basically you should expect relatively similar results to the pallidotomy per se.

Next, please. This goes a little bit over the different results of different series that they wanted to be performing more pallidotomies and pallidal stimulation in this case. One of the studies that have been observed in this kind of stimulation that we don't have with the thalamus target is that some patients could reduce their medication and this is something that was observed in some cases even after pallidotomy. So those other parts of the spectrum of the disease with the thalamus perfect for tremor. All the other symptoms, really, they have not been addressed with the current approved treatment, with stimulation in the VIM. So this is the reason to consider these other targets.

Next, please. Next. Please go to the type of complications of pallidotomy that I already mentioned.

Next, please. This is thalamic stimulation and at some point this is in regard to the GPi. Now in terms of the subthalamic nucleus that is

where that has been some more experience to go into the third component of this problem and experience, especially that began in the European centers, some of the -- Dr. Benabid that was mentioned today in the original presentation, they observe, they went to target similar to the regional insert and with some modifications to the specific subthalamic nucleus. You can go to the next, please. And in these cases, they observe also some benefit in tremor, minimal.

They did observe the same effect in the dyskinesias and at the same time for the first time they started observing or what was reported as a relatively clear decrease in the dose of medication necessary for these patients and this is where the subthalamic nucleus became an issue in this arena.

As I mentioned before just early in the 1950s, 1960s, there were a few surgeons performing ablative procedures of the insert, but those were abandoned and ablative procedures were more done in thalamus and in GPi because it was a better target, that you have less morbidity. The subthalamic nucleus, one of the problems is a very critical packet

with many important structures around and when you go to the ablative procedure and you perform lesioning, you get some thermal spread effect in the surrounding and this was accompanying in many cases with important problems, especially with confusion and patients that their mental functions were really impaired after the procedure. As a result that was eliminated. Now with the stimulation, as we're not producing an ablative procedure, it becomes somehow a little bit safer to go there and place electrodes where you are going to perform a lesioning and avoids this complication, so next, please.

So this is where it comes to these procedures of stimulation because it's reversible, plus if the patient in theory has problems due to the stimulation, you can stop the stimulation in theory, even remove the electrodes and the other is that you can change the parameters so in some patients you may obtain the effect that you desire and you can avoid these effects in the mental and basically avoid what you want in these patients.

Next, please. So -- there are a few more

slides you can go over. It's just to give perspective of where we are in terms of this treatment.

Now in terms of the -- you can continue, please, with the slides and I will just summarize a little bit, this portion. From my perspective, in terms of discussion and I am concerned that maybe in terms of an approval of the system for DBS, other than for deep-brain stimulation, other than thalamic and the first question is that we need to answer is that if we can really show or this present review, really show a clear improvement or benefits other than the tremor, as we know we have a good already alternative treatment and there's a little bit of concern to me when I read this proposal that we cannot define and it's because of -- as we see it's very divided even in the literature about this. We cannot define to the doctors that are going to be doing this procedure, even which target to use, either GPi or subthalamic or always is a good resource for one or the other.

As we need to have concern of the issues of safety, we know that the thalamic target is a very safe target, the VIM, other than the complications

that are probably inherent to any surgical procedure. It's relatively safe. GPi is a little bit more complicated target and subthalamic I think and I have some personal experience in the subthalamic, I think it's a very difficult target and I think the issues like training and how people are going to be trained to get to the STN if this isn't available, alternative for any neurosurgeon, how it's going to be accomplished the training.

I think there's enough evidence in the literature that deep-brain stimulation for subthalamic or GPi, they have some role -- they have some improvement in some specific patients. It's very difficult to determine up front which patients are the ones that are going to benefit and these are issues that I think we need to consider in the discussion.

I think in something that is open to the full community of neurosurgeons we should define better what would be the patient indication or the selection of these patients and define the target that is going to be considered the target of choice or how to get to the target, to define the cases that need to

be unilateral or bilateral and probably place in perspective to the patients, really a very clear indication of what is the real benefit of this therapy. When we're not talking about tremor, all the other ones are very difficult, I think, for the patients to understand what they should expect of this therapy and this is something I think we need to address very clear and at the same time I wonder if 12 months follow-up that this is what we have in the present study and it's a question that I raise is enough time to approve it before full usage in the general neurosurgical community.

So in conclusion, the last comment for my point of view of the analysis of this, and knowing somehow this area, working in this area, I think there is enough evidence that this may be very important advances in the treatment of Parkinson's. There's no question that GPi thalamic may have a role in some patients. I don't know if we know which patients are the ones that are going to really benefit from this and I don't know if we have very clear understanding, the performers of this technique in a general setting,

neurosurgical setting. All the experience that was shown with the few sectors that we discussed and most expert people in this arena and as we review, there is a number of complications even with this expertise. So I think you can extrapolate to almost 5 to 10 times that kind of complications when you get to open a procedure to the general community.

So these are some of the concerns that I have after reviewing this and some of the areas that I would like that we discuss with the final.

CHAIRPERSON CANADY: Thank you. I just want to share with everybody a sense of where we're going so that we can make choices as we go through our conversation. We have two hours to complete our work today. We're going to have Dr. Nuwer, Dr. Piantadosi give us presentations efficiently, I'm sure, and then I'd like you to begin crafting your questions and as much as possible be efficient in those questions and no later than probably 4:15 or 4:30, we need to begin to address the FDA questions.

So we have approximately 45 minutes of general conversation left and I would ask people to

keep that in mind.

Dr. Nuwer?

DR. NUWER: Thank you. And I think I'll speak from here because I specifically didn't bring any slides, recognizing that time is a certain constraint here.

In going through the main questions that are posed, that is the main points at which this device would be labeled as useful, I did try to separate out in the statistical complexities from the impressions of whether there is a clinical efficacy or not and I agree that there are some problems that have to do with the concurrent decrease of medications and the questions about a placebo effect, but overall I thought that the first four questions that we had seemed to have evidence in favor of there being a clinical efficacy and those questions were that of suppressing the cardinal motor symptoms, of reducing dyskinesias, improving the ON as opposed to OFF time and allowing greater independence and functional ability.

I had more questions though that came up

about can you reduce medications based on the statistics and the numbers that we reviewed. I recognize that that is something that speakers today have tried to address and have indicated is one of the usefulnesses of this medication. I just found the numbers a little weaker on whether or not you can reduce medicines and I noted that they only found statistical significance in their subthalamic nucleus subpopulation.

The area that I thought was lease supported by the data was that of the Global Disability Rating and there there was more modest and mixed results and I found that least impressive. I am still concerned about the safety issues. It seemed that overall, if I could take it very roughly, 10 percent of the patients do have clinically significant adverse side effects such as intracranial hemorrhages and that that is a significant safety issue that the panel as a whole is going to need to weigh later, is that we do indeed have some reasonably there is some clinical efficacy and then is the safety issue really sufficiently controlled that we would consider it not

only efficacious but also safe, given the other numbers we've looked at.

And I think some of the side effects such as dysarthria and confusion and dyskinesias that were reported by patients I felt were an acceptable proportion and less than what would be expected in Parkinson's patients, in general, so that I was not so impressed by those kinds of side effects. I was more impressed by the hemiplegias and intracranial hemorrhages as effects of the implantation itself.

There was some data in here in the large pile, the 24 inches of material we were given about the autopsy results and relative lack of long-term side effects from having brain stimulation so I was not concerned about the long-term effects of the electrical stimulation and I thought that the effects of the stimulation itself were relatively modest, so they did not appear to be safety concerns. I noted the convulsions or seizures and I agree that it was more likely a result of the implantation side effects than of the running electricity through these structures.

It was not clear to me about some of the issues of surgical implantation. I know that micro-electrodes were needed for when ablations were done for globus pallidus, but there is no mention of micro-electrodes in implantation of these devices and I take it that then is not a part of this procedure.

My concerns about implantation have to do more with accuracy of being able to target the structures and what I've heard today is that there is not a concern about accuracy if the surgeon is well trained and if they have enough experience and the right equipment.

Other concerns, age effect, the study had a cutoff at 75 years of age. Average age of the study participants was about 58. A lot of the Parkinson's patients who may end up treated, being treated with this device though would be older, that is some moderate proportion probably above 75. So that the question still remains as to whether Parkinson's is sufficiently a homogeneous group of patients so that the results that we've got here in patients who are in their 50s and 60s really can be directly extrapolated

to those who are in their 70s and 80s and I think that still is somewhat of an open question, although obviously the needle points toward it likely being efficacious. It's just the data to prove the point are not quite there.

I assume that we're not talking about anybody getting four placements here. We're talking about people getting bilateral subthalamic nucleus or bilateral globus pallidus, but I assume too we're not talking about a patient who has had let's say bilateral pallidal implants coming back and getting two more implants in the subthalamic nucleus, although I throw that out as a concern because it didn't seem to be objectively addressed at any point here.

And finally, the duration, the question of how long does the effect really last? Not how long does the battery last, but how long does this effect really last and I think the jury is still out as to whether or not the effectiveness lasts beyond these first few years or whether as in some other movement disorders, the movement disorder gradually breaks through the treatment and the treatment becomes

relative less effective or ineffective after several further years have gone on. I guess that's just an open question.

Those are the principal things that I saw as I went through as a clinician trying to assess what do I think the data, both from a safety and an efficacy point of view.

CHAIRPERSON CANADY: Thank you very much, Dr. Nuwer. Dr. Piantadosi.

DR. PIANTADOSI: Thank you. I think maybe I'll show one transparency and stand up just because I'm tired of sitting, is that okay?

CHAIRPERSON CANADY: That's fair.

DR. PIANTADOSI: Thank you. I'm just going to show the topics that I'm going to cover and try to do so fairly briefly. I feel the need to qualify myself a little bit because many of you are probably wondering why somebody with a focus in oncology would be at such a panel meeting and I think it's a fair question. I've had a lot of years in clinical trial methodology, probably 18 or so and I've served in a number of capacities around the Agency,

including several years on this same committee as well as ODAC and Anti-Virals. And I know a small amount about Parkinson's, not as much as I'd like to, but I have donated some time to the Scientific Advisory Board of the Parkinson's Study and some to NINDS in a data safety monitoring capacity for some other trials in Parkinson's.

What I'd like to bring though is a fresh perspective on methodology, both to the device issues as well as the particular clinical issues here and render some informal comparisons to the way I see this methodology and its use in this particular setting compared to what I see in other areas. And my experience with surgical trials, not only from a regulatory point of view, but from an academic view is that they tend to get very strongly colorized by the initial impressions that surgeons and others have of the treatment and this sometimes carries over very late into development and all the way into clinical practice uses and this, I think, is in keeping with the traditions and respect for opinion that is prevalent in the surgical community.

The first thing that I do when I look through these materials was to examine the framework for the investigation and in the simplest incarnation, I think the framework was good, but it became bloated very quickly. You have to ask yourself why should stimulation work? We saw some evidence as to why it might work, but these ideas are actually not on par with current thinking about drug mechanisms and receptors and targets and things like that. So the rationale for stimulation is probably no better than it is for ablation. There's a biological model at work, but it's fairly crude by comparison. Not a big problem, but certainly an issue when trying to interpret some of the empirical data.

The putative treatment effect appears to be large when you look through the data, but really not when you consider how early in the post-treatment period it's measured and if you're concerned about the efficacy or the side effects that occur from ablation as opposed to stimulation, you'd have to wonder whether or not these two treatments are, in fact, invoking some sort of common pathway and that they

should be looked at more as a whole rather than separately.

So the somewhat unsophisticated framework, or unsophisticated biological model then would lend itself to a feasibility study which I believe this was initially, could be characterized in those terms, but then as I'll discuss in a minute, I think it became bloated very quickly.

This lack of a strong biological framework is the reason for being more rigorous, not less rigorous int eh experimental designs and whatever inferences that we make from these data, they need to generalize very strongly to the population and we have to be very careful about how they're going to be used.

Now you could ignore all of this, I suppose and proceed entirely on an empirical basis. In other words, it would be possible to design an experiment, conduct it and collect the data, analyze the data in a way that obviated the need for anything except the crudest of biological models about how the therapy worked and obtain a reliable answer that way. But as we'll see in a minute, I don't think we're

there, but nevertheless we need to move on and talk about the second topic which is the second thing that a methodologist would do and that is to look at how the data production comes about, hopefully through the process of design. And one of the fundamental things that we try to do is to control extraneous variation and I think there's been a rather poor job of that in this particular study. For example, there has already been expressed concerns about center effects. We didn't talk very much yet about prognostic factors, but in some of the analyses buried in the back of the materials, there are the strong prognostic factor effects, including which area was chosen for stimulation, the age of the patient and so on and probably the individual patients' baseline scores are also important. These extraneous sources of variation don't necessarily need to cancel each other out. In fact, we'd be worried that they didn't do that and that they may, in fact, be masquerading as a treatment effect, wholly or in part.

The second principle for design data production is that we account for all the patients

treated and all of the time at risk. Here again, I think there's some notable, but maybe not glaring deficiencies in the study. For example, the protocol mentions the principal of intention to treat which one would normally apply in a randomized parallelled group's design where any patient who met the eligibility criteria and received a treatment assignment would be accounted for in the analysis of the data. Here, that's not quite the case because some of the patients were essentially removed from consideration at the very beginning. Others experienced some sort of attrition along the way and it's not clear, really, how we should represent that effect when we talk about things like average scores and average time on this or time off that. Should those patients simply be ignored and we pretend that they were never part of the study? That's hardly appropriate and hardly keeping in with the spirit of the intention to treat principle that's stated in the protocol. Should we assign values that are zeros for those people or worse case values or average values? It's not clear, but there are some systematic

approaches to this that should be explored and I don't think have been yet.

The third principle under data production is the control of bias and there's an explicit acknowledgement of the potential for this because of the use of masking and the concern over the placebo effect in the study. In addition, we would normally use randomization in a parallel group's design to help control for these effects. Here though, looking at the primary stated endpoint the 3-month so-called double blind randomized crossover trial, the use of randomization is altogether different and I'll get to that in a second, but we can't fall back on that, reassuringly, and think that that randomization has, in fact, balanced or covered all of the potential biases that we hope that it would.

A fourth principle is selection of a relevant endpoint and here, you really have to distinguish very strongly between a developmental trial and one that's intended to show strong evidence of clinical benefit and I think that here again, there are some very notable weaknesses in the evidence

that's put before us. The point in time that's chosen in a particular outcome measure are wholly consistent with the original design of the study which was the feasibility trial, but as a measure of definitive clinical benefit, these are quite lacking. They don't show us anything about the durability of the benefit. We don't have much information about long-term risks and in a sense, this outcome and the point at which it's measured is more akin to a surrogate outcome rather than a definitive clinical endpoint.

A fifth point in design data production is control of random error. And this is something that we normally expect from an adequate sample size. This was given an explicit consideration in the original design, although it resulted in a surprisingly small sample size, but nevertheless hard to argue with. But here in the crossover study and I'm going to refer mainly to that three month evaluation in the crossover study, the patients are not randomized and it's important to understand that. Every -- the patients all receive both treatments. They are not randomized. And so you can't look to the randomization to help

cancel out the systematic effects that might come from imbalances or prognostic factors in the patients. What is randomized is the order in which the treatments are given. That helps us to do valid tests of the period effect and so on, the carryover and period effects, but it doesn't really help us to eliminate bias as a source of treatment effect. So the validity of this crossover design is not based on the same theory and it cannot be interpreted in the same way as a large randomized parallel group's design. It simply is not the same thing. In fact, I would argue that the use of the term randomization here is a bit of a misnomer, although it's literally correct because it only validates the tests of period and carryover. Both of those are underpowered and so you have a Catch-22. If you would like to eliminate the period and crossover effects as being influential in the outcome, you essentially have to inflate the sample size up to where it would have ordinarily been for a independent group's design.

And then finally under design data production, I think that we probably should be able to

see some results that are adjusted for some of these extraneous factors not relying on the experimental structure itself and in particular, I'd be interested to know about the treatment effects adjusted for age and some of the other factors that were identified in the briefing material as strong prognostic effects.

The next step to evaluate the methodology is to look at the research process. Here, I think that the a priori hypothesis is okay. The study protocol, however, as a second item raises some red flags in my mind, particularly when compared to the current state of the art. It's very odd, in fact, the way that the sample size became so inflated. This enormous increase from somewhere in the range of 10 or 20 patients to 50 patients to 150 patients is wholly inconsistent with the stated study goals. And it raises concerns about what people were thinking, what additional information was brought to bear on the problem, whether there's any kind of gaming with respect to outcomes. This kind of thing would be a strong consideration, certainly in oncology trials.

I think that it's a good thing, in a way,

that the agency was not sort of part of the decision to turn this study into something much larger than it originally was planned for. It would have been a huge tactical mistake by the FDA to permit this kind of enlargement. What should have been done was to analyze this original study as a feasibility trial which is the way that it was designed and then to take on a second protocol with explicit clinical benefit endpoints assessment of long term risk and an endpoint that spoke to true clinical efficacy and durability.

Another point under the process is accounting for the dropouts and the missing data and I already commented on that a little bit. Only 82 of the 96 patients who were eligible for participated in that crossover portion of the trial. This can be a problem especially for longitudinal analyses where you have continued attrition and what you have is that the endpoints become distilled out so that you see the best performing subsets of patients as time moves along and this is quite a different effect than what you think of in your mind when you hear about a randomized trial and these analyses with the still

best subset of patients are not protected by either the masking or the randomization.

And then finally I would characterize the research process that we're seeing now the summary as really an attempt to show convincing clinical evidence from what could only be described as an overinflated feasibility trial.

The next point has to do with clinical benefit or clinical efficacy and here we'd expect to see an emphasis on the magnitude and relevance of the clinical effects rather than on statistical hypothesis tests. I think there's some stylistic deficiencies in the application in this regard, but I hope that my clinical colleagues will be able to sort those out.

I do agree with the points that have been made that the comparison should be to a standard therapy or in the presence of effective anti-Parkinson's medication and not to no treatment. I think it would be very odd to consider otherwise. The data, as I understand it, and that were presented by the sponsor this morning suggests that a fair amount of the effect can, in fact, be replaced by

drug, apparently, not all of it, but the question is what remains after that is that placebo, is that bias or is that therapeutic benefit.

I'd also be concerned about safety. These points have been mentioned earlier and I don't need to emphasize them, but the frequency and severity of serious adverse effects are to me quite noteworthy. So it really comes down to a question of the risk benefit that I think is primarily clinical and not a methodologic issue.

Indications is really an important consideration. We would hope that this point in the process with a definitive clinical benefit trial to have some help with the set of patients for whom this therapy were indicated. In fact, I don't believe that that question or the answer to that question is within the scope of the current inference, given the data that we have and I think it's an important issue that will have to be left unanswered.

Finally, I should mention the reduction in medication in my opinion is not a relevant question at this point. What we should be focused on is whether

or not this particular treatment works and then later we can decide either through additional data or additional studies whether or not it's appropriate or desirable to reduce the medication in the presence of stimulation if it comes into use.

I'd like to say just a couple of words about the regulatory overlay because I think it's important to provide some opinion to the Agency in regard to that and sort of the precedent that is being set by the way that this application is reviewed.

My first question here is whether devices are somehow special or not and I think that they are to a degree with respect to early developmental studies. There are some efficiencies that can be gained there in devices and we don't need to go into that now. It's probably arguable. But I don't agree that they're special when one looks for relatively small degrees of clinical benefit as is the present case. I think that devices are very much analogous to drugs in that regard in that they demand rigorous trials and they demand control over all of the sources of error that I outlined earlier.

I'm sensitive to the regulatory precedent that might be set here, the need to have a study that's designed conducted analyzed and reviewed strictly from clinical benefit point of view, the ability to isolate the effective interest, using good design and I've already mentioned some of the problems there. And also the point that when there are other effective treatments for a serious condition as there are in this case, the regulatory hurdle can be set fairly high, because the consequence of making a mistake in the presence of other effective treatments is probably worse than it would be if this were the first thing to come through the pipeline for treatment.

One of the things that devices do very well and that this particular device might do is to remove from consideration worries about compliance and that's a terrific advantage, but may not carry the day by itself.

I'm somewhat reassured in the regulatory framework by the fact that the analyses of period one alone seem to support efficacy at least within the

other constraints I mentioned about, possibilities for systematic error. There is a concern over the randomization and the imbalance, but I think that's probably answerable, perhaps even on the back of the envelope. My calculation done mostly in my head suggests that the deviation from a 50-50 randomization is not outside of expectation, but certainly that can be checked in a straight forward way.

I think that in the regulatory setting this particular application from a statistical point of view does not provide the usual reassurances that we'd expect from a study done in this size or done in this heterogeneous a population and it's basically going to come down to a question of whether you believe the treatment effect exceeds any possibility of a placebo effect.

So my conclusions are first that this study shows some significant signs of methodologic distress. This is clearly seen from a larger perspective. The design is not robust as you might expect from a quote randomized trial in 150 patients, not robust to the influence of some very important

extraneous factors. The outcome from the perspective of the decision that needs to be made about clinical benefit is in my opinion poorly chosen. The analyses are suboptimal because of the effects I mentioned, longitudinal effects and the potential bias from data omitted from patients who have dropped out and I think that the data in their current form are actually rather poorly seeded for the regulatory purposes to which they are put. In other words, I wouldn't call this trial the way that it's presented right now well controlled. The portion that is well controlled is for the reasons that I outlined earlier somewhat irrelevant. It's more of a feasibility study.

It's possible that a new trial or new views of the data perhaps trying to address some of my concerns could be considered well controlled and would provide a convincing evidence that's needed. Now I would mention, however, that a crossover trial is almost always the wrong design and if I were a Parkinson's advocate, quite frankly, I'd be very annoyed with the sponsor at using the degree of resources and time and effort and so on to generate

evidence of this type that is really marginal and not as convincing as it should be.

I don't believe that the needs of the patients are effectively met by this kind of design, not so much the design, but by this quality of evidence and I certainly wouldn't want to see a premature approval of this application until everybody is totally comfortable with the issues and totally comfortable that they're seeing that accurate picture of the treatment effect and not systematic error.

Thank you.

CHAIRPERSON CANADY: Thank you very much. Presuming that Dr. Piantadosi is not the only one who wants to stand up. I'd suggest that we break for five minutes and I do mean five minutes. In that five minutes, I'd ask the panelists also to locate their questions or if they don't have one, Ms. Scudiero will be happy to see that you have them because this will be the focus of our discussion when you return.

(Off the record.)

CHAIRPERSON CANADY: During this portion of the meeting we're going to go through the claims of

the sponsor, one by one. In front of you you should have hopefully a portrait, landscape questions labeled FDA questions. What we're going to do is go through the questions one by one. In bold print is the actual questions. On the second or in some cases several pages following that are the issues that have been raised by a number of our speakers and the FDA members regarding these questions. We're not going to go through those one by one, but I want you to consider them as you make your comments in your discussion of the issue. Really, it's the question at the bottom on the first one, does the data support the firm's proposed claim which we will address our conclusions to.

We will not be voting at this time. We are just going to discuss these issues. We'll have an open hearing and then proceed directly from that to the voting just so everyone knows how we're going to proceed.

The first question is Active Parkinson's Control Therapy effectively suppresses the cardinal amotor symptoms of Parkinson's disease. Comment.

Open for comments by the panelists.

Dr. Hallett?

DR. HALLETT: I would like to ask either Dr. Olanow, Dr. Montgomery or Dr. Vitek, in relation to postural instability, if there were a patient who presented with very significant postural instability as a major symptom that was not well treated with levodopa, would that be an indication for this treatment? And I'd like to ask a similar question with respect to freezing, that isn't actually on there, but so I'd like to address those two issues. If that was the principal symptom as opposed to tremor, rigidity or akinesia, postural instability specifically and not being responsive to dopa, would this be an appropriate therapy?

DR. OLANOW: Well, I think you're getting at patients with atypical Parkinsonisms who have postural instability as a primary feature and are not responsive to levodopa.

In this particular trial we confine it by definition to patients whom we thought had idiopathic Parkinson's disease that were responsive to levodopa.

In independent observations, I would have to say to you that there is no evidence that these procedures help patients with atypical Parkinsonism as yet. But in this study, it was confined to patients with Parkinson's disease.

DR. HALLETT: Right, but if there was a patient who had what you thought was Parkinson's disease, but had as a problem postural instability as one of the major problems which certainly can be the case. I mean it is considered one of the four cardinal features of Parkinson's disease, so it isn't necessarily seen only in atypical Parkinson's disease, can be seen in typical Parkinson's disease, so in that case if it was a typical patient with Parkinson's disease, had postural instability as one of the major aspects, but that particular element wasn't doing well with dopa, would this be an appropriate procedure?

DR. OLANOW: I would have to say in my opinion, no, that generally this provides a benefit that is comparable to levodopa in that regard which I would like to comment on later with respect to what that means because I think it's very important that

one understands that working as good as levodopa all the time is very different than levodopa which only works as good as levodopa, a very small percentage of the time in these patients who fluctuate widely and may spend 80 percent of their time even though they're on levodopa not responding and the other 20 percent having dyskinesia. This differs dramatically from this therapy which gives you the best of levodopa without the dyskinesia, virtually all the time and I think that's an extraordinarily important point that the panel needs to keep in their minds in evaluating this therapy.

DR. HALLETT: Would you also address freezing?

DR. OLANOW: I would make the same response.

DR. HALLETT: Thank you.

CHAIRPERSON CANADY: Dr. Cohen?

DR. COHEN: I have a general question about patient selection. I was going to ask this earlier, but I think it's very pertinent now. On what types of patients are you recommending this treatment

be used for and are there some objective criteria or even professional judgment criteria by which you could determine a patient that would benefit from this treatment versus a patient that wouldn't be recommended for this treatment and what proportion of patients do you think that represents?

MS. PRITCHARD: I would ask Dr. Vitek to respond.

DR. VITEK: Basically, my feeling about this and I think everybody else would agree with me was involved in a study in doing this work right now is that patients with idiopathic Parkinson's, with a clear diagnosis of Parkinson's disease with a history of responsiveness to levodopa and even those patients who were advanced and have lost their response, where it's unpredictable, but they even get a minute or five minutes in a day where they get a response to medication and their balance may improve or their freezing improves, then I think these are patients for deep-brain stimulation because we have seen that those patients can definitely respond to stim even though they may have a very unpredictable response to

medication, so those are the patients that I would consider and I personally would consider either target for patients with midline symptoms, who have freezing, balance problems, the numbers themselves do not differ that much, but the number of patients that were enrolled in each target do differ and so you'll see patients who respond very well with DBI stim and some patients who may not respond that well. And you'll see the same thing with STM.

DR. COHEN: And the question was raised by the previous speaker this comparing this treatment to as a general purpose treatment and from what I understand you're not recommending, are you not, seeking approval for a general purpose treatment, but it's only for a select group of patients?

DR. VITEK: What we have studied are patients with advanced Parkinson's who are at the point where medical therapy is no longer effectively controlling their symptoms.

DR. COHEN: So the medical therapy is not an acceptable comparison?

DR. VITEK: These patients were all on

medical therapy and were at a point, basically, where they were no longer able to be controlled with medical therapy so they had a lot off time. They had motor fluctuations. When they were on they were dyskinetic, very unpredictable responses as I said. Those are the kinds of patients that were studied here and these types of patients are at the end of their rope, so they have no other alternatives. Their options are gone.

DR. COHEN: And what proportion of patients are included in this category?

DR. VITEK: What proportion of patients in the whole population of Parkinson's patients?

DR. COHEN: Yes.

DR. VITEK: That are diagnoses?

DR. COHEN: Uh-huh.

DR. VITEK: Anybody else? What do you think the numbers would be. Thirty or 40 percent, that high?

Our feeling is that if you take the total population of Parkinson's patients and go over their whole history, then certainly by the time -- if you

take all the patients, let them go over time, probably 30 percent of that population is what I would feel will get to a point where they're going to be in this position and I think that's conservative. Some of my colleagues may think that's not, but I think it is.

DR. COHEN: But at any one time --

DR. VITEK: I don't know if I can comment on any one point in time what number of patients are out there that would need this therapy.

DR. COHEN: Okay.

DR. VITEK: I can tell you that of all the patients that have Parkinson's disease, at least I would think 30 percent of those patients will be candidates for this surgery.

CHAIRPERSON CANADY: Dr. Nuwer.

DR. NUWER: Is it reasonable to say that this technique is useful, would be used for severe or advanced Parkinson's, but not say that it's a technique to be used for mild or initial stages of Parkinson's?

DR. VITEK: No, I don't think I would say that. I think there's no data for us to address the

use in early onset and patients who are mild or early in the course of their disease, that's a whole different question that needs to be addressed.

Would it be effective? I believe it would be, sure.

DR. NUWER: So that's a very different question --

DR. VITEK: Very much --

DR. NUWER: For which we don't have data at this time.

DR. VITEK: Are we warranted to do this in early -- earlier in the course of disease or not, that wasn't the question addressed in this study. This study addressed the question if patients were no longer getting adequate control with medical therapy, then they become then effectively cared for with deep brain stimulation, can we improve them? And I think that's been shown to be true.

CHAIRPERSON CANADY: Other comments? Dr. Hallett?

DR. HALLETT: One more question, this one for Dr. Lozano or Dr. Wilkinson. If a patient came in

who you thought was indicated for this procedure, which target would you use and why?

DR. LOZANO: So again, this procedure we feel should be used in patients who cannot be made better despite any available drugs. I want to emphasize that. These are patients are at the endpoint who cannot be made better by medical drugs. They've all had the maximum medical therapy and these patients are disabled. They're at risk of losing their jobs, at risk of losing independence. So these are severely advanced patients. And it's really these patients for whom the ratio of benefit to risk is the greatest and we think that these are the most appropriate patients.

Which is the best target? That's a wonderful question. Is it GPi or STN? I wish we knew. And because of the study we weren't able to answer that question. It was not designed to answer that question. The patients were assigned to either one target or another based on the individual center's preference. There are now underway several studies by several groups to actually assign patients randomly to

one target or another and associate facts and I am part of one of those studies. And so the answer is if a patient comes to me now and satisfies that criteria I would enroll them in a randomized trial to determine which is the best target for that patient.

CHAIRPERSON CANADY: Dr. Edmondson.

DR. EDMONDSON: Excuse me, could I follow up on that for a second?

So you do agree then that that still is an open question? I'm puzzled. I really don't understand how you can recommend the treatment when you really don't know which treatment to recommend.

DR. LOZANO: Because we know the alternative of no treatment. The alternative of no treatment is these patients can't move. These patients are writhing uncontrollably and we know that either treatment, whether it's GPi or STN has a striking effect on signs and symptoms of these patients, restores movement, restores function and so at this point we know that both targets provide a striking benefit in these patients.

Which target is the best for which

patient? That we don't know. Both targets work. Both targets restore function. Both targets restore quality of life in patients.

CHAIRPERSON CANADY: Dr. Massaquoi?

DR. WILKINSON: Could I just follow up on that?

CHAIRPERSON CANADY: I think he was very elegant.

(Laughter.)

Dr. Massaquoi?

DR. MASSAQUOI: I was just wondering if there were any of the neurosurgeons, is there, in general, an age related increased risk of intracranial hemorrhage, severe, let's say serious intracranial hemorrhage and if so, first of all, in your study, is that something that was looked at even if unofficially and does that alter, you say that the risk benefit ratio tends to improve as time goes on because the people are more disabled, but does the risk actually potentially increase at a sufficient rate so that the risk-benefit ratio is flat?

MS. PRITCHARD: I'd like to have Dr.

Wilkinson respond to your question.

DR. WILKINSON: Yes. In the study itself, the predictor of age didn't factor into the outcome in terms of the risk. Overall, I think certainly it's more of a biologic agent. That's how we look at the patients, not at specific chronological age, but a debilitated patient would obviously be at more risk than a healthier, vigorous patient and usually that goes somewhat with chronological age.

DR. EDMONDSON: How many patients did he have between 65 and 75?

CHAIRPERSON CANADY: Ten. There were 10 patients greater than 70 I recall.

DR. WILKINSON: Yes. Twenty greater than 70 in the study.

CHAIRPERSON CANADY: I'd like to move on to some discussion of the second question which is Activa Parkinson's Control Therapy decreases the occurrence of dyskinesias associated with medical therapy for Parkinson's disease. Comments from the panelists?

(Pause.)

The third question, Activa Parkinson's Control Therapy increases the duration and quality of "on" time and decreases the duration and severity of "off" time.

Comments? Questions?

DR. EDMONDSON: I think that might be an important area to review.

DR. COHEN: I'd like somebody to clarify because I thought I heard some of the presentation, some differences in what was meant by "on" time and "off" time. I know what it feels like, but I think for some patients, I mean if you're taking Sinemet, you have on time and off time, but it may mean a different thing to be on and off under this kind of treatment. I'd like somebody to address that.

MS. PRITCHARD: Dr. Olanow?

DR. OLANOW: Generally, we medically use the term "on" time to reflect the fact that they're responding to levodopa and the Parkinson features are under control. We use the term "off" to reflect the fact that the medicine isn't working and that they are suffering from Parkinsonism.

Now when a person is "on", they can have "on" time in which they're just good and able to move or that "on" time can be complicated by involuntary movements which potentially can be as bad or even worse than the Parkinson features themselves. So in the extreme state you have patients fluctuating between bad "on" and bad "off" but never getting the good time which is the "on" time without dyskinesia.

CHAIRPERSON CANADY: Other questions? Then I'd like to move on to the fourth question which is Activa Parkinson's Control Therapy allows patients with Parkinson's disease to regain their independence and functional ability.

Comments or questions?

DR. EDMONDSON: I think it would be helpful to just recap some of these different functional scales, global disabilities scale versus ONER and so on. As I understand it, the global scale does not show an impressive gain in independent level of function, but perhaps on some of the other subsets there are greater gains that's discerned. I was wondering if we could just recap those results.

MS. PRITCHARD: Dr. Montgomery, if you could comment on that?

DR. MONTGOMERY: Well, to address your question, the Activities of Daily Living subscale or the UPDRS is a valid and well-documented method of assessing clinical disability. If you look at the individual items within that scale you will see that they are specifically related to functional ability. In fact, the degradations, for example, between a score of 2 and 3 often relates to the amount of independence or dependence that the patient shows, so for example, if a patient has a value of 1 or 2, that means they're still fairly independent in their Activity of Daily Living for that particular activity of daily living or if they have a 3 or 4 that means they have to depend on someone else. So I think that the items within the ADLs are quite appropriate for assessing the levels of disability. I would take issue with this notion that as listed there that it's not a good measure because patients can time their activities to their "on" and "off" state. It's a rare patient who can time their clinical activity to their

"on" and "off" state and therefore that would not bias the results. In fact, Marsden looked at a number of patients and looked at the day to day "on" and "off" periods and it's highly, highly variable. It's only when it's averaged over many many days does a characteristic pattern that emerges that could result in a systematic bias. So I think the activities of daily living are an appropriate measure of functional disability and the increase in the -- or the improvement in those ADL scores reflects therapeutic effect. I would take issue with one of the results pointed out by the statistician where he showed that the 25 percent improvement level did not fall within the 95 percent confidence interval in terms of the activities of daily living score. That I think is kind of -- may represent more of a nonstatistic than to what we have to deal with clinically. I would suggest that a 95 percent confidence level may be a little too strict and my question would have been if it had been a 90 percent confidence interval would that then have excluded the 25 percent improvement and I suspect that it would. And why choose a 90 percent

confidence interval versus a 95 percent confidence interval? I mean I would love to -- I would gladly accept a 10 percent chance of being wrong in saying that this person improved, given the alternatives that these patients have. So I am very confident that the data does reflect improvement in functional independence and reduction in disability.

CHAIRPERSON CANADY: Other comments? The next question Active Parkinson's Control Therapy allows most patients to reduce their anti-parkinsonian medication consumption and that's for the STN group only. And we might keep that in mind for later.

Go ahead, Dr. Massaquoi.

DR. MASSAQUOI: I have a question to anyone. Since there seems to be a natural trade off, say for levodopa therapy between parkinsonian rigidity, some of the "off" symptoms and dyskinesias and since there's a trade off in any individual, one can, depending on the dose sort of go back and forth. We saw a lot of summary data in terms of averages for the groups. Were there analyses performed on the individuals to know whether individuals who -- were

there any individuals that both reduced their dyskinesias as well as improved their rigidity or were there actually sort of subgroups in which only one of the two would occur and it was a matter of a trade off?

DR. OLANOW: Well, I think you've really touched on what really is the special thing about this treatment and what differentiates it from every other treatment we currently have and perhaps I didn't make it clear in the presentation and perhaps I should have added it to the answer I gave you. I can make any patient turn on by giving them levodopa and make their rigidity go away, but now they have terrible dyskinesia.

I can make dyskinesia go away in any patient by simply lowering the dose of levodopa, but now they're frozen and they can't move. What I can't do up until now is make a patient turn on and have rigidity, tremor, bradykinesia and postural instability go away without the complicating dyskinesia and other problems that are associated with currently available medical therapies.

DR. MASSAQUOI: So that's definitely what one would try to do. Was that particular thing looked at sort of individually on a case by case basis to see whether most people fall into that category or whether it's the rare patient that has both benefits?

DR. OLANOW: Well, I think you got a sense of that when I showed you the results of home diaries that the patients filled out where really off time just about went away. We're on time with dyskinesia almost went away. When you had a group of patients that were not functional, that had now been rendered into a state where they were on without dyskinesia for almost all of the day, every one of us who does this procedure has pictures of patients who are either in bed worse than anything you've seen today or flailing with dyskinesia, worse than anything you've seen today with no dyskinesia. And you turn on the stimulator and they can get out of bed and start walking and functioning without any of these involuntary movements. You don't have to see 10, 20, 50, 100 patients to see this. You see one and I'm telling you there's no other therapy I know that can make a

patient behave like that.

CHAIRPERSON CANADY: Other questions? Dr. Hallett?

DR. HALLETT: Would it be fair to say that in fact, with STN stimulation that patients must reduce their anti-Parkinson's medication, otherwise they will have dyskinesia? It isn't only a matter of allows, but they really must do it because otherwise they will have dyskinesia with their benefit.

Is that true or not?

CHAIRPERSON CANADY: Could you please speak in the microphone? It's being transcribed.

DR. OLANOW: I think what you say, Mark, is partially true and that one of the reasons that people lower the dose is because of the fact that as you stimulate STN you may initially some dyskinesia and that's what's led to the initial reduction of the dose. However, I did a study and Jose Obeso did a study in which we deliberately kept the dose constant in order to try and see what would happen and in both cases over time dyskinesia just gradually disappeared, despite the fact that we maintained them on the same

dose of levodopa.

CHAIRPERSON CANADY: Other questions? Dr. Piantadosi?

DR. PIANTADOSI: I just wanted to make a comment and point out that the answer to this particular question is not part of the design of the study. It's really based on a post hoc analysis and is subject to even more of the potential biases and variability. It's really hard to provide a definitive answer for something like that's not been explicit outcome of the study or an explicit objective of the study.

CHAIRPERSON CANADY: Other comments? Mr. Cohen?

DR. COHEN: Yes. The question that I asked earlier I don't think was fully elucidated. I wanted to be clear. Is there a difference in the "off" state under deep-brain stimulation than there is under levodopa therapy? I mean there's "off", for example, I have "on" and "off" during the day, but it's not nearly as severe as was shown in the films. And I think that's a quality of life issue that should

be considered here. That if you can get better and you could be "on" and not be that effective, in functioning in your life, and if you could get a better "on" state that that would be a valuable contribution.

Is that true?

MS. PRITCHARD: We'll let Dr. Montgomery respond to that.

DR. MONTGOMERY: Your points are very well taken. And in fact, as the data was shown here, the degree of the off periods were much reduced, so with the deep-brain stimulation, even those patients that did have some off periods with the brain stimulation. The magnitude of those off responses was much, much less, so the therapy not only decreased the amount of off time, but when the patients were experiencing off time, it was significantly reduced as evidenced by the UPRS scores and particularly the Activities of Daily Living.

CHAIRPERSON CANADY: Other comments regarding this question? And then the final question, Bilateral Activa Parkinson's Control Therapy is safe

and effective in controlling the symptoms of Parkinson's disease that are not adequately controlled with medication. In addition, Activa Therapy is effective in controlling dyskinesias and motor fluctuations associated with medical therapy for Parkinson's disease.

Dr. Fessler?

DR. FESSLER: I have one very simple question. As an academician with degrees in psychology and pharmacology and physiology I have a great fondness for debating subtleties in research and data analysis and statistical methodology, but as a neurosurgeon I know that when all of that is done you come down to a very basic bottom line decision.

So I would like to ask each of our esteemed physicians here by a show of hands, given your experience with this technology today and its risk and benefit ratio, if your 77 year old gray haired mom was a candidate for this therapy, would you ask your colleague to do bilateral STN or GPi implants?

Everybody who would, raise your hand.

Thank you.

CHAIRPERSON CANADY: For the record, that's uniform.

Any other comments regarding this question?

DR. EDMONDSON: Yes, I'd like to just follow up on that a bit. I think in this question bilateral Activa for Parkinson's therapy, the words "safe and effective" should be definitely underscored. The bottom line, you know, when we traverse the process of making a decision here is in spite of the pitfalls perhaps in study design and some of the statistical concerns, it's the balance between the science which is the foundation likened to the steel frame of the high rise and the art which is everything else that makes that pretty building.

For the clinician the bottom line is really what works and we've seen some dramatic demonstration that this can be effective in very disabled patients. The area of concern for me though revolves around the safety issue because we have smaller numbers of patients to analyze that are over

70 and in fact, a growing population of patients in years to come who will be potential candidates for this that are elderly. And so even if we extrapolate these results to encompass all Parkinson's patients who would fit the bill of being candidate to go on and have deep-brain stimulation, I think at least in labeling if we get to that point we'll have to put some strong conditions regarding safety of bilateral stem, especially revolving around the issue of confusion, encephalopathy and the like because as someone gets older, intuitively they're more vulnerable to these side effects and that's not minor. If you have an elderly person who is confused for a few weeks, the likelihood of getting aspiration pneumonia and other things can be really a very mortal risk and so basically, given the tenuousness of some of the information that we have we really have to bear that in mind.

CHAIRPERSON CANADY: Dr. Witten?

DR. WITTEN: I was just going to say this isn't actually the last, but it's the fourth from the last question, but for this one and for the ones that

follow I'd appreciate it if anybody else in the panel, if we could just run around the panel and see if anybody has anything to add for comment on this that hasn't already been said.

DR. GARCIA: Before I lose my nerve, can I go ahead and say something? Thank you.

We're so focused on the safety issue and I think that's really valid, but as a consumer representative it seems to me that the patients aren't so much looking for safety as efficacy and I would like to see that looked at a lot harder. If you told me I had 1 in 20 chance of doing poorly in a treatment, I'd still say go for it because what would happen to me if I didn't go for this treatment is set. We already know what's going to happen to end state Parkinson's. So as we look to safety, please, let's remember efficacy and the patients' choices in actuality.

MS. MAHER: I'd like to follow up on that a little bit. I think I've heard some comments here today about the statistical design of the study, that the numbers aren't as good as they could have been.

I think we need to remember this was a device study for a feasibility study where the sponsor actually saw some good information and came forward. Maybe they came forward a little earlier than some strict statisticians would have liked to have seen, but that's what the panel is here to do is to look at the risk of the treatment over the potential benefit for the patients for this particular device. So I think we should all keep that in mind as we're moving forward.

CHAIRPERSON CANADY: Other comments? Dr. Piantadosi?

DR. PIANTADOSI: Thank you. I certainly don't mind the marginalization of study methodology. I'm actually quite used to that.

(Laughter.)

Especially in a device context. But I would like to comment generally on this question and in fact, all of the questions for that matter. I find that I'm very uncomfortable with the way that they're worded. They impress me as being rather definitive and rather sweeping. They ignore some of the obvious

limitations in the study. They are completely ignorant of the eligibility criteria for the study and some other things that would temper their interpretation by people who haven't delved into the data to the extent that we have. And I think if you read all the questions from that perspective, they all suffer from the same limitation. They made categorical statements about the disease and about patients with the disease that are wholly unsupported by the data.

DR. EDMONDSON: I think at least from my standpoint I'm not straining in any form, in any constipated fashion regarding efficacy. But I think in terms of methodology we still have to use that as a springboard in trying to discern, especially when we think of regulatory concerns and labeling concerns that the claims made are not inflated in any way.

I think for me the process of deciding whether or not this is safe is a greater internal deliberation here because I think a lot of these patients are at the end of their choices in terms of being able to function so I think having an added

measure that would grant them the ability to function better with less freezing and some of the other cardinal signs of Parkinson's it's very important. I think though the data, for example, does not support that it reduces all cardinal features of Parkinsonism and certainly has not done that sufficiently for postural instability. And so in deciphering all of these labeling concerns, for example, that has to be reflected. I mean the data and methodology should reflect in the reservations that we make if this goes to approval.

CHAIRPERSON CANADY: Dr. Hallett.

DR. HALLETT: I think it's clear from all the things that have been said so far that this particular study was very poorly designed. One of the things that we haven't really considered very much, however, today is there are some published studies already in the literature of this device. They're relatively small studies. They are, in general, better designed than this. They do come to a positive outcome for this procedure even though they're relatively small studies and generally preliminary,

but they do come to the same view. I think one of the things that I'm impressed with as I look through this data is that despite the fact that the study is poorly designed and there's a lot of statistical problems with it that the benefit seems to be so dramatic in many circumstances that the benefit is clear, even though the statistics are very poorly describing it and I think one of the problems, for example is that the primary outcome measure was the wrong primary outcome measure to choose. As Dr. Olanow pointed out, the principal important aspect here is how many hours of on time are there during the day. That turns out to be a secondary measure here, rather than the primary outcome measure, but that is the most important thing that we are, in fact, concerned with. How many hours during the day is someone on, that is, in fact, the issue for daily living and all the other aspects. That was a secondary measure, but in fact, the most important one from all points of view.

So I think that while there's an extraordinary number of problems, the benefit of the procedure appears to be so strong that you can see it

even with all the different problems that there are with the study.

CHAIRPERSON CANADY: If you'll turn to the second to the last page is a summary of the labeling recommendations which the first group of which really recapitulate the questions we've addressed. One of the issues that's not here and I'm not sure that we've figured out a way to address, but have repeatedly expressed concern about is the surgical issues and surgical training issues.

Any comments regarding that?

DR. WITTEN: Should we put up the surgical -- the question about technique options?

CHAIRPERSON CANADY: Right. On the previous page there's some technical issues which I'm not so sure can be addressed in this forum, but there has been a repetitive theme of concern about who is going to do the procedure, how they're going to be trained and within that context is there some way in which we can either add to the label in terms of recommendations of labeling or somehow reflect that concern.

Dr. Walker?

DR. WALKER: Let me answer the one that's on the right here and my answer is yes, if I was a Parkinson's patient I would be in the position to make those judgments with the exception of (a) and Dr. Lozano has already alluded to a study that's going to try and elucidate the answer to that a little bit better than the state of unknown that we currently know. (E) where I think we do need to include some discussion which is the true electrode design should be used in which case because they will have very different electric field distributions. And also (I) which optimization of this system is very critical and I believe there needs to be some written guidance to the physician that specifically says how you tune the system and that information cannot be anecdotal or simply passed on orally. It needs to be a very, very clearly written protocol, otherwise people will be overstimulated or understimulated or not experienced the full amount of battery life that they would otherwise be.

CHAIRPERSON CANADY: If I might ask, Dr.

Walker, that we continue this open discussion, you might begin to think about potential wording for such labeling recommendations.

DR. WALKER: I was afraid you'd say that.

CHAIRPERSON CANADY: I thought you might. Other discussion regarding that?

DR. COHEN: I'm concerned about the credentialing of physicians who are allowed to perform this procedure and I don't know what the answer is, but as a patient I would want at least have information from the professional society or from the patient foundation or something that gave me an indication that the physician had received rigorous training to perform this operation.

CHAIRPERSON CANADY: Dr. Hallett?

DR. HALLETT: I think you're absolutely right, but I think that the problem that you raise is true of all of medicine and that is one of the problems with the way medicine is regulated in the United States. It is true of anything, even doing an EMG study I would say the same thing. It is certainly true, but I don't know how to fix it without altering

a lot of rules about how one actually regulates the whole practice of medicine in the United States.

CHAIRPERSON CANADY: Dr. Fessler?

DR. FESSLER: I would argue that the mechanism to train and credential is already in place and has been for the last 50 to 75 years. Neurosurgeons train eight years to do this. Bottom line is this is one of the easiest things we do. No disrespect intended. We all think what we do is the hardest.

The mechanism to train and credential exists. It's already there. We don't need to re-credential for every single thing we do.

CHAIRPERSON CANADY: Dr. Edmondson?

DR. EDMONDSON: I think a statement from the FDA in any event would be helpful to really underscore that they should be done by highly trained physicians. I know the onus of responsibilities in individual hospital and JCUHO regulations and all of that and that there are too many factors to consider here and we don't want to press on dictating how physicians should practice. But I think it really

should be underscored that this should be done by physicians experienced in stereotaxic procedures.

CHAIRPERSON CANADY: Can I ask that you work on the labeling amendment for that as I move on to the open public hearing portion of the meeting?

DR. WITTEN: Excuse me, I'm sorry to interrupt again. Can you just -- I just would like to know if there are any comments on the safety question?

CHAIRPERSON CANADY: I thought we discussed that.

DR. WITTEN: We didn't talk about that. And also any additional comments on the last question which we kind of have already covered. This one we haven't.

If there are any additional comments on the safety question.

DR. COHEN: I have another comment.

CHAIRPERSON CANADY: Dr. Cohen?

DR. COHEN: Does this panel recommend follow-on studies to demonstrate, for example, there is a fairly high percentage of adverse consequences. Would there be, could there be studies that would be

done that --

CHAIRPERSON CANADY: That can be one of our recommendations within our final motion, yes.

DR. COHEN: Okay.

CHAIRPERSON CANADY: Other comments? There is a plan sponsor summation. Separate from that, are there any comments from the public? If we could then move on to the sponsor summation and the FDA summation. The FDA is first this time.

DR. WITTEN: We don't have any additional comments.

CHAIRPERSON CANADY: Medtronics.

MS. PRITCHARD: Yes, we do. I'd like actually to have each of the five physicians make a couple of --

CHAIRPERSON CANADY: All I can say is you have about 15 minutes and I'm going to be quite strict on that.

MS. PRITCHARD: I understand. We're going to start with Dr. Olanow. And then if the rest of you just want to --

DR. OLANOW: Well, I think we'll speak all

fairly quickly. I would like to really restrict my comments to issues that have been raised by Steve and one or two of the others. Firstly, with respect to the biologic basis and why there are two different targets, the findings in the laboratory indicate that the subthalamic nucleus and global pallidus parus interna which connect to one another are both overactive. Therefore by shutting down the activity in both of those targets one assumes that one can restore normal activity and thereby improve motor function. That's true physiologically as well as by metabolic studies and a variety of other things. In the laboratory when either of those is destroyed, you see benefit and clinically we're seeing the same thing. So there's no rational reason at this point to pick one target over the other and I think that the only way that we'll resolve that is in further trials in which they're designed specifically to answer that question.

In that regard, I point out to you though that the rational basis for moving forward with this type of therapy is actually stronger than the rational

basis for which we first used levodopa and we know more about this therapy today than we know about levodopa. I just think that that's perhaps worth knowing.

The second thing I want to emphasize is what this treatment can do. The Parkinson's patients, as they reach their advancing stages, fluctuate between these terrible extremes. The problem isn't that levodopa doesn't work. The problem isn't that the levodopa "on" effect isn't acceptable. The problem is that represents 10 percent of the day. The rest of the day, the levodopa is not working and they're frozen, or the levodopa is working, but they have these involuntary movements. What these therapies have the potential to provide in a way that I personally have never seen with any other therapy and what represents to my eyes an advance in science comparable to when levodopa was first used in Parkinson's patients is that it takes patients who are literally bed-ridden and it restores them to being able to be on and without these kinds of motor complications.

So I think the magnitude of this effect is something I really want to try and impress on you as you look at the deficiencies that existed in the study that we tried to do.

Finally, I want to speak to the issue of adversity. Right now there are a series of procedures that physicians and surgeons can do without any appeal from the FDA or anyone else, thalamotomy, pallidotomy, etcetera. These are destructive procedures. They have more adverse events than the kinds of procedures we're talking about now and the benefits that you obtain are not even in the same order of magnitude as what we're seeing. I think again, it's important to interpret adversity in the light of the kind of clinical benefit that we've described in these patients who could not be improved with any other therapy we currently have.

CHAIRPERSON CANADY: Thank you. Ten more minutes, gentlemen.

DR. VITEK: I just want to say two things and one is the -- I get into biology. I spent years in a lab with models of Parkinson's disease and I

think the biologic basis for this is well substantiated as well as anything that has ever been done as far as I can tell.

The second thing is that the current therapy, the kind of benchmark right now is really pallidotomy and pallidotomy is used unilaterally, not bilaterally. The biggest problem we have with patients who come to us is if they have gait, balance and freezing problems as I say it's an inconsistent benefit with pallidotomy. We don't do it bilaterally because of the consequences of hypothalami. This is a procedure you can do bilaterally and if you should develop some consequences as a result to stimulation you can modify it. You can adjust it to optimize the patient's benefit and minimize the side effect profile. It gives you a lot of flexibility.

And lastly on the Global Disability Scores, I mean I think those are marked changes. They go from 70 percent to marked and severe down to 10 percent of patients. I mean I think that's huge.

CHAIRPERSON CANADY: Thank you. Next.

DR. WILKINSON: I would just agree with

the two previous speakers. I think it's a very dramatic therapy and compared to the other surgical therapies, the adverse events and the risks are certainly less and the benefits are much greater.

CHAIRPERSON CANADY: Thank you.

DR. LOZANO: I think when considering novel therapies one has to consider the cost of not adopting novel therapies and for these patients the cost is just very high. These patients are patients that will lose their jobs, patients that will lose their social interactions, that may lose their independence. The alternatives for these patients are ablative surgical procedures like pallidotomies, bilateral and so on. And the side effect profile for those are just not as favorable as it is for DBS and so here we have a better procedure with a better profile of benefit to risk and we have here the possibility of providing really a very striking benefit for patients for whom there are no real alternatives.

CHAIRPERSON CANADY: Thank you.

DR. MONTGOMERY: Well, I'd like to address

a couple of issues and first, I'd like to start by the issues of the statistical analysis. This study was not done in a vacuum. This study doesn't rely solely on what was presented in a statistical package. We've had over 100 years of experience with patients with Parkinson's disease. We deal with patients with Parkinson's disease every day. We've seen them through numerous trials of other treatments and we know what and how they respond and we know what we can expect. I think all of us have been incredibly impressed with the value of this treatment and just to discount all that clinical experience and all that clinical knowledge gained over a 100 years, I think would be a horrible mistake. I would not be apologetic for bringing our clinical expertise, our clinical judgment and our clinical experience into this decision making process.

As for the issues of safety and credentialing, I understand the concerns. We went through this ourselves at the Cleveland Clinic trying to establish what would be appropriate credential for this sort of process. And there is a mechanism in

place. Every hospital has to credential a physician to do every procedure. Every year, I have to apply for credentials to do this procedure in our hospital. Our hospital has established criteria by who should do this. No physician can just walk in off the street and do this surgery. It has to be done with the permission of the hospital where the FDA, where the professional societies can play a role. It's helping hospital credentialing committees establish the appropriate types of credentials.

And one last point about the adverse effects. I just want to share with you a patient that we had at the Cleveland Clinic. This was a patient with very severe Parkinson's disease who underwent bilateral subthalamic nucleus stimulation. She had a remarkable response. She did tremendously better.

But within a few weeks the incision had opened up and the leads become exposed. We discussed the situation with the patient. We outlined the risks of infection and the potential that we may have to remove those leads. And the patient said no way. There is no way you're going to remove those leads.

You can do anything else you want to me, but don't take that away from me.

This poor woman had been so immobile during her off periods that she was as paralyzed as anybody with a broken neck. And if anything is worse her condition teased her with periods of brief and unpredictable mobility, only to dash her hopes a few minutes later with severe off periods.

The benefit to this patient was extraordinary and I tell you quite frankly I know -- I have to go back to work Monday morning and I have to see these patients and whether it's 30 percent or only 5 percent I have to offer them something because short of this for many of these patients there is nothing else to offer. Please allow me to offer them that.

Thank you.

CHAIRPERSON CANADY: Any other comments from Medtronics?

Thank you very much. We're going to move into the portion of the meeting now for voting. I would remind the industry, consumer and patient representatives that they don't get to play in this

portion unless there's a tie.

(Laughter.)

I don't get to vote. Ms. Scudiero now will read the options available.

MS. SCUDIERO: These are the panel recommendation options for pre-marker pool applications. The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990 allows the Food and Drug Administration to obtain a recommendation from an expert advisory panel on designated medical device premarket approval applications that are filed with the Agency. The PMA must stand on its own merits and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information. Safety is defined in the Act as reasonable assurance, based on valid scientific evidence that the probable benefits to health (under conditions on intended use) outweigh any probably risks. Effectiveness is defined as reasonable assurance that, in a significant portion of the population, the use of the device for its intended

uses and conditions of use, when labeled, will provide clinically significant results.

Your recommendation options for the vote are as follows:

(1) Approval, if there are no conditions attached.

(2) Approvable with conditions, the panel may recommend that the PMA be found approvable subject to specified conditions, such as physician or patient education, labeling changes, or a further analysis of existing data. Prior to voting, all of the conditions should be discussed by the Panel.

(3) Not approvable, the panel may recommend that the PMA is not approvable if the data do not provide a reasonable assurance that the device is safe, or if a reasonable assurance has not been given that the device is effective, under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

Following the voting, the Chair will ask each panel member to present a brief statement outlining the reasons for his or her vote.

CHAIRPERSON CANADY: I'd like at this time to entertain a motion from the panel.

DR. WITTEN: Excuse me, may I just make one clarification. This is from the questions slides, but that's the indications statement is up there.

CHAIRPERSON CANADY: The labeling they have recommended.

DR. WITTEN: Requested. And it's in your package.

CHAIRPERSON CANADY: It's the second to the last page, I believe.

DR. WITTEN: This one, yes. Just so you know what you're voting on.

CHAIRPERSON CANADY: Dr. Nuwer.

DR. NUWER: I'd like to move that these are approval with conditions.

CHAIRPERSON CANADY: Do I have a second?

[Seconded.]

CHAIRPERSON CANADY: Discussion. Any discussion of conditions? Dr. Walker?

DR. WALKER: Do you want me to do a condition first?

CHAIRPERSON CANADY: Yes sir.

DR. WALKER: First condition, since I've got the wording written.

(Laughter.)

First condition that I would suggest is that the Physician's Manual should include a written protocol for the selection of electrodes and for the optimization of all stimulation parameters.

CHAIRPERSON CANADY: A second?

[Seconded.]

CHAIRPERSON CANADY: Any discussion regarding that amendment? Then we will entertain a vote on that amendment.

Dr. Walker, I presume is a yes.

DR. WALKER: Yes.

(Laughter.)

CHAIRPERSON CANADY: Dr. Zamorano?

DR. ZAMORANO: Yes.

DR. HALLETT: Yes.

DR. NUWER: Yes.

DR. MASSAQUOI: Yes.

CHAIRPERSON CANADY: Any additional

amendments?

DR. EDMONDSON: Yes.

CHAIRPERSON CANADY: Dr. Edmondson.

DR. EDMONDSON: Back to my obsessions about safety in some of these labelings and claims. I think the statement that reduces cardinal motor symptoms in Parkinson's disease should probably omit postural instability or qualify it because it's not really demonstrated dramatically enough to be included.

CHAIRPERSON CANADY: A second for that amendment?

[Seconded.]

CHAIRPERSON CANADY: Discussion? Dr. Hallett.

DR. HALLETT: That is clearly a problem, but I was thinking about raising something of that point myself, but it's a little bit hard to know exactly how to properly phrase. As it is phrased in that statement it probably is okay because it can suppress postural instability as compared to nothing so that it has efficacy and postural instability where

it doesn't help is if it is not levodopa responsive.

So what I was thinking that might be an alternative type of way of dealing with that is to perhaps in the first one, the first line, in the first paragraph controlling the symptoms of levodopa responsive Parkinson's disease or something like that because it's in the sense of the patients that are, in fact, responsive or the symptoms that are responsive are the ones that are going to be responsive to this type of therapy.

CHAIRPERSON CANADY: So you would put the levodopa responsiveness where?

DR. HALLETT: In the first sentence, safe and effective in controlling the symptoms of levodopa responsive Parkinson's disease. Well, I'm not sure that that's exactly the right place. I haven't quite figured out exactly the right place to put it, but it would -- I mean the point that I would --

CHAIRPERSON CANADY: This is the time for right places.

DR. HALLETT: This is the time to find the right place, I know.

(Laughter.)

I wish I could find the right place.

CHAIRPERSON CANADY: While you're doing that, Dr. Fessler had a comment I think.

DR. FESSLER: I have a question in relation to that is do we know that it will not control the non-levodopa responsive symptoms? Or have you only tested it in patients who are levodopa responsive?

DR. HALLETT: Well, that goes back to what I was asking questions about earlier and I think that when postural instability is not dopa responsive and when freezing is not dopa responsive what I asked Dr. Olanow before I think he agreed that it wouldn't be responsive to this type of therapy and of course, aspects like dementia haven't been tested. Autonomic function haven't been tested. So I think that one could deal with the whole issue just by saying it's the levodopa responsive symptoms that will, in fact, respond. I'm not exactly sure where to put it. Mark?

DR. NUWER: Then we could maybe change the first sentence in the top bolded paragraph to

Bilateral Activa Parkinson's control therapy is safe and effective in controlling the symptoms of levodopa responsive Parkinson's disease that are no longer adequately controlled with medications.

CHAIRPERSON CANADY: Dr. Piantadosi, you had a question?

DR. PIANTADOSI: Well, I was just going to lend my support to that idea and also the generic idea of making sure that these reflect what we know in the data and not wishful thinking. I made this point earlier and I don't know how much support there is for it in this context now that we're down to brass tacks, but I'm uncomfortable with the unqualified use of the term Parkinson's disease and the unqualified use of the term patient. Again, going back to the principal of reasoning from the data that are in hand.

CHAIRPERSON CANADY: Other comments? Can I read it as I understand Tony's amendment so that we all know what we're voting on which would be now Bilateral Activa Parkinson's control therapy is safe and effective in controlling the symptoms of levodopa responsive Parkinson's disease that are not adequately

controlled with medications.

DR. NUWER: That are no longer.

CHAIRPERSON CANADY: No longer adequately controlled.

DR. HALLETT: No, that isn't correct, no longer responsive -- what you want here is as I understand the situation is you want to essentially prolong the best -- so that you want to take symptoms that are, in fact, responsive to levodopa at the time, but are not maintained at the time and so that one is essentially maintaining those symptoms for a much longer period of time than before so that they are symptoms that are still responsive, but only responsive for a very short time as opposed to a long time.

DR. EDMONDSON: But I think the word "adequately" might qualify --

CHAIRPERSON CANADY: You think the way it's written now is adequate?

DR. EDMONDSON: I would think so.

CHAIRPERSON CANADY: Discussion?

DR. NUWER: I would think adequate control

could be understood as pertaining to the timing of when the medicine is controlling the patient.

DR. HALLETT: As opposed to the symptoms.

DR. NUWER: And unless there's a better wording I think adequately controlled still covers what you are talking about.

CHAIRPERSON CANADY: So let me go again so we all understand where we are. Bilateral Activa Parkinson's control therapy is safe and effective in controlling the symptoms of levodopa responsive Parkinson's disease that are not controlled with medications.

DR. EDMONDSON: Or no longer adequately controlled.

DR. HALLETT: I don't think "no longer" is necessary.

DR. EDMONDSON: Okay.

CHAIRPERSON CANADY: Not adequately, is that acceptable?

DR. HALLETT: Yes.

CHAIRPERSON CANADY: Call for the vote then. Other comments? Go ahead.

MR. COHEN: Is this somewhat like the Bible where there's a commentary on it?

CHAIRPERSON CANADY: Actually, it's less than the Bible because we are, in fact, only recommending.

(Laughter.)

Just for clarification, the panel makes a recommendation to the FDA on which the FDA acts. So it is possible that what we do could in fact be --

MR. COHEN: Is there like an explanation of this wording or it's in the transcript, I suppose.

And the issue I wanted to raise was -- I can't read your name, Dr --

CHAIRPERSON CANADY: Dr. Piantadosi.

MR. COHEN: He raised the issue of defining Parkinson's patient which I thought ought to be addressed as well.

CHAIRPERSON CANADY: To some extent we have in terms of levodopa responsiveness. The question, I guess, would be raised in conversation as to whether we wish to exclude specifically --

DR. HALLETT: I don't think that we have

to worry about that particular problem, given the fact that we have specifically noted it as levodopa responsive disease. I think that that helps to make clear what the diagnosis is as well. It really serves two purposes.

CHAIRPERSON CANADY: Dr. Piantadosi?

DR. PIANTADOSI: I would just add to that you have to look very carefully at the patients who were studied. The eligibility criteria for this trial are fairly restrictive and I personally would be very uncomfortable with statements that allowed one to extrapolate very far beyond that. These patients all had advanced Parkinson's disease and in fact were a fairly restricted subset of patients by everyone's own admission.

CHAIRPERSON CANADY: Dr. Edmondson, I think would be responsive to additional comments regarding this particular issue.

DR. HALLETT: Would you like to add the word "advanced"?

DR. EDMONDSON: Well, I think that would be helpful, yes.

CHAIRPERSON CANADY: So would we like to say "symptoms of advanced levodopa responsive Parkinsonism"? Would that be acceptable to you, Dr. Edmondson.

DR. EDMONDSON: Yes, it would be.

CHAIRPERSON CANADY: Let me read it again. Bilateral Activa Parkinson's control therapy is safe and effective in controlling the symptoms of advanced levodopa responsive Parkinson's disease that are not adequately controlled with medications and then as written.

Is that -- any discussion? Could I call for the vote then?

Dr. Walker?

DR. WALKER: Sold.

CHAIRPERSON CANADY: Dr. Zamorano.

DR. ZAMORANO: Yes.

DR. HALLETT: Yes.

DR. EDMONDSON: Yes.

DR. NUWER: Yes.

DR. MASSAQUOI: Yes.

DR. FESSLER: Yes.

DR. PIANTADOSI: Yes.

CHAIRPERSON CANADY: Very good. Other amendments that people would like to add?

Dr. Zamorano?

DR. ZAMORANO: I think in order to define the role of this therapy maybe an analysis of the existing data should follow these patients for two years, three years so that we can have some response of that.

CHAIRPERSON CANADY: So you would like to recommend a long term follow-up?

DR. ZAMORANO: Yes, that would be my motion.

CHAIRPERSON CANADY: Can you give me a little phrase saying that?

DR. ZAMORANO: A little phrase could be further analysis of the system data to have two years or three years result.

CHAIRPERSON CANADY: Dr. Witten, is that acceptable, a recommendation would be a long-term follow-up of three years?

DR. WITTEN: And she stated the purpose

also.

CHAIRPERSON CANADY: Dr. Hallett?

DR. HALLETT: I wonder if I could add to that that it would be important to include cognitive and other neuropsychological features to the follow-up studies. That's one aspect that is really lacking at the moment. I think we need more data on that point. So if we could include that specifically the follow-up, I think it would be useful.

CHAIRPERSON CANADY: So we would wish a long-term study of the effectiveness over a period of three years, including cognitive and neuropsychological factors.

MR. COHEN: I think we also, excuse me, I think we also have to address the question of what specific types of patients and --

CHAIRPERSON CANADY: Actually, Dr. Cohen, I'm afraid that I don't think you have conversation in this part.

Any other comments or does that cover everyone's concerns?

Dr. Piantadosi?

DR. PIANTADOSI: Yes. I still have a couple of generic concerns where I think the scope of these statements may go well beyond the data that are available.

I refer specifically to the last point which states that the therapy allows most patients to reduce their --

CHAIRPERSON CANADY: I'd like to wait on that. We're talking just on the amendment on the first statement.

DR. PIANTADOSI: I'm sorry, okay.

CHAIRPERSON CANADY: Any other comments on the first amendment, the current amendment on the table?

Can I entertain a vote then, Dr. Walker?

DR. WALKER: Yes.

CHAIRPERSON CANADY: Dr. Zamorano?

DR. ZAMORANO: Yes.

CHAIRPERSON CANADY: Dr. Hallett?

DR. HALLETT: Yes.

CHAIRPERSON CANADY: Dr. Edmondson?

DR. EDMONDSON: Not sure.

CHAIRPERSON CANADY: Is that an abstain?

DR. EDMONDSON: Abstain.

CHAIRPERSON CANADY: Dr. Nuwer?

DR. NUWER: Yes.

CHAIRPERSON CANADY: Dr. Massaquoi?

DR. MASSAQUOI: Yes.

CHAIRPERSON CANADY: Dr. Fessler?

DR. FESSLER: Yes.

CHAIRPERSON CANADY: Dr. Piantadosi?

DR. PIANTADOSI: Yes.

CHAIRPERSON CANADY: Now I would entertain any other amendments?

DR. PIANTADOSI: Again, two points. Reiterate my concern over the unqualified use of the term patients throughout the remainder of the questions and also the last point which states that most patients are able to reduce their anti-Parkinsonian medication consumption believe this is based entirely on a post hoc analysis and was not a designed objective of this study and I'm not comfortable with that being included with the other statements that do have a basis.

CHAIRPERSON CANADY: Could I suggest that we do separate those two, that you make an amendment suggesting that we replace "patient" with "advanced levodopa responsive Parkinson patients".

DR. PIANTADOSI: Yes, I would agree with that.

CHAIRPERSON CANADY: Can I have discussion on that amendment? Can I get a second on that?

DR. NUWER: Yes.

[Second.]

CHAIRPERSON CANADY: Discussion? Can we have a vote on that amendment?

DR. WALKER: Read it to us again.

CHAIRPERSON CANADY: That where we comment on patients in the other indications that we use the phrase that we've developed which is advanced levo responsive Parkinson patients.

DR. WALKER: For all use of the patients?

CHAIRPERSON CANADY: That's correct. Any other comment or discussion?

I'll entertain a vote. Dr. Walker?

DR. WALKER: Yes.

CHAIRPERSON CANADY: Dr. Zamorano?

DR. ZAMORANO: Yes.

CHAIRPERSON CANADY: Dr. Hallett?

DR. HALLETT: Yes.

DR. EDMONDSON: Yes.

DR. NUWER: Yes.

DR. MASSAQUOI: Yes.

DR. FESSLER: Yes.

DR. PIANTADOSI: Yes.

CHAIRPERSON CANADY: Then I heard an amendment suggesting that the last submitted indication be dropped?

DR. PIANTADOSI: That would be my proposal.

DR. NUWER: I would second that.

CHAIRPERSON CANADY: Discussion? That the Activa Parkinson Control Therapy allows most patients to reduce their anti-Parkinson medication.

Any comments, discussion? I'll entertain a vote. Dr. Walker?

DR. WALKER: I abstain.

CHAIRPERSON CANADY: Dr. Zamorano?

DR. ZAMORANO: Yes.

CHAIRPERSON CANADY: Dr. Hallett?

DR. HALLETT: Yes.

CHAIRPERSON CANADY: Dr. Edmondson.

DR. EDMONDSON: Yes.

DR. NUWER: Yes.

DR. MASSAQUOI: Yes.

DR. FESSLER: Yes.

DR. PIANTADOSI: Yes.

CHAIRPERSON CANADY: Any other amendments that people would like to make?

DR. EDMONDSON: I have another one.

CHAIRPERSON CANADY: Dr. Edmondson.

DR. EDMONDSON: Since we don't have enough data for older patients, we probably should and maybe I should just inquire rather than mention this as a true motion, concerns regarding confusion or disabling dysphasia. Perhaps in older patients the procedure should be staged. And I don't know if that would be appropriate in labeling.

CHAIRPERSON CANADY: I don't know if we have any data to go to that.

DR. EDMONDSON: We don't. But the question is do we also have enough data for the older patients getting bilateral implants in terms of safety.

CHAIRPERSON CANADY: How would you like to phrase your amendment?

DR. EDMONDSON: Perhaps just that. For patients over 70, either recommend staged implantation rather than simultaneous.

CHAIRPERSON CANADY: Do I have a second for that?

No second.

Other amendments.

DR. HALLETT: I wonder if I could perhaps speak to your concern. One of the exclusion criteria for the study was dementia and we heard it already argued that sort of physical status is perhaps more important than age. Would you be satisfied with a concept that if patients had dementia then that would be a contraindication for the procedure? For example, and that would certainly be in keeping with the way that the study was designed in the PMA data in front

of us.

DR. EDMONDSON: Not completely. Because we do know that older patients are more vulnerable to cognitive dysfunction after an UTI and a variety of other things very operatively, even without any pre-morbid dementia. Since this is an unknown territory, it's my, it's our concern.

CHAIRPERSON CANADY: Other amendments or comments?

DR. MASSAQUOI: A possible amendment. The next to last statement that the therapy allows patients with Parkinson's disease to regain their independence and functionability. Given that that wasn't a primary endpoint, it seems just a bit strong. It seems in the correct direction and I'm just wondering whether a qualification at something like many patients to significantly improve or some other minor weakening of that statement which is a very broad sweeping possibly over-welling statement.

CHAIRPERSON CANADY: Would this be in keeping with what you have in mind, "Activa Parkinson's Control Therapy allows many patients with

Parkinson's disease to improve their independence and functional ability" or is that too strong still?

DR. MASSAQUOI: No, that is that much better for me.

CHAIRPERSON CANADY: Is there a second to that amendment.

[Second.]

CHAIRPERSON CANADY: Any comments or discussion?

DR. WALKER: Didn't we redefine patients?

CHAIRPERSON CANADY: We did. It would include the redefinition.

DR. WALKER: Okay.

CHAIRPERSON CANADY: Thank you. Can I have a vote on that then, please? Dr. Walker.

DR. WALKER: Yes.

CHAIRPERSON CANADY: Dr. Zamorano?

DR. ZAMORANO: Yes.

DR. HALLETT: Yes.

DR. EDMONDSON: Yes.

DR. NUWER: Yes.

DR. MASSAQUOI: Yes.

DR. FESSLER: Yes.

DR. PIANTADOSI: Yes.

CHAIRPERSON CANADY: Dr. Hallett?

DR. HALLETT: One of the things that we heard was that there were a lot of problems with the current statistical analysis and a lot of missing data and a lot of things that need to be completed. I would think that we would want to have all of those questions that were raised from a statistical point of view answered in some way to make sure that that doesn't produce any significant question that hasn't arisen yet at this point. So I would urge that we have a completion of the answers to the statistical questions raised and present that data to the FDA prior to its being approved.

CHAIRPERSON CANADY: Can you phrase that for me?

DR. HALLETT: The company should complete, should answer the statistical questions raised to the FDA prior to approval.

CHAIRPERSON CANADY: A second for that?

DR. PIANTADOSI: I second that and I

appreciate the demarginalization of statistics.

CHAIRPERSON CANADY: Any comments, discussion?

DR. WALKER: Yes. We started this morning with a discussion of least burdensome and in my opinion the sponsor has shown through within the spirit of least burdensome, safety and efficacy. This opens the door to forcing the sponsor to do additional human trials before they can move forward with the marketing of this product and I'd be very, very opposed and if this is paperwork clean-up that's fine, but if this is go back and do more trials, I am absolutely opposed to that.

DR. HALLETT: No, I was not suggesting any further clinical trials. I was suggesting cleaning up the paperwork which there were a lot of problems that should have been cleared up, it seems to me in my -- for example, there were a lot of drop outs for which the data weren't really included. I think that they should be included and we should get a clear analysis of things like that and that would give a clearer answer to the data that have already been collected.