the methodology of the study. Can you tell us was Dr. Olanow the principal investigator on the study?

MS. MCBANE: Good afternoon, I'm Laurie McBane. I'm an employee of Medtronic in their Clinical Research Activities. Dr. Olanow was one of

the principal investigators on the study.

DR. PIANTADOSI: And how many principal investigators were there?

MS. MCBANE: There were, well, there were 18 Clinical Centers and I believe two of the Centers had shared PIs, so that would be 22 principal investigators.

DR. PIANTADOSI: I see. So there wasn't a single individual who took responsibility for the development of the protocol and the implementation of this study?

MS. MCBANE: Actually, Medtronic worked with a group of physicians to develop the protocol. I believe Dr. Olanow was one of the physicians, as were several of the European physicians. They worked with us to develop the study protocol and oversee its implementation.

DR. PIANTADOSI: One of the very unusual characteristics about the protocol was that it explicitly called for a sample size of ten patients per group augmented by three in case of drop outs, for a total of 26. That was stated repeatedly in the

documents, explicitly in the reading material to the U.S. protocol. Repeated in the statistic section of the protocol and then again in the European protocol. And yet we're looking at data here of over 150 patients. How did that happen?

MS. MCBANE: I would like to refer to my colleague, Teresa Nelson. Pardon me. The study was implemented in, under and IDE in the United States and it was also implemented at several European Centers. And the protocols, there were two versions of the same protocol that really stated the same patient enrollment criteria of the 13 patients in each patient group.

DR. PIANTADOSI: Yes, I understand, I've seen the protocols. And what I'm trying to figure out is how the sample size got from 26, perhaps times two, to 150?

MS. MCBANE: Well, you may recall from reading materials that there was an amendment to the European protocol to increase enrollment to increase enrollment to approximately 100 patients. And then the IDE protocol was implemented in one Canadian

Center and two Australian Centers as well to add about 30 patients to it.

DR. PIANTADOSI: And what was the level of awareness as to the data and discussions that were made about increasing the sample size? What interaction did the Agency have in this decision? Could you just describe a little bit of the thinking and circumstance that went into this?

MS. MCBANE: Well, in the United States the IDE was originally approved for ten patients. And we did request and receive approval from FDA to enroll 26 patients. And I believe that was the nature of the discussion with FDA.

DR. PIANTADOSI: And what data were available at the time this was done?

MS. MCBANE: At the beginning of the study? I believe when we were requesting approval to expand the study from ten patients to 26 patients, we were just into implementing the study and about ten patients had been enrolled but it was in the early phases of their study participation.

DR. PIANTADOSI: Are the documents that

are in the, I guess it's Volume 6 of the materials, the protocols, are they the original study protocol documents?

MS. MCBANE: Yes, yes, they are.

DR. PIANTADOSI: I notice that the European protocol had a date of March on the face page, but the pages themselves were dated in August. Is that the correct face page for that protocol?

MS. MCBANE: It is the face page that was available and we, there was a, use of the word processing software, the date of the printing of the first, the face page and the date of printing of the subsequent pages were printed on different dates --

DR. PIANTADOSI: I see.

MS. MCBANE: -- and that's what, the discrepancy.

DR. PIANTADOSI: And the U.S. protocol had no dates anywhere on it, as far as I can tell. Is that correct also?

MS. MCBANE: Individual pages weren't dated, however we do have a date of approval of the, and of submission of the IDE protocol to FDA.

CHAIRPERSON CANADY: Dr. Hallett.

DR. HALLETT: I have several questions. One of the things in the protocol is that individual Neurosurgeons or PIs had a choice of GPI or STN. And it isn't completely clear to me how that decision was made by, for each individual patient. And when we finally get the final data, are there any differences by site or by investigator or by time during the course of the investigation as to which site was used?

And I suppose in the final analysis, what is the recommendation for site choice, given the way that the protocol was actually conducted?

MS. PRITCHARD: I'd like to ask Dr. Jerrold Vitek to respond to that question.

DR. VITEK: My name is Jerry Vitek, I'm a Neurologist at Emory University and I have no financial interest in Medtronic. They did pay my way to come here. This is an interesting situation with choice of sites, I think, because what happened initially is people who were first implanting thought that STN was a better structure for midlining symptoms such as gait, balance and freezing.

And there was a feeling, a general feeling, not backed up by the scientific data, that GPI would be a better site for dyskinesia, I think partly based upon the study of pallidotomy, where pallidotomy is when you ablate that area so you reduce dyskinesia dramatically. All the data that we gathered don't really support one site or the other site for one symptom versus another.

So there's really no data that supports doing one site for this symptom versus another site for that symptom. What we see is we see efficacy for virtually all the symptoms across both sites. And from personal experience, I can tell you that we certainly haven't seen that with our randomized trial we've been conducting at Emory.

DR. HALLETT: Right, I mean one gets that impression from looking at the data. But I guess one of the questions I had is how did people decide then when they were actually enrolling the patient so that if there were patients that had dyskinesia they would be more likely to be GPI patients? And if they, I mean would that be the case, for example?

DR. VITEK: I think that's true in some Centers. But there are other Centers where clearly people are more biased towards STN and most patients were implanted with STN, for example, in some of those Centers. So whether they had dyskinesia or not. And you can see from the data that a lot of patients the STN implants had dyskinesia to start with and they were improved after stim from the reduction of the dose.

So whether that is statistically significant across the Centers, I can't speak to that. I'd have to ask the Medtronic people to tell me if that's true or not. But I think, in general, you'll find a smattering of people with a variety of symptoms with both groups, both target sites.

DR. HALLETT: Okay.

CHAIRPERSON CANADY: Dr. Fessler.

DR. FESSLER: I'm just wondering why you specifically, not this necessarily for you, Jerry, but why did you specifically choose to use a non-parametric analysis rather than something like, for example, repeated measures analysis of variance?

MS. NELSON: I'm Teresa Nelson, I'm a Contract Biostatistician and an employee of Medtronic, paid by Medtronic. We used a non-parametric method just to not make any assumptions about distribution. We have run the open-label, total motor exam data through repeated measures analysis and have found that the significant affects were medication, stimulation and then the interaction between medication and stimulation.

CHAIRPERSON CANADY: Dr. Walker.

DR. WALKER: A couple of questions about the dose response relationship. Certainly we've heard that at the high end of stimulation dosage because of current spread there are some untoward side affects. But given this is a very expensive device and given that it has to be surgically replaced as the battery is depleted, could you give us some information about dose response relationships at the low end with a view toward saving the patient's money and not having to replace the battery so often?

MS. PRITCHARD: Maybe if Dr. Olanow could come back and talk about that?

DR. OLANOW: I think you've touched on a very important issue and one of the keys to trying to make this therapy practical is figuring out how to do the adjustment in an easy and effective and most practical way. In our group we have begun to approach this is a very systematic way. And the way we currently do it is for each possible retro-configuration. We look for the threshold that first induces benefit, the threshold that induces intolerable adversity.

And what we find is the best electrode configuration is the one that has the widest separation between the two that uses the lowest voltage which gets to your issue. We never go above 3.6 or 3.7 volts, which I think is the doubler affect, so we keep under that. There is an issue with respect to battery life and how, and as you can see people are leaving the battery on 23, 24 hours a day.

Fortunately, no patient in this study in our group has yet run out of their battery, so we don't have real good data to give you and perhaps you have some information on how many people needed

battery replacement. But we are very sensitive to trying to use the lowest voltage at the site that gives us the best result.

DR. WALKER: Is the electrode, all of these people have the same electrode design? Or were there two different electrode designs as variables in the study?

DR. OLANOW: There were two different electrodes that were used, but they were basically the same electrode. The only difference was in the spacing between the contacts.

DR. WALKER: Which speaks to the current density, which speaks to these issues?

DR. OLANOW: And again, I have no data to tell you what the difference in battery life is between them. I don't know if the company does. Do you? Do you happen to know how long the battery survives?

MS. PRITCHARD: No. I'll ask Lynn Otten, who is the principle Design Engineer on this product to answer that question.

MS. OTTEN: My name is Lynn Otten, I'm a

Senior Principle Design Engineer for the Activa System. I'm employed Medtronic. I may be able to address your questions. Because of the variability of patients' requirements with the system, etcetera, I have a slide that I represented where I took the three-month average data of these patients. Because the parameters are based on whether they're bilateral or unilateral, what the impedence in tissue is, etcetera, we do have this problem.

Therefore I prepared this slide for you. Three volts which in STN in monopolar configuration with the high voltage of 3.0, to 3.0 volts, 85.4 microseconds and 158.1 hertz over a 24-hour usage would have a 41-month average, which is 3.4 years. And the low point, to low voltage of 2.1 volts with 75.6 microsecond and 138.4 hertz would run up to a 90-month average or 7.5 years.

In the GP you see very similar results in fact because of the voltage differences and usage differences we'd have from 35 months, which is 2.91 years to 8.0 years. Again, it's highly dependent upon the individual patients and the requirements. Does

this answer your question?

DR. WALKER: I think so, yeah.

MS. OTTEN: Thank you.

CHAIRPERSON CANADY: We're going to go back to Dr. Hallett, who I cut off, and then Dr. Edmondson.

DR. HALLETT: Sorry, I had four more questions. In the medication-on situation, did stimulation produce any significant benefit in any of the different parameters that were measured? That wasn't clear. Most of that was very close and most of the actual statistics we were given was from the med-off situation. So in the med-on situation, other than the on-time, which is a very important parameter obviously, was there any difference in any of the measured elements?

MS. PRITCHARD: We'd like to have Dr. Olanow speak to that.

DR. OLANOW: The results were not as dramatic but there were significant improvements with stimulation-on in the medication-on state in both groups. They weren't of the same magnitude. In the

STN, I think, with off it was about 49 percent improvement and with on it was somewhere in the 20's. And with GPI, both, I think about 38 percent in the off, and I need the left-hand one too, to be equal to that. And --

DR. HALLETT: So that would be the difference on that slide in the two red dots?

DR. OLANOW: Exactly.

DR. HALLETT: And that was in fact statistically significant --

DR. OLANOW: That's correct.

DR. HALLETT: -- the two red dots?

DR. OLANOW: That's correct. Could you give me the equal? So the medication-on it was nine to 31 percent improvement in comparison to pre-implant and in comparison to the same medication-off, stim-off, the same visit. And those were each significant at P less than .005.

DR. HALLETT: Right, but that's, that's in comparison to the pre-implant state and to the stimulation-off state. But what I'm asking is in the on state of medication, on and off stimulation, which

is the comparison with the two --

DR. OLANOW: Yes, that's with that same one. I may have worded it improperly, but it's medication-on, stim-on is significantly better than medication-on at baseline and medication-on, stim-off at each visit. And each of those --

DR. HALLETT: I see.

DR. OLANOW: -- is P less than .005.

DR. HALLETT: Okay. Right. The second question is in regard to postural instability as one of the individual factors in which was claimed that there was no, in which there was no difference. I don't think that's clear, that there was not any significant difference with postural instability?

DR. OLANOW: There was for us.

DR. HALLETT: Okay. How about with respect to freezing, was that particular element looked at?

CHAIRPERSON CANADY: We need you to come to the microphone to answer questions. This is getting transcribed.

DR. OLANOW: This is going to get me in

shape.

CHAIRPERSON CANADY: There are all these empty chairs there. Come on now.

DR. HALLETT: We just want to get you some exercise, Warren.

DR. OLANOW: Okay, but just to answer your first point, postural instability was not improved with GPI but it was improved with STN.

DR. HALLETT: And that's in the medication-on?

DR. OLANOW: That was in the medication-off state, medication-off, stimulation-on.

DR. HALLETT: Right, but again, what I'm talking about is the medication-on, stim-on and off.

DR. OLANOW: I don't know that I know the cardinal features --

MS. MCBANE: I would like to bring up slides E-15 and E-16, please? Slides E-15 and E-16. Okay, this is looking at the freezing scores for patients with, receiving GPI bilateral stimulation at the six and 12-month visits in the off time there was a significant improvement at six months. I apologize,

I can't quite see the p-value for 12 months. I think it's borderline significant.

And in the on assessment of freezing the results were not significant when comparing follow up to baseline. E-16 should have the same results for STN stimulation and this is for bilateral STN stimulation. Significant improvements during off periods as well as during on periods when comparing follow up to baseline.

DR. HALLETT: All right. Thank you. The next question is in relation to unilateral STN stimulation, almost all the data that you presented this morning, at least, was with respect to bilateral stimulation. With respects to unilateral stimulation, particularly in the STN, I wonder where there was any problem with that? My understanding is that that can lead to significant difficulties because of asymmetries, particularly given the fact that the dose has to be lowered.

So could you, could someone comment about unilateral STN procedures?

MS. PRITCHARD: And I will call on Dr.

Jerrold Vitek again.

DR. VITEK: One of the issues there, I think, is that there is only five patients done unilaterally with STN, so there is no statistical data that we can provide. I can tell you based on my experience from doing it that there may be some patients that you do one side, in fact a patient that was in this trial, we did one side and had to reduce his doses. And we needed to then to go to the second side more quickly, because by reducing the dose to stop the stimulator side we went off on the other side and so we were forced to implant earlier than we wanted to.

But I can also say there is an equal number of patients who after implantation on one side, we've had good benefit. That's not to say that those patients aren't better with the bilateral stimulator, they are. But they can certainly do well with unilateral implantation, we're not forced to rush in to doing a second side, for example. There's a variable based on the patients.

CHAIRPERSON CANADY: Dr. Edmondson.

DR. HALLETT: Sorry, one last question. One last one. That is that the target was clearly STN or GPI, yet there's a certain mention of GPE as being the target in a number of circumstances. And was that an error or, in terms of localization or was that by design? Because it wasn't formally part of the protocol?

MS. MCBANE: One patient had been reported to Medtronic as receiving a bilateral pallidal system implant. One side being internal globus pallidus, the second side being the external globus pallidus. However, that was an error in reporting from the investigator. So, in summary, no patients received stimulators in the external globus pallidus.

DR. HALLETT: So all of those were errors made by the, how many cases were there? Was there just one?

MS. MCBANE: One patient, right.

DR. HALLETT: One in the entire study?

MS. MCBANE: Yes, yes.

DR. HALLETT: I see. I had the sense reading it that it was more, but perhaps it was

mentioned more often. So was that an error then of the surgeon in making the placement? Was that the --

MS. MCBANE: It was an error in documentation on the case report form.

DR. HALLETT: Oh, so it actually was GPI?

MS. MCBANE: Correct, correct.

CHAIRPERSON CANADY: Is that it?

DR. HALLETT: Yes.

CHAIRPERSON CANADY: Dr. Edmondson.

DR. EDMONDSON: Three years ago there was some concern raised by the panel regarding bilateral stim for VIM with regards to morbidity. It was raised by some of our panel members that there was some concern regarding cognitive dysfunction, dysarthria, a variety of other potential ill effects. We now have data, of course, of numerous patients implanted bilaterally in the STN and also in the globus pallidus.

There seem to be a preponderance more for the STN stim than for globus pallidus stimulation bilaterally. I was wondering if the Neurosurgeons could give us an idea if a breakdown of some of these

side effects seen with bilateral stim? I notice that in some of the material we had a chance to peruse in preparation for this meeting that, for example, on patient went berserk on the table during bilateral stim simultaneous implantation, same day, and a couple of other patients have had some cognitive behavioral problems.

In fact, some attempts to implant bilaterally ended up with some abortion of the procedure entirely. So my question is this, let me just try to crystalize this. Number 1, the breakdown in terms of whether or not separating the bilateral implantation into two separate session if there is some evidence that separating it rather than doing it same session lessens the side effect? That's one concern.

The other is whether or not even though there is more data for STN than there is for globus pallidus stimulation, whether or not bilateral stim in one group versus the other is more likely to cause some of these side effects? And the third question is more related to how long the stim is externalized if

there is some sense of how long you would recommend, what's the outer most time course before internalizing the device to limit infection rate?

MS. PRITCHARD: I'll ask Dr. Steven Wilkinson to address your questions.

DR. WILKINSON: My name is Steven Wilkinson, I'm a Neurosurgeon at Kansas University. I'm a Consultant to Medtronic. My trip here was paid for. I also have ownership in the corporation that had licensed technology to Medtronic, but in a different application. I might have to ask you again to go through those three points, but I think from the first one for the bilateral implantations, when we originally, from our own experience, when we originally started to do the implants, we would do them as staged procedures.

But as time has gone on, we are doing them now as simultaneous bilateral lead implants with the leads externalized and then implant the pulse generators later. And I don't really think that there was a big difference in terms of those morbidities, whether they were staged procedures or whether they

were bilateral simultaneous. I think there probably is a little bit higher incidence of confusion and some of the transient, perioperative morbidity in the bilateral patients, because you're obviously affecting both sides.

But for the most part those were transitory effects. In terms of the externalization of the device, obviously the shortest time possible is the best. I think that the longest that we've ever externalized a patient has been in the order of about ten days to two weeks. But I think that there have been other patients that have been externalized for longer periods.

DR. EDMONDSON: And in these patients who are extended out to over a week, are they on antibiotic prophylaxis the whole time?

DR. WILKINSON: Well, I can't speak to every Center, but in our Center yes they are on antibiotic prophylaxis.

DR. EDMONDSON: And breakdown for STN versus globus pallidus in terms of some of the neurocognitive side effects?

DR. WILKINSON: I think that they were, at least in our experience, I think that they were equal. I don't think that one target is inherently more risky or dangerous than the other.

CHAIRPERSON CANADY: A final question from Dr. Massaquoi. Oh, you have one more?

DR. MASSAQUOI: Just quickly, I think there was some concern on the part of a statistical Consultant about the possibility of placebo effect affecting the randomized study data. And the question is for people who have an implanted stimulator, are they aware in general of effects aside from, well let's just say, what types of awareness might a patient have when the device is turned on versus turned off, let's say immediately when it's turned on versus turned off? And what effect that might have on a placebo effect in your study?

MS. PRITCHARD: I'll ask Dr. Erwin Montgomery to respond to that.

DR. MONTGOMERY: Good afternoon, I'm Erwin Montgomery. I'm a Neurologist at the Cleveland Clinic Foundation in Cleveland, Ohio. I have no financial

interest in Medtronic. I am a Consultant whose time is being compensated for by Medtronic as well as my expenses. To answer your questions about the placebo effect, that certainly is an important consideration and multiple studies have shown that the placebo effect can be quite significant in patients with Parkinson's Disease.

But speaking as someone who has participated in numerous placebo-controlled clinical trials in Parkinson's Disease, I don't think I have ever seen any kind of, the magnitude of improvement that has been demonstrated in the presentations today and I'm sure my colleagues who have similar experience in placebo-controlled clinical trials would share that observation. Also, I do think though there are some pieces of data that have been presented that speak to the issue of placebo effect and that has to do with the three-month randomized study where patients were initially randomized to stimulator-on versus stimulator-off.

And in those two situations it was, and these patients did not know what the stimulator status

was at that time, there were clear differences in the UPDRS as far as on the motor examination. So that certainly suggests that there was an effect that survived any placebo effect. Also I think the issue was raised earlier about a potential carryover effect from the first period stimulation to the off stimulation subsequently.

If there was in deed a carryover effect or a placebo effect, it wouldn't serve to lessen the degree of difference or the degree of improvement noted. And the fact that there were highly statistically significant differences in the results, I think is, speaks to the efficacy of the study. In other words, if there was a placebo effect I think it would have reduced the differences that we would have seen and made it harder to detect a difference.

And the fact that a difference was detected speaks to the efficacy. And then your next question about how much do the patients really know that the stimulator is on? As Dr. Olanow mentioned, patients very often will get transient paresthesia or transient, a funny feeling or something like that when

the stimulator is first turned on. These are transient and typically are gone within a few minutes of having the stimulator turned on.

In fact, we did a study at the Cleveland Clinic where we would turn the stimulator on for the patient, we'd wait a period of time and then we'd either turn the stimulator off or leave the stimulator on and we would blind the patient as to that and ask them whether they could then guess whether they were on or off. And of the 15 patients that we studied, only one patient was able to reliably state that the stimulator had been continued on or had been turned off.

So again, these kinds of things are really transient. So once the stimulator is turned on, patients usually don't feel anything that would unblind them. In terms of turning the stimulator off, in our own experience, I've never seen any effect that a patient could never tell in terms of paresthesia or something like that, when the stimulator was turned off.

They certainly could tell when the

stimulator was off because their Parkinsonian symptoms got markedly worse.

DR. MASSAQUOI: All right. In summary, then, is that part, is the randomized part truly double-blind or is it almost consistently not blind from the point of view of the patient. The patient, if at one time the stimulator is turned on, even if transiently, they are aware that the stimulator is now on. Is that generally the case?

DR. MONTGOMERY: Again, I was not the, I didn't participate in this investigation, but I can ask Dr. Olanow to speak to that issue.

DR. OLANOW: As in many double-blind studies it is hard to make them perfect. And it reminds me of the study we did with Comtan where there was discoloration of urine for people who took it and it does impair your ability to do a double-blind. So if some people experience paresthesia before they have their benefit, it potentially unblinds.

As of course, as Erwin has said, does the magnitude of improvement that they experience. Nonetheless, not all people experience this effect.

We did everything we could to try and preserve and maintain the integrity of the blind. And I would like to just reinforce the point that Dr. Montgomery stated. That I've done lots and lots of double-blind placebo-controlled studies and we've actually reported on the placebo effect in our controlled studies and never have we seen anything of the magnitude that is obtained in this.

Not that that is necessarily reassuring to you, but it does speak to the kind of effect that these patients are experiencing.

DR. MASSAQUOI: I guess, and so when the statistical analyses were applied that you used, what, were they applied with the assumption of double-blindedness?

DR. OLANOW: Yes, they were and unfortunately we did not do a blindedness evaluation.

CHAIRPERSON CANADY: Dr. Cohen.

DR. COHEN: Yes, I have a few questions about how this technology might be applied to patients. One has to do with the qualifications and training of the physicians that would do this

implantation. And Dr. Lozano, I believe, mentioned earlier that the Stereotactic Society does training or, my question is, is there any kind of certification mechanism that would get this society, professional societies could do to assure patients that they were getting well trained physicians?

And second of all, earlier Mr. Elliott in his presentation said that the professional associations provided information to patients. Would professional associations provide that information on who was trained or what kind of training they had? And with, another, maybe you could answer and then I could ask the other question?

MS. PRITCHARD: I'll have Dr. Lozano address your issues.

DR. LOZANO: So this is an important issue. With respect to these associations, I can think of two examples where associations or organized medicine have taken initiatives to try to address this issue. One is to publish guidelines. So for example recently several Neurologists and Neurosurgeons were involved in the assessment of surgical procedures for

Parkinson's Disease in general. And this was done, a therapeutic assessment with the Academy of Neurology and there was an assessment of surgical procedures with guidelines as to what procedure should be done and how they should be done, what kind should be done.

So that's one initiative. Another initiative is within the neurosurgical stereotactic and functional neurosurgical community and the American Society. We have also, are working on guidelines for doing these procedures, what are the requirements that we recommend as a Society for doing these procedures. So these will be guidelines that will be published and available.

We don't have a policing function, but we simply establish these guidelines and say this is what we recommend.

DR. COHEN: Do you have an certification mechanism?

DR. LOZANO: No, there is no certification. The certification is just you are a neurosurgeon, that is a certification. You are certified as a neurosurgeon, within that you, you do

whatever procedures you feel you are competent in doing.

DR. COHEN: As a patient, I wouldn't want somebody operating on me after they watched a videotape. And do any of the professional, the patient association provide this kind of information?

DR. LOZANO: No, I agree with you. We want these procedures to be done by experienced Centers, by people that are qualified. And you know, it's our job to ensure that that training is available and that patients have access to Centers that have the training and experience to do these procedures.

CHAIRPERSON CANADY: I'm going to ask for one more question. I would remind people that there will be an opportunity for these discussions later as well, this isn't the only shot.

DR. COHEN: Can I ask one last question?

CHAIRPERSON CANADY: Okay, Dr. Cohen.

DR. COHEN: This is on a different issue.

CHAIRPERSON CANADY: I'd rather wait on a different issue until later, if we could.

DR. COHEN: Okay.

CHAIRPERSON CANADY: Because it is already 1:00. Okay. We're going to break for lunch now at 1:00, and you will return at 2:00. We will have at that time the FDA presentation. We will then have an opportunity for discussion and that includes an opportunity again to direct questions to the industry representatives.

(Whereupon, the foregoing matter went off the record at 12:55 p.m. and went back on the record at 2:05 p.m.)

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

(2:05 p.m.)

CHAIRPERSON CANADY: It's now 2:05 p.m. I'd like to call the meeting back to order. I would remind the public that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

We will now have the FDA presentations on PMA 9600009/S7 for the Medtronic, Inc., Activa Parkinson's Control System. The FDA presenter is Captain Marie Schroeder. She will be followed by Mr. John Dawson.

Captain Schroeder?

CAPT. SCHROEDER: Thank you. Good afternoon, everyone. My name is Marie Schroeder. I'm a Captain in the United States Public Health Service and a licensed physical therapist. And the other members of our review team are John Dawson who will also be talking right after me, and Robert DeLuca who is with us, but he won't be speaking, but he's available for questions.

I wanted to thank everyone first of all for coming today to discuss this very complex, but important medical condition and I really thank you for all the attention. It's very obvious everyone is really taking a lot of effort to focus on all of the questions that have to be dealt with today. So thank you very much.

Okay, I just wanted to start off with a brief reminder of the original approval for the Medtronic Activa Tremor Control System was approved in 1997 and there were certain conditions of approval at that time in order for that approval to go through which included further characterizing long-term safety and effectiveness, assessing neurotoxicity, assessing carcinogenicity, obtaining follow-up on mortality and autopsy information and evaluating patients following implantation of multiple leads and re-implantation of leads.

The study objectives for the studies that we are considering today for the new indications for use for this product are to define in the protocols as being to assess the safety tolerability and

effectiveness of electrical stimulation of the subthalamic nucleus and the globus pallidus for the treatment of patients with advanced Parkinson's disease.

The scope of the study, the European study protocol calls for 26 patients at five investigational sites. This was amended in June of 1996 to call for 50 patients per target site at ten centers because the low number, that is the 26, would not result in general clinical acceptance and therefore they wanted to increase the number in the study.

The U.S. study was approved for 10 patients and three investigational sites originally and went on to be conditionally approved for 26 patients at five investigational sites.

The study size of the Canadian and Australian studies, they used the IDE version so I assume that they were looking at 26 patients as well.

Study duration, they anticipated it would take about 18 months, the follow-up times, but that they would continue their study until their primary objectives were met and they would have follow-up

times for patients at 1, 3, 6 and 12 months after implantation of the second deep brain stimulator because this was a bilateral study.

Inclusion criteria, I will only point out the sponsor already went over these. There was a discrepancy between the European IDE protocols in that the European called for two out of three cardinal features. The company has told us that most of the patients in the European study as well had three out of four symptoms.

We can go to the next slide. One of the other discrepancies in inclusion criteria were just in the wording regarding this one, absence of dementia and absence of psychiatric and hallucinations due to dopaminergic and anti-cholinergic therapy at least one month prior to surgery and you can see below the wording for the European protocol. Again, the sponsor addressed this in this last volume of your panel package.

Exclusion criteria, I'll just read through quickly: not anyone who was not determined to be a surgical candidate, people who had previous

neurosurgical histories or withheld informed consent, those with demand pacemakers and patients who needed repeated MRIs, patience with a history of substance abuse, secondary or drug-induced parkinsonism, patients that had sustained depression with vegetative symptoms and suicidal thoughts or intent as determined by Part 1 of the UPDRS.

Trial design, again, there were two different protocols. They were similar, but did have some differences that were noted in the summary by the sponsor and in the last volume of your panel package. In the IDE version there were four centers in the U.S., two centers in Australia, one center in Canada and the European had 11 centers. They prospective, open-label designs for the most part. Both of them had the double-masked, randomized, crossover assessment on Day 2 of the 3-month follow-up only.

Pre-implant assessments, the open label assessments were conducted twice within one month of the anticipated impact. I believe most patients had that data averaged, but there were some patients it was not averaged.

Implantation, bilateral implants were either implanted simultaneously or they were staged. There was no mention of how that decision was made in the protocols. Timing of the staging was to be from 0 to 3 months from the time of the first impact. That was not the case in several patients. Several patients went longer than that.

The second implant could be canceled if there was concern for patient safety, there was a satisfactory result after one implant or the patient declined the second implant. A breakdown on the numbers of patients that received one implant for those different reasons is not available at this time.

The treatment schedule, according to the case report forms, the treatment could be applied continuously, during the day only, during the night only or some other schedule. The physician was to indicate that on the case report form and inform the patient.

Follow-up, the open-label assessments were done at 1, 3, 6 and 12 months after implantation of the second implant. Appropriate follow-up data was to

be collected during the period between the implants. I did not see anything in the PMA that discussed that data, but may be available.

Randomized, double-blind assessments at the 3 month visit was done at Day 1, I'm sorry, at Day 2 of the three month visit.

Patients that were not implanted or internalized were also to be followed at 1-month and 6-months for safety purposes. Not all patients received those follow-ups. It's a little unclear quite how many that was. They were to follow the evaluations that were done for the pre-implant assessments.

The target sites were as we discussed earlier, -GP or -STN. There was not a defined algorithm or decision making instruction in the protocols. It was chosen at the discretion of the investigational center. Standard imaging and stereotactic techniques were used as you can see up there and optional use of micro-electrode recording techniques and stimulation techniques could be used and there were two different leads that could be

implanted as was discussed earlier this morning.

Again, just a summary of the protocol defined a number of assessment measures for effectiveness. Form 5 was the patient diary information on motor fluctuations. There was a Sickness Impact Profile to be conducted. The Unified Parkinson's disease rating scale, UPDRS, the complete assessment. The Dyskinesia Rating Scale which was a modified Obeso scale. The objective assessment which included Step-gait and Tapping Speed and Form 10 was a subset of the UPDRS. It was Section 3, the motor exam. The European version did not actually have a separate piece of paper for the open label assessments that said Form 10. The third section of UPDRS was marked as Form 10. So Form 7 and 10 were merged.

Form 11 was the Global Assessment. Form 12 was only for the U.S. protocol. It was clinical fluctuation assessment that was supposed to be done over a 6-hour period, however, that was the approved protocol in 1995. It was eliminated in 1998 and there was a videotaping done, but there was no form available for assessments of the videotape.

Now I'd like to talk just a little bit more about the effectiveness measures. At the randomized, double-masked, crossover assessment that occurred at 3 months, just for a reminder because it does get confusing as to the status of the patient during these assessments, for the 3-month, again, we're looking only at the meds off situation and they were compared and assessed at Stim OFF and Stim ON for these four assessments. The videotape, the motor exam, the objective assessments and the dyskinesia rating scale.

The Dyskinesia Rating Scale, objective assessments and the motor exam was assessed at all four combinations of medicine, Meds ON, Meds OFF and Stim ON, Stim OFF.

And just as a reminder on the next page the European version of the UPDRS, Sections 2, 5 and 6, they assessed everything except the Stim OFF phase and therefore with these sections, you can't make any comparison between Stim OFF and Stim ON. And then for the sections 1 and 4, it also did not allow for comparison to Stim OFF.

It's a little unclear if you are looking at the protocols and the case report forms, it's unclear as to what the Meds Stim status and/or motor fluctuation status was with these following ones, the diary, the sickness impact profile, the IDE version of the UPDRS, the pre-implant UPDRS motor exam for the IDE version and the global assessments.

Looking at primary effectiveness endpoints, the sponsor defined as motor examination portion of the UPDRS with Meds OFF/Stim OFF compared to Meds OFF and Stim ON. It was to be double-masked, of course, we talked earlier today about the masking issues. It was randomized in crossover design and it was done only 3-months after the last implant. It was in the bilateral staged implants. It was done because you did it after the last implant, it could have been done as much as 6-months after the first implant.

The second area of efficacy endpoints, there were none specified in the protocols. Safety endpoints, there were none specified in the protocols. They did talk about monitoring safety.

Case Report Forms, as far as the primary

endpoint, I just wanted to clarify that for the primary effectiveness measure done at the 3-month time point, the European Case Report Forms for the second evaluation had the wrong response options provided for tremor at rest, action or postural tremor of the hands and for rigidity. It occurred only on the second form, but by doing that, there was some potential for the patient to have no change in status and still look like they had improved or worsened.

The diary, just to point out the fact that it was nice that they recorded Meds dosage and times and ON/OFF times and ON times with dyskinesia, but they did not prompt the patient to indicate when they were using the stimulator or when they were not using the stimulator and since that was a variable schedule, that would have been nice to have.

Videotape, there were no accompanying forms the follow-up protocols were somewhat inconsistent with respect to the medication and stimulation status.

Concomitant therapies. The Parkinson's disease medications, the inclusion criteria in the

protocols called for stable medications for one month prior to enrollment. Elsewhere in the PMA it described that during this study they should hold pre-operative medications constant throughout the study duration, although it may not be possible for all patients. The sponsors reported that most of the STN patients had medicines reduced.

The non-pharmacological therapies, there were no instructions. They were silent on that aspect.

Just in study masking, the 3-month visit again was supposed to be double masked. There is some question about the masking of the patients which does not seemed to have been monitored. It doesn't look like they assessed to see whether the patients were truly masked.

Next slide. Again, protocol definitions, the sponsor already went over, but I just wanted to point out that they're looking -- they were initially looking at this from Meds OFF to Stim ON -- or Meds OFF with Stim ON to Meds OFF with Stim OFF and it did not take baseline into account.

Protocol definitions of success, also as far as it didn't specifically come out and describe individual patient success and failure. The safety information was not considered in the current reporting of overall whether the patient was a study success. And there was one example where at least one patient was defined as success based on the 3-month randomization motor scores, but if you look at 12-month visit they were terminated due to infection necessitating lead explanation.

Global measure of success was not included in their definition such as they had done this sickness impact profile and they also did a complete UPDRS which might have given a more comprehensive picture of the patient.

Assessment of the second implant as compared to what benefit did the second implant provide over the first implant was not discussed. And I point this out because there were at least two patients that were considered successes at 3-month time point, but later went on to get implants, but the reasons why they needed the second implant were not

provided.

I'll just throw this up just as a reminder because this application has data from different data bases. The top one is looking at the 1998 data base closure. Most of the effectiveness assessments were done with that data. For instance, they start out with 95 bilateral STN patients and we have about 42, 43 percent of those patients at 12-months. GP bilateral, we start out with 38 and there's about 22 at the 12-month time point.

And then down at the bottom chart it's the 1999 data. They have a lot more patients that they are reporting in their 1999 data base, but some of these assessments do not include those additional patients. Our statistician will talk about missing data in his presentation.

Just another piece of information. It was a little unclear or difficult to understand in the PMA, but after reviewing the data it looks like, if you're looking at attempt at lead implantations it looks like there were at least 13 attempts in 12 patients that were a problem. Six of these individual

attempts resulted in no implant in 5 patients. One was a bilateral attempt and 4 of them were unilateral attempts.

Four attempts resulted in 1 implant instead of 2 implants and that was in 4 patients and 3 attempts of unilateral placement failed, but later received bilateral implants and that occurred in 3 patients.

And additional 16 patients with successful unilateral implants were also reported. The reasons for not being implanted with the second device were not specified.

It appears that 6 out of the 159 patients enrolled had the second implant more than 3 months after the first implant which was a protocol deviation. They were considered unilateral for some effectiveness timepoints and they were considered as bilateral patients for other time points. So I'm not exactly sure how these mixed data with mixed unilateral versus bilateral stimulation were handled in the effectiveness analyses. The reason for the implant delay was not explained and the reason for the

second implant when the 3-month assessment was deemed successful, it wasn't clear they went on to implant the second one, the second device.

Adverse events, the company looked at a number -- the safety in a number of different ways. They looked at overall summary of first occurrence of all adverse events reported by greater than or equal to 2 patients. They looked at deaths. They reported on other serious adverse events, the extent of exposure to implanted devices, adverse events by overall etiology, reliability and tolerability of the device.

This is just one of their -- the first page of listing of their overall occurrence of adverse events. The second column is total serious adverse events and then total ongoing adverse events and I'm just flashing them up there as a reminder that there are quite a number of adverse events that should be taken account, although as you can see, some of the numbers are low in occurrence.

87.4 percent or 139 out of 159 patients, of enrolled patients experienced 1 or more adverse

event. 86.7 percent in the STN group; 88.9 percent in the GP group. The overall summary of first occurrence of all adverse events reported by greater than two or more patients. It only reports the first occurrence of the adverse event so we don't get a good feel for the frequency of the occurrence even within patients or the duration and interventions are not provided.

52.2 percent of the enrolled patients experienced one or more adverse, serious adverse events. 49.5 percent of the STN patients and 57.4 percent of the GP patients. I just wanted to point out that the tables in the adverse events section list again only first occurrence and they report only on those that were experienced by equal to or greater than 2 patients.

Some patients were omitted from the tables, but you can find that information elsewhere in discussion, but in case you're just relying on tables I wanted you to know that there are some additional patients mentioned in the text, for instance, the subarachnoid hemorrhage is omitted. Hemiplegia is not listed as an adverse event and they do not reflect

serious adverse events discovered during the statistical analyses that were determined after data base closure and the summaries lacked frequencies, durations and interventions.

Again, the sponsor has already discussed there were six patients who died, 3 during the 12-month period and 3 after. One in this 12-month period had end-stage Parkinson's disease as the reason for death and after the 12-month duration of the study one died of pneumonia related to Parkinson's disease.

I just wanted to discuss hemiplegia/hemiparesis. It was not listed in the tables, but it is discussed elsewhere in the submission. However, after reviewing the information, it appears that from the narratives, it seems to describe six cases of hemiplegia/hemiparesis, but only lists one under that heading hemiplegia. There's one listed under paralysis and there's five serious cases listed under asthenia. There are also four other hemiplegia cases that are listed under asthenia and one of them that's listed under asthenia seems to be a general weakness.

Hemorrhages, there were 10 intracranial hemorrhages listed overall in the table. Six of them were reportedly serious. However, there was also a serious subarachnoid. One serious case of subarachnoid hemorrhage that was reported in a narrative, but not included in the table. I believe that the numbers from the sponsor this morning included that as an intracranial hemorrhage as well.

Intracranial and subarachnoid hemorrhage, the imaging studies for the safety parameter was not required by the protocol. 13 of 29 first reported first occurrences of confusion are considered to be procedure-related. Assessments demonstrating that confusion was not due to intracranial hemorrhage was not provided. And cognitive evaluations were not conducted.

And then looking at explanted and replaced devices, the complications -- they do have a nice table summarizing that, however, complications don't include all the clinical consequences and interventions do not include pharmacological or other clinical interventions. For example, one of the

patients developed a scalp wound, required hospitalization for antibiotic therapy, but the interventions indicate only device explanation.

The primary effectiveness measure, if we're looking at effectiveness results -- switch gears here. The primary effectiveness measure assessed Meds OFF status only, but the device we just ask you to consider that since it will be adjunctively with medications to take that into consideration in your deliberations.

Benefit from stimulation beyond benefit of the microlesioning procedure with Meds cannot be determined because it did not assess the patient when the Meds were on.

The errors in the European Case Report Forms for the 2nd randomized assessment creates some problem with how to interpret those scores. Assessment, they assessed the effectiveness of the permanent impacts at the 3-months only, as far as primary measure was concerned and again it does not address how clinical outcome varies over time when the electrical stimulation and whether electrical

stimulation effects diminish or not over time.

Looking at the open label scores and results, the sponsor evaluated within visit comparison of Stim OFF to Stim ON. Comparisons were not focused on baseline, comparison to baseline. The within-visit comparisons do not accurately describe the extent of the clinical change from true baseline measures.

The Meds ON/Stim OFF motor scores were often worse than pre-implant Meds ON scores, but the medications were reduced so at least for the STN patients which may account for the worsening of those scores after implant.

For the bilateral STN patients, the UPDRS Motor Exam improvement from pre-implant to the best follow-up score after implantation demonstrated a little less than 25 percent improvement and I think the best score was at 6 months. But they were close, but at all time points similar.

Medications. Medications were reduced in most STN patients. Reasons for the reductions were not provided. The Meds were to be held constant according to the protocol, but the Meds reduction in

at least one case indicated failure instead of success, so I thought that this medication analysis might need to have some more description, for instance, in one case the patients' dyskinesias got a lot worse and they had to just cut the medicines back. The patient also experienced behavior disorder characterized by hallucinations and being aggressive and ultimately died due to end-stage Parkinson's disease.

I also ask you consider focusing on Stim OFF to Stim ON within visit assessments. Again, if we look at the walk time from one of the objectives assessments that were conducted, you can see that at pre-implant the average was -- the mean value was 11.4 and at one month it was increased to 15.3 so it got slower which is the worsening effect, whereas if you look at just the Stim OFF Stim ON, there is a small difference of 0.1 and although it's deemed to be statistically significant, I ask you to consider the clinical meaning of that difference and whether it might be more appropriate to look at comparison to the baseline.

I have a number of graphs I won't dwell on. We will have -- this is the bilateral STN group. On the left we had Meds ON. On the right we have Meds OFF. And I just basically am putting these up to again give a little more visual comparison to baseline, the pre-implant values and also to give you a better concept of for instance with Meds ON on the left hand side, their starting values on the UPDRS Motor Exam which goes from 0 to 108 score, possible 108 maximum score which is worse, they start down lower in the range. So to consider clinically what does that mean for both of those.

The next one is doing the same thing, but it's for the Bilateral GP patients. Again, just wanted you to take care, notice the pre-implant versus post-implant scores as well as the Stim OFF to Stim ON comparison and again with the medications on the scores are lower than they are in the medication OFF state.

The company is making claims that include reduction in tremor, rigidity, bradykinesia, postural instability, so again, just very quickly tremor scores

you can see on the left side, left graph the ON medication state, the average was 1 point something at baseline on medications and actually the scores got worse without the stimulation after surgery. That may be accounted for by the fact that medications were reduced, but then if you're just considering Stim OFF to Stim ON values without comparing to baseline, you may get a different picture than if you're additionally doing a baseline comparison.

This is again tremor, it's the GP patients. You can see with Meds ON there's not much difference and there again, they're starting off very low on the scale for tremor.

Next. Rigidity. This is the bilateral STN group. The left hand side is on medications. The right hand side is off medications.

I think we can go on to the next one. Bradykinesia, we have Meds ON on the left hand side and this is the bilateral STN group. And on the right side is the Meds OFF.

Next. This is the bilateral GP group. The left hand side is on medications. And the right

hand side will be off medications.

This is just postural instability. On medications for the bilateral STN group and on medications on the left, off medications on the right.

This is the GP patients, bilateral GP. On medications on the left and off medications on the right.

In summary, I just ask you to note that as far as safety summary, in some areas it's difficult to understand, it's a little difficult to get a complete picture of what was experienced. There's a lot of information there, but some of it appears in some places and not in other places. So it's a little difficult to pull together.

No total PDRS score analysis was provided and there was some concern about whether that can be done because of the questions about the different sections of the IDE case report form being unclear as to the patient status, when they took, when they were assessing the different sections. Surgical treatment options, there were multiple confounding variables. Please take that into account. Testing with

medications off was the focus of the application, but we ask you to consider how dose that relate to the clinical experience when it's used adjunctively with medications.

There were changes in medications during the study that make it a little more difficult to interpret the results. Masking, you already have discussed the issue with masking of patients which was not assessed to assure that blinding had occurred or masking had occurred and pulling of studies, the sponsor provided a number of statistical analyses that they claim shows poolability. We also ask you to consider whether these analyses are clinically meaningful as well. Thank you very much.

CHAIRPERSON CANADY: Good afternoon, Mr. Dawson.

MR. DAWSON: Good afternoon. I'm John Dawson. I'm the FDA reviewing statistician on this application. I appreciate the opportunity to speak to you this afternoon. I have to note a couple of caveats very quickly. First of all, I know that stimulator is spelled S-T-I-M-U-L-A-T-O-R. I think

it's spelled correctly on the handbooks. Next point is that as Captain Schroeder pointed out, there was no IDE for the pivotal clinical trial that we're reviewing today, so consequently there was no statistical review of the protocol covering the issues such as sample size and methods of analysis, just to mention a couple of things that we would normally look at.

And finally, everything that I'm going to talk about in the next few minutes is based on summary results in the PMA, sample size, means, standard deviations, percents. Normally, we like to do some kind of a review of the raw data in machine readable form, at least sufficient to verify some of the principal endpoints, but we haven't done that in this case unfortunately.

I want to focus on sponsor's choice of the primary effectiveness endpoint. I promise I'm going to add something to this, but I do want to point out the precise statement of the primary effectiveness endpoint. It's the comparison of the motor examination score, TME, of the UPDRS with stimulation

ON compared to stimulation OFF and a double blind randomized assessment at the 3-month follow-up.

I point out that it was only at the 3-month follow-up and also as of this morning, based on what Dr. Montgomery and Dr. Olanow said, I think that double blind is a misnomer. Based on their statements that when the stimulator is turned on the patient who has been off stimulator knows at least initially that it has gone on and also that if a patient is off the stimulator after a period of time they're going to know that it's off because the symptoms come back and in the randomized study it was a two hour period over which to notice these effects.

So basically I think from a statistical point of view you can consider this study to be basically part of the open label, so-called analysis. The only difference is that there was a two hour washout whereas at 30 minute there was one hour was used in the regular part of the open label follow-up.

Next slide, please. I want to point out a couple of critical levels for the TME. First of all, the inclusion criteria, the TME had to be at or

above 30 in the OFF Med state, so above 30 is basically what we consider to be I guess to be sick, below 30 is somewhat better than that. And in this statistically clinically significant change from Stim OFF to Stim ON in the PMA was stated to be 25 percent.

If we can accept the proposition that there is a placebo effect, the question that I have and can't answer is how many of those 25 percentage points are placebo and how much beyond that is clinically meaningful change? That's unfortunately just unknown at least at this point.

Next slide, please. I have a simple table based on the PMA numbers. It covers 82 of the 96 implanted patients. 82 is the number that were entered into the randomized trial at 3-months and the term randomized, I hope applies, although I have a question about that later.

And this assembles all of the numbers from the crossover design and reduces them down to the average TMA score in the Stim OFF state for those 82 patients and you see that that's a 50.1. I would point out that the mean Stim OFF TME score,

pre-implant was 54, so basically at this point at 3-months when they're off stimulation for 2 hours or actually in excess of 2 hours in some cases in one half of the study, they're basically back up to the pre-study level.

The Stim ON number at 29.0 is a mean. A good thing about that is that it's not above the 30, so basically they're on the good side of the inclusion criteria. These patients have the 29. None of them would have been eligible for the study.

Now the key number that I want to point out here is the percent difference, the -42.1. Compare that to the 25. The 25 was the targets. 42 is above the 25. Next to that number is the standard error, 3.2. And that's the calculation that I did to which I inserted a mild positive correlation between TME at Stim OFF and Stim ON which is not a conservative thing to do. It's somewhat on the liberal side. And so the confidence interval at 42.1 from -35.6 up to 48.3 is not by any means too narrow. I think it's reasonable. And what I want to point out, the key thing on this slide from my point of view

is that the confidence interval excludes 25 percent.

So if this difference here between the 50 and the 29 is purely treatment effects of the Activa, then that's a strong showing of a treatment effect. That assumes that there's no placebo part that needs to be somehow factored out of that.

Next slide, please. This is basically the same analysis but it's done using only the original randomization assignments in a crossover design and this is pretty much the standard thing to do in light of the lack of statistical power for testing the carryover effect.

What you do is you throw out the whole second part of the study. You go back to just what people entered into first, whether they were first with Stim OFF or first with Stim ON and you look at those numbers and it gives you a reasonable look at the difference and you see that the 48 and the 31.8 are pretty much like the overall numbers for the entire design. The confidence interval on the difference, 25.9, up to 42.7, still excludes 25. So this means that under a conservative use of the

experimental data, it still supports a strong showing of a treatment effect, if in fact it is only a treatment effect.

The one thing I'm concerned about here is that in period one of that crossover design, 44 patients were randomized to Stim OFF and 37 to Stim ON. And this is why I said that I would have to raise a question about the randomization. He would not expect that much of an imbalance. We cannot think about an explanation that would result in things being that lopsided. One possibility is somehow people were randomized first to one arm and then for one reason or another switched to the other. But unfortunately, we don't know.

Next slide, please. This is the open label data. You've seen that in a couple of forms already. What is added here is the difference, the percent difference over time and you want to compare that to the critical level of 25 on the vertical scale. You see that that percent difference is always above 25.0. I did the test, my follow-up period, and it always excludes 25 so that strong apparent showing

of a treatment effect holds up in the open label data across the 12 months.

Next slide, please. This is the same graphic for the patients at medication ON in the OFF label. If I didn't say it I meant to, in the randomized study it was only with the medication OFF. In the regular follow-up Day 1 clinic visit, they went through OFF/ON on both medication and Stim and in this situation also I would call your attention to the percent difference and I did the significance test on all those means, ON and OFF. There is nothing that is based on the baseline measure. These are strictly contemporaneous ON, contemporaneous OFF. And again, the confidence interval always excludes the 25 percent.

Next slide, please. Maybe I can move a little faster on this. This is the GP bilateral. This is again taking the randomized study, reducing it down to a number for Stim OFF and Stim ON. The means, the mean for Stim OFF is 46.7. The mean at pre-implant for these patients was 51. So again they're back up in the pre-implant neighborhood. For Stim ON,

it's now borderline at the 30 critical point. The average difference or the difference in the averages, I should say, is -34 which is above 25, but when I do the significance test on that, it goes down to 23.3. It does not exclude 25. The showing is simply not as strong for GP as for STN.

Next slide, please. This we can go over very quickly. This again is just looking at the period 1 results. The confidence interval and the difference again fails to exclude the 25 percent, so again it's just not as strong as the STN numbers.

Next slide, please. This again looks at the open label results for the follow-up periods out to 12 months and the percent difference, as you can see, hovers around the 25 and I think, as I recall, the endpoints that is at one month and 12 months it's excluded 25 percent, but not in between.

Next slide, please. And again, this is with the medication ON . Once the medication is on, clearly there's simply not that much to be contributed, it seems by the stimulation, at least when they're used together, the results of this study.

Next slide, please. Okay, now I want to just recapitulate what the claim is, claim number 1, the sponsor has five of them, numbered 1 through 5. Number 1 is that the stimulator suppresses PD motor symptoms. The data source is the in-clinic assessment of TME from the UPDRS.

Next slide, please. The key points sponsor makes in the PMA is that basically you get about a 48.3 percent reduction in TME score, going from Stim OFF to Stim ON and about -37.7 percent for the GP targets, reducing by about a half for the STN, by about a third for the GP.

Next slide, please. These are the issues that I want to call to your attention. Some of this has already been gone over. Can the patients tell when the stimulation is on? The answer apparently is yes, initially, they can tell when it's turned on. How much in light of the fact that there is an anticipation of therapeutic benefit, how much does it account for the change in TME? I don't know the answer to that.

The third point, warning in the informed

consent. If there was some question about whether there was a placebo effect, I just wanted to point out that the patients were warned in the informed consent in a half a dozen or so unpleasant ways that they could tell when stimulation is ON. Literature and placebo effect, there is literature. It's not a new subject and surgical intervention for treatment of Parkinson's is difficult to avoid placebo effect. Final point under placebo, I just want to raise the question as to whether it would be possible to get follow up data beyond 12 months. I have seen other surgical intervention device type studies where you can really get a lot of reassurance that placebo isn't accounting for a great deal, if you can follow people beyond that 12 month time point. Since the study was -- the data base was closed quite some time ago, it might be possible to get further follow-up.

Intent to treat analysis. We don't have all the patients accounted for on the TME scores. There were 96 bilateral patients on the STN target. Eighty-six of those were tested out to 12 months. There are another 10 not accounted for. The sponsor

indicated in a February amendment that there are 20 drop outs all together in the study. I would like to know what the TME scores are for the patients that are not in that summary.

I've already raised the question about the imbalance in randomization. It is certainly a source of concern on my part.

Next slide, please. Coding rules are not explained in the PMA. However, the TME item nonresponse matters handled, the TME is 14 questions. Each question has an ordinal score, 0, 1 through 4. I meant to mention this earlier, but that 15 that I had on the first slide means that that's an average of 50 points for those 14 points on the TME, part of the UPDRS.

I'm just certain that there must have been some that didn't get filled in and I don't know how that was handled. Other issues, under-powered subgroup analyses with a total of 159 cases enrolled. Sophisticated analysis of a multivariate nature are under-powered in the sense that if some kind of regression were enova, it's done and you don't get a

significant effect, that's good from sponsor's point of view, but you don't know that it's just because you didn't have a lot of data. And if we had a chance to review the protocol, we would have told sponsor that. Sorry.

Next slide, please. Claims 2 and 3, reduction in dyskinesia time, increase in the ON time without dyskinesia. The data source is self-reporting conditions at half hour intervals in the 2-day diaries preceding follow-up clinic visit.

Next slide, please. Basically, Dr. Olanow gave you these numbers this morning. The improvement in the amount of time reported on those diaries for ON time with dyskinesia and ON time without dyskinesia, those are certainly favorable numbers.

Next slide, please. What I'm concerned about there again is the placebo effect and under intent to treat analysis, the PMA says that the only diaries used were those that were 90 percent complete and we only have 71 out of 96 STNs bilateral implantations with a 12-month diary. I would like to see what the results are, some kind of a proc. free or

other accounting of what the scores are for those patients that don't get into that analysis. Obviously, what I'm wondering is those patients that don't get into that diary analysis that provides those favorable changes in the number of ON hours, are they simply worse is something I think you'd want to take into account, that if you have a certain anticipation of a benefit in terms of ON hours, you'd want to know what your chance is to be in that favorable category.

Next slide, please. Coding rules, again, the PMA doesn't explain how the diary item non-response was handled. It's an extensive diary with many questions. Again, it's just about a physical certainty that some of those were not filled in. We don't know what was done with those blanks. Other issues again, there was not an IDE for this clinical trial so if there had been we would have urged sponsor to work out a quantitative hypothesis for each of these claims. I think you can see -- I think it was beneficial in claim No. 1 to be able to look at that 25 percent. We don't have anything like that for the diary results.

Extent of Stim use as covariate. One thing that was asked at follow-up was how much people used the stimulator. I think Dr. Olanow indicated this morning that practically everybody had it on all the time, so this may be a moot point.

Next slide, please. Claim No. 4, improvement in functional ability based on in-clinic assessment of the activities of daily living, part of the UPDRS.

Next slide, please. Sponsor's assertion there's a reduction in median OFF medication ADL score from the implant to 12 months, 47.6 percent for STN, 34.7 percent improvement. Almost the same numbers as for the TME, just a coincidence, I guess. But anyway that's favorable.

Next slide, please. So what are the concerns about that? I wonder about the relevancy of comparing ADL pre and post-implant with Stim ON and post-implant. I just don't know really what that means. I think there was an explanation this morning about that.

There was a problem also on the

pre-implant form that when the UPDRS, when you pick up the UPDRS and look at page one, it says evaluate and Meds OFF and then when you get to the ADL part it has a place to fill in both for Meds ON and Meds OFF and we're just guessing that maybe somebody in this study looked at it and thought well, it's all Meds OFF, so the comparison of Meds ON a baseline is a problem

Next slide, please. Finally, the reduction in patients' PD medication, the data source is form 3 in the follow-up package.

Next slide, please. And sponsor indicates that almost half of the patients reduced PD medication by 25 percent or more at one month and somewhat more than half had reduced by 25 percent or more at 12 months.

Next slide, please. My question about that is whether reduction dose is always good. This is the kind of nettlesome question we would ask if we reviewed the protocol ahead of time. If, in fact, what the device does is reduce the dyskinesia which is a side effect of the medication, the patient would have the option of increasing the dose. Anyway, that

puzzled me.

The 25 percent reduction on the previous slide looks like a very nice kind of target, but we only see that post hoc. So we don't know why 25 percent would be a target there.

Next slide, please. Finally, I just want to wrap up, covering what I think are the main points. One, all of these variables that show change over time, even if it's just one time to the next in a given day are subject to placebo effect. We don't know how much that accounts for anything, but it's in there somewhere and to some extent. It would be nice to see performance data beyond 12 months. Might shed some light on the placebo. The STN in the TME analysis made the 25 percent target. The GP target did not. There are issues of item nonresponse on all aspects of the UPDRS instruments in the TME diary of ADL endpoints. We need to know of the patients that don't make it into the summaries.

Thank you.

CHAIRPERSON CANADY: Thank you very much. At this point it's our custom to have reviews by our

panelists who have been designated in advance. Any questions for the FDA personnel?

We'll go on to the portion of our panelists' reviews. I would ask at this point since there have been a number of presentations that insomuch as possible those points which have already been presented, you might just mention and move on rather than have the extensive discussion you may have prepared in advance on issues that we've previously discussed.

We're going to have three presentations done in a very efficient fashion by Dr. Zamorano, a neurosurgeon; Dr. Nuwer, a neurologist; and Dr. Piantadosi and I apologize in advance for the third time, our statistician. It would be a statistician that would have a name like that.

Dr. Zamorano.

DR. ZAMORANO: Should we do it here?

CHAIRPERSON CANADY: However you would prefer.

DR. ZAMORANO: I had a presentation with slides, but --

CHAIRPERSON CANADY: However, if you want to go stand there that's fine. However you prefer. We'll still know you're one of ours.

DR. ZAMORANO: Originally, I was assigned to make a review of the problem of surgical treatment of movement disorders specifically in Parkinson's disease and this is a little bit what I have in the slides, but I think I will make it a little faster and focus to the discussion as many of these issues have already been covered in the prior presentations.

Next slide, please. Basically, to place it in the scope of what we are discussing at this moment, first of all, stereotactic surgery was used to treat tremor disorder already 30 years ago and as has been already mentioned with the use of L-dopa for Parkinson's disease these surgeries were rarely performed during the last two decades.

Next slide, please. Some of the limitations of the drug treatment and especially some new understanding of the pathophysiology of Parkinson's disease as well as technical advances in neuroimagining and electrophysiological recording.

Surgery has again considered an alternative treatment.

Next slide, please. And it has been focused already that the four cardinal symptoms of Parkinson's disease of tremor, rigidity, kinesia, postural instability and the medical treatment with L-dopa, one of the main problems that we're focused with the periods of dyskinesia with these patients and involuntary movement.

There are other problems involving in Parkinson's disease with dementia, freezing and other problems that make this a very devastating disease.

The main topic and I think this is not in discussion any more and just to place in perspective, the surgical options on patients with Parkinson's disease is the use thalamotomy.

Next slide, please. And this gives an idea, this is like a diagram that gives you an idea of the different structures that we have been involved all during the presentations during the day, the thalamus, basically and we have this striatum here where we have GPi and influence the thalamus and we have STN that is influenced indirectly the GPi through

this, the thalamus and there is another, you see all there is a direct cortex to the spinal cord and cortex to the exterior influence.

And all of these are inhibitory or exhibitory pathways. So it's a very complex physiopathology and basically act in different levels is where we try to achieve some effects in these patients.

So the first one is the thalamus with the VIM, with a specific nucleus and it's here where we start all the surgical procedures. Basically, performing destruction in an ablative procedure of this specific destruction.

Next, please. With the thalamotomy, specifically in the ventral nucleus of the thalamus. Next. One of the clear -- this is just an example to show how it looks, these ablative procedures.

Next. The end result of the thalamotomies is basically we have a relatively good improvement in tremor and there is some morbidity related, but it was acceptable and these became a procedure to consider. As you can see, some of the persistent morbidity that

has been addressed today.

Next, please. But basically, there is a 90 percent 95 percent response to this ablative procedure in the thalamus with thalamotomy.

Next. Let's see, we can skip that. Next, please. Okay, complication of thalamotomy and any other ablative procedure. We have the hemorrhage, the infection and other transient postoperative adverse effects. We have mentioned confusion is one of the most important and other major complications with hemorrhage you can have hemiparesis and dysphasia.

The next. The bottom line is thalamotomy is a good alternative treatment for tremor and with a relatively low incidence of complications and obviously when most of the patients have bilateral symptoms, it goes to the bilateral thalamotomy and here, over more than 25 percent of the patients experience different types of problems and this morbidity becomes somehow unacceptable and this is the reason that bilateral thalamotomy is apparently not performed at most of the centers.

Next. In order to avoid this problem, it

becomes common sense to go to a different alternative approach, is to use the same target, but with a different approach to the stimulation and the deep brain stimulation with the thalamus in the VON nucleus is what is already approved, has FDA approval already. Basically, the pathology is similar.

Next. And we have a good alternative treatment for tremor. But as we mentioned at the beginning tremor is probably not the major problem of these patients and this is the topic of the review we're doing today. If there is a place for surgical treatment in any of the other symptoms of Parkinson's disease and that becomes a little bit more complicated to analyze.

The first thing that happens is that pallidotomy and this again, an ablative procedure, was considered in patients with Parkinson's disease in order to alleviate other symptoms than the tremor.

Next. And next. We'll go a little faster over these slides. But basically the lesion of the globus pallidus interna involves some of the parts I already showed you in the first slide.

Next, please. Laitinen, basically was the one that re-explored in the modern era of this use of posteroventral pallidotomy and it was reported with the ablative procedure int eh pallidum, patients will have some improvement in tremor, not as high as with thalamotomy, but an important improvement in maybe 50 percent. But at the same time there was an important improvement maybe in bradykinesia, akinesia, in the rigidity and probably the main indication and probably the only significant conclusion so far with this pallidotomy is that these patients improve the dyskinesias secondary to the medical treatment. So patients that have the dyskinesias, this undesired effect of medication, these patients they do benefit with a pallidotomy so they have less dyskinesias. Dyskinesias can be very incapacitating and can be as bad as the disease over the life of these patients.

Next. So the pallidum becomes a very important target not just to treat the tremor, but basically, especially the patients with medically intractable symptoms, specifically the undesired effect of L-dopa. In most of these patients as was

addressed today, they do respond to L-dopa, but they become averse to this medical treatment because of dyskinesias.

Next. So the pallidum -- we can go to the next, please. So the pallidum becomes very, it's a second target that becomes some choice for these patients and you can go over this slide. This is just to give some idea of the improvement that has been reported using this target.

I must mention that in the 1950s and 1960s there were some other centers in Europe where they did have experience with the target close to the subthalamus at the insert and could result in tremor, also some of the -- they did report that it was an improvement in the rigidity and maybe in the akinesia, but at that time the ablative lesioning of the insert was with a very high morbidity in terms of patients have confusion and other problems. That's the reason that procedure didn't take so much -- wasn't used so much as the thalamotomy.

Next, please. So in this case it becomes an issue, you know, the target of the pallidum as an

alternative and also this thalamus and when we're talking obviously of the ablative procedure, then the stimulation becomes an important point. From the technical point of view, pallidotomy is a little bit more difficult target than the thalamus. The thalamus is relatively large and the pallidum is a small target were it to be done for the surgery to be effective. Second, there are two structures very close to this internal portion of the pallidum and one is the optical tract, the visual pathway and the internal capsula where it has relationship with movement of the contralateral side. So it becomes -- it's more difficult to perform a right pallidotomy. I think most of the surgeons will agree with that. It requires a little bit higher degree of expertise.

Next. But it may be there is some controversy and we can see in this analysis today there are different techniques to define the precise location, if you use more or less functional information in the procedures.

Next. The next, please. But the GPi can be performed somehow, can be performed pallidotomy

even the ablative procedure with a relatively low risk with some morbidity in the patients main effect probably number one would be the degrees of dyskinesias secondary to L-dopa. They do have improvement of the tremor in maybe 50 percent of the case and over time they become probably maybe improve this percentage of response to the tremor and maybe some response to the bradykinesia and the akinesia of these patients and they may improve postural instability.

Next, please. The next. This tells you which of the patients are the best candidates for a pallidotomy would be a patient that has very few of the other symptoms and the main symptom is the dyskinesias, secondary to the L-dopa. So with the pallidum stimulation -- next -- one of the advantages of pallidum stimulation versus the ablative would be to have less complications because you would not have the effect in these structures, basically, the optical pathway and the internal capsula, so you will have less complications.

Next. But the rest of the procedure