

UNITED STATES OF AMERICA
 DEPARTMENT OF HEALTH AND HUMAN SERVICES
 FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH
 MEDICAL DEVICES ADVISORY COMMITTEE

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NEUROLOGICAL DEVICES PANEL

+ + +

February 22, 2013
 8:00 a.m.

White Oak Campus
 Building 31- Room 1503, The Great Room
 Silver Spring, Maryland

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MICHAEL A. ROGAWSKI, M.D., Ph.D.	Temporary Voting Member
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MICHELLE L. LANE	Patient Representative
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MEETING

(8:00 a.m.)

DR. YANG: So I would like to call this meeting of the Neurological Devices Panel of the Medical Devices Advisory Committee to order.

I am Dr. Lynda Yang, the Chair of this Panel. I am a neurosurgeon and associate professor at the University of Michigan.

I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel participating in the meeting today has received training in FDA device law and regulations.

For today's agenda, the Panel will discuss, make recommendations, and vote on information regarding the premarket approval (PMA) application for the NeuroPace RNS System sponsored by NeuroPace, Incorporated. The device is indicated for use as an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures for no more than two foci that are refractory to two or more antiepileptic medications.

Before we begin, I would like to ask our distinguished Panel members and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position, and your affiliation. Let's start to my left.

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Dr. Krauthamer.

DR. KRAUTHAMER: Good morning. I'm Victor Krauthamer.

Since November 1st, I've been Acting Director for the Division of Neurological and Physical Medicine Devices.

It's actually been a pleasure to do this job with both the professionals and working with companies as well. So I just want to give a couple of words and just say, when we see this, it sometimes resembles a jury trial and a jury sitting up here, but it's not really. The real problem and the real enemy is the disease. So even though it seems as though there are two parties with different views, we should keep the long view in mind, that we're dealing with a very difficult public health problem.

Thank you.

DR. TOLEDANO: Good morning. My name is Alicia Toledano. I'm a biostatistician with 20 years of experience in device clinical trials, and I'm President of Biostatistics Consulting, LLC.

DR. BALISH: Good morning. I'm Marshall Balish. I'm a neurologist. I'm a local fellow. I'm at the Washington, D.C. Veterans Affairs Hospital, and I was on the faculty at Georgetown.

DR. CAVAZOS: Good morning. My name is Jose Cavazos. I'm a clinical and basic scientist in epilepsy for the last 25 years. I work at the University of Texas Health Science Center in San Antonio and have an appointment at the San Antonio VA.

DR. ROGAWSKI: Good morning. My name is Michael Rogawski. I'm Professor of Neurology at the University of California Davis School of Medicine in Sacramento. I do basic and translational research in epilepsy.

DR. HAINES: I'm Steve Haines. I'm a neurosurgeon and Chairman of the Department of Neurosurgery at the University of Minnesota.

DR. NIKHAR: Good morning. I'm Nirjal Nikhar. I'm a neurologist here in Bethesda in private practice.

DR. CONNOR: I'm Jason Connor. I work for Berry Consultants, and I'm an assistant professor at the University of Central Florida College of Medicine, and my expertise is Bayesian adaptive trial design.

MS. FACEY: Natasha Facey, Designated Federal Officer for the Neurological Devices Panel.

DR. ENGEL: I'm Jerome Engel, Jr. I'm Director of the Seizure Disorder Center at UCLA.

DR. FESSLER: Good morning. I'm Richard Fessler. I'm Professor of Neurosurgery at Northwestern University in Chicago.

DR. PETRUCCI: Good morning. Ralph Petrucci, a clinical professor at Drexel University College of Medicine and a neuropsychologist.

DR. BALTUCH: Gordon Baltuch. I'm a neurosurgeon at the University of Pennsylvania, with a lifelong interest in treating epilepsy, people with epilepsy, as well as devices.

DR. AFIFI: Good morning. My name is Abdelmonem Afifi. I'm

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Professor of Biostatistics at UCLA, and my area of expertise is the biostatistical methods of clinical trials and multivariate and multi-level statistical analysis.

DR. PRIVITERA: Michael Privitera. I'm Professor of Neurology, and I direct the Epilepsy Center at the University of Cincinnati, and my experience is in clinical trials of antiepileptic drugs.

MS. LANE: Michelle Lane. I am the Patient Representative today. I have epilepsy. I was diagnosed at the age of 13. My day job, I work as a legislative director at the House of Representatives.

MS. MATTIVI: Kris Mattivi. I'm the Consumer Representative. I'm a physical therapist and manager of analytic services at the Colorado Foundation for Medical Care, the Medicare and quality improvement organization for the State of Colorado.

MR. MUELLER: Good morning. My name is David Mueller. I am the Industry Representative. I am currently with American Medical Systems in Minnesota but have a long history in the neurological sciences and regulatory affairs.

DR. YANG: Thank you.

If you have not already done so, please sign the attendance sheets that are on the tables by the doors.

Ms. Natasha Facey, the Designated Federal Officer for the Neurological Devices Panel, will make some introductory remarks.

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MS. FACEY: Good morning. I will now read the Conflict of Interest Disclosure Statement and Deputization to Temporary Voting Member Statement.

The Food and Drug Administration is convening today's meeting of the Neurological Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S. Code Section 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with the Federal ethics and conflict of interest laws. Under 18 U.S. Code Section 208, Congress has authorized FDA to grant waivers to special Government employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussions of today's meeting, members and consultants of this Panel who are special Government employees have been

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screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S. Code Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss, make recommendations, and vote on the premarket approval application for the NeuroPace RNS System. The device is indicated for use as an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures for no more than two foci that are refractory to two or more antiepileptic medications.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in accordance with 18 U.S. Code Section 208. A copy of this statement will be available for review at the registration table during this meeting and will be included as a part of the official transcript.

Dr. Lynda Yang will be serving as the Acting Panel Chair for the duration of the Neurological Devices Panel of the Medical Devices Advisory Committee meeting on February 22, 2013.

David H. Mueller is serving as the Industry Representative,

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acting on behalf of all related industry, and is employed by Mueller and Associates.

For the duration of the Neurological Devices Panel meeting on February 22, 2013, the following individuals have been appointed as temporary voting members:

Dr. Michael Rogawski, a special Government employee, serves on the Peripheral and Central Nervous System Drugs Advisory Committee in the Center for Drug Evaluation and Research; Drs. Marshall Balish and Jose Cavazos are regular Government employees and consultants to CDER.

Ms. Michelle Lane, a regular Government employee and patient representative to CDER, has been appointed as a temporary non-voting member.

These individuals have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

The appointment was authorized by Jill Hartzler Warner, Acting Associate Commissioner for Special Medical Programs, on February 21st, 2013.

Appointment to Temporary Voting Status.

Pursuant to the authority granted under the Medical Devices Advisory Committee Charter of the Center for Devices and Radiological Health, dated October 27, 1990, and as amended August 18, 2006, I appoint

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the following individuals as voting members of the Neurological Devices Panel for the duration of the meeting on February 22, 2013:

Dr. Abdelmonem Afifi, Dr. Gordon Baltuch, Dr. Jason Connor, Dr. Jerome Engel, Jr., Dr. Richard Fessler, Dr. Nirjal Nikhar, Dr. Ralph Petrucci, Dr. Michael Privitera, Dr. Alicia Toledano.

For the record, these individuals are special Government employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting. This has been signed by Dr. Jeffrey Shuren, Director, Center for Devices and Radiological Health, on February 15th, 2013.

We would like to remind members and consultants that if the discussions involve any products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all other participants to advise the Panel of any financial relationships that they may have with any firms at issue.

Before I turn the meeting back over to Dr. Yang, I would like to make a few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting, Incorporated. They can be contacted at (410) 974-0947.

Today's meeting will be webcast. The web link is

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<https://collaboration.fda.gov/cdrh02213/>.

The press contact for today's meeting is Synim Rivers.

I would like to remind everyone that members of the public and the press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until after the meeting agenda has concluded.

If you are presenting in the Open Public Hearing session today and have not previously provided an electronic copy of your slide presentation to FDA, please arrange to do so with Ms. AnnMarie Williams at the registration desk.

In order to help the transcriptionist identify who is speaking, please be sure to identify yourself each and every time you speak.

Finally, please silence your cell phones and all other electronic devices at this time.

Thank you. And I will turn it back over to Dr. Yang.

DR. YANG: So we will now proceed with the Sponsor presentation.

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

I would like to now ask the Sponsor to approach the podium and begin their presentation.

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DR. MORRELL: Thank you.

Good morning. My name is Martha Morrell. I am a neurologist, epileptologist, and a Clinical Professor of Neurology at Stanford University. I'm here today as the chief medical officer of NeuroPace, a company founded in 1998 to develop the first implantable responsive brain stimulator to treat patients with medically uncontrolled partial onset seizures. NeuroPace is seeking FDA approval for the RNS System.

During today's presentation, we'll show that the RNS System is an entirely novel medical device that provides patients with medically intractable partial onset seizures with a new treatment option. We will establish that treatment with the RNS System reduces the frequency of partial onset seizures and improves quality of life in a substantial number of patients.

You will see that the RNS System's safety profile is acceptable, especially considering the risks of comparable or alternative procedures and the considerable risks of ongoing seizures.

The clinical data provides valid scientific evidence as defined by FDA and confidently establishes a reasonable assurance of device safety and effectiveness.

The RNS System is cranially implanted. A tray is fixed within a craniectomy, and then the neurostimulator is secured within that tray. There is no direct contact of the neurostimulator with the brain. Two leads are

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connected to a neurostimulator and placed at the seizure focus. These may be depth leads, subdural strip leads, or a combination, depending on the target.

The neurostimulator continuously monitors electrographic signals, and when specific patterns are detected, the neurostimulator provides responsive stimulation. Each time these patterns are detected, brief stimulation pulses are delivered. The physician selects the patterns to detect, as well as the stimulation frequency, pulse width, duration, and current. The total amount of stimulation that is typically delivered is less than five minutes a day.

NeuroPace has submitted for approval the RNS System as an add-on therapy to reduce seizure frequency in persons 18 years of age or older, who have partial onset seizures arising from one or two seizure foci that have not been controlled, despite treatment with two or more antiepileptic medications.

Here's our agenda. Dr. Gregory Bergey will begin by discussing medically intractable partial onset seizures and the clinical use of the RNS System technology. I'll review the study design, the patient population, and the effectiveness results. Dr. Robert Gross will present the safety data. Then I will return to discuss physician training and our plans for a post-approval study. And finally Dr. Bergey will place this clinical data into context.

Let me turn the lectern over to Dr. Bergey.

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DR. BERGEY: Thank you, Dr. Morrell.

My name is Greg Bergey. I'm Professor of Neurology and Vice Chair for Research in the Department of Neurology at Johns Hopkins University. I'm also director of the Johns Hopkins University Comprehensive Epilepsy Center and co-director of the Epilepsy Research Laboratory there.

I have served as an investigator in the RNS System studies. NeuroPace is reimbursing me for my travel expenses to be at this meeting, but I am not being paid for my time, nor have I ever received any honoraria or consulting fees from NeuroPace.

I am here because I believe in this technology, and I believe it is important for patients to have additional treatment options.

Epilepsy is one of the most common neurologic disorders. It affects at least 1% of the population, young and old. People with epilepsy have recurrent, unprovoked seizures that are caused by sudden discharges of abnormal brain electrical activity.

Partial onset seizures are a type of epilepsy seizures that arise in one or more foci of the brain and then spread. The exact symptoms of the seizure and the severity of the seizure depend on where the seizure starts and how much of the brain is ultimately involved. Although these types of seizures are called partial, these seizures nevertheless can be severely disabling and dangerous.

During a simple partial motor seizure, normal motor activity

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function is lost. There may be involuntary movements of the face, the arm, or the leg.

During complex partial seizures, consciousness is impaired. The patient may be unable to respond, speak, react normally, or even remember.

Generalized tonic-clonic seizures or convulsions cause loss of consciousness, stiffening, jerking of the arms and legs. The patient may bite his or her tongue, lose their urine, and even their bowels. After a seizure it is not unusual to feel confused and fatigued for minutes, hours, or even days. These are the types of seizures that are experienced by the patients that were entered into the RNS System trials.

The International League Against Epilepsy, a global organization of professionals who treat persons with epilepsy, has recently redefined intractable epilepsy as "a failure to control seizures after two medications that have been appropriately chosen and used."

Thirty to forty percent of patients with partial onset seizures continue to have seizures, even though at present there are now more than 20 antiepileptic drugs available in the United States. Although the goal of treatment is always seizure freedom, this is often not obtainable. If a patient doesn't respond to the first two medications, the chances of seizure control with trials of other medications is less than 5%. Therefore, reduction in seizures is considered a valuable clinical goal.

Contemporary antiepileptic medications have been approved

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for this patient population based on reductions of seizures of 12% to 20% in the active population when compared to control.

An equal number of patients have antiepileptic medication side effects that can negatively impact lives, such as problems with cognition, coordination, depression, and fatigue. As you will see, these types of side effects do not occur with treatment with the RNS System.

Depression and suicidality are highly prevalent in patients with epilepsy. More than half of the patients followed with epilepsy surgery centers are depressed, rates of suicide are five times higher than in the general population, and rates of completed suicide are three times higher. With affective disorders, the suicide rate increases 32-fold.

The risk for psychiatric comorbidities is highest in those patients who have frequent and severe seizures, such as the patients that were entered into the RNS System studies.

Unlike many antiepileptic medications, you will see that treatment with the RNS System does not negatively impact mood.

Another consequence of intractable partial seizures is cognitive impairment and even decline. More than half of the patients in a recent survey conducted by the International Bureau for Epilepsy reported that cognitive impairment significantly affected their ability to engage in work, education, leisure activities, and had a negative impact on their family and their relationships. This cognitive dysfunction can get worse as the seizures

continue over years, and are most severe in those who have epilepsy for many years, who have frequent seizures and who must take high doses or multiple medications.

As you'll see from the data today, patients in the RNS System studies have all of these characteristics that place them at risk for severe and worsening cognitive dysfunction. Unlike many antiepileptic medications, you will see that treatment with the RNS System did not have a negative impact on cognition.

One of the most concerning consequences of intractable partial epilepsy is shortened life expectancy. The death rate for patients with intractable epilepsy is three times higher than that expected in the general population. Most of these deaths are due to epilepsy, the direct result of a seizure or status epilepticus, seizure-related accidents such as trauma or drowning, and the well-described but poorly understood phenomenon Sudden Unexplained Death in Epilepsy, called SUDEP.

SUDEP is believed to be a consequence of autonomic events triggered by ictal or interictal activity, leading to cardiorespiratory disturbances. The rate of SUDEP is 9.3 per 1,000 person-years in patients followed in an epilepsy surgery program. This is the patient group that is most similar to the patients in the RNS System trials. The RNS System trials are gathering data on SUDEP, and there is no indication that the risk of this horrible event is increased.

Other than antiepileptic drugs, there are two options in the United States for treatment of partial onset seizures: the vagus nerve stimulator, or VNS, and epilepsy surgery. The FDA has approved the VNS as adjunctive treatment for medically refractory partial onset seizures.

Randomized controlled trials in patients with intractable partial onset seizures showed that stimulation in the effective range reduced seizure frequencies by 23% and 24% compared to 6% and 21% reduction in the control group that received subtherapeutic stimulation. This gave a difference of between 3% and 17% between the treated and active groups.

The reduction in seizures at one year was 31% and at two years was 41%. This suggests that efficacy of the stimulation improves over time, similar to what you would see in the RNS System studies.

The most common types of adverse events in the VNS control trials were related to stimulation of the vagus nerve, as you might expect, and with recurrent laryngeal nerves. And this included voice alterations, increased cough, paresthesias, and dyspnea. Infection occurred in 11.6% and infection leading to explantation in 1.8%. As you will hear, more than one-third of the patients in the RNS System trials had already tried the VNS.

Another very important option for patients is surgery to remove the seizure focus. The best candidates for seizure surgery have a seizure focus that can be precisely localized to an area of the brain that can be safely removed. However, only about 20% of patients are candidates. Up

to three-quarters of carefully selected patients who have mesial temporal onset seizures can be seizure free after temporal lobectomy.

Other types of seizure surgery are not as successful. Surgery outside the temporal lobe to remove a well-defined lesion, such as a tumor or a vascular malformation, can achieve one year of seizure freedom in about half of patients.

The risk of these surgeries include hemorrhage and infection. The risk of neurologic complications depends on the area of the brain in which you're operating and the size of the resection, but is about 3% to 10%. This doesn't include the visual field defects that would be an anticipated complication of an anterior temporal lobectomy. Some patients have too high a risk to memory, motor, sensory, visual, or cognitive function to have surgery.

As you will see, patients participating in the RNS System trials were not considered to be candidates for epilepsy surgery.

Many patients who are disabled by epilepsy are not helped by the available treatments. Although seizure freedom is the goal, treatments that further reduce the frequency of seizures can reduce the risks for cognitive dysfunction, depression, suicidality, and even death.

According to the recent Institute of Medicine report in 2012, "New treatment options are needed for those whose epilepsy does not respond to available treatments or who have unacceptable treatment side

effects." These are the patients that live with the impact of epilepsy every day and the wide-ranging impact on their families and themselves. They've already accepted the risks of multiple different treatments in their hope that their seizures can be controlled and their quality of life can be improved.

The RNS System provides another treatment option for patients who have failed, who are not candidates, or do not choose to pursue additional antiepileptic medications, VNS, or epilepsy surgery.

Dr. Morrell will provide an overview of the RNS System and how it works. I'm going to provide a little bit more detail and focus on how the physician uses this device.

The RNS System provides responsive stimulation to terminate abnormal electrographic activity. The cranially implanted neurostimulator contains custom integrated circuits, a battery, and a connector assembly. The neurostimulator is connected to up to two leads. These can be subdural, depth, or a combination of the two. Each lead has four electrode contacts. The leads are placed at the seizure focus for that patient, which has been identified by standard localization tests we've done at our epilepsy centers.

Since the RNS System is stimulating the brain directly, the vast majority of patients are totally unaware that the device is working. There's no pain or discomfort, the device is not visible, and most patients cannot even feel it under the scalp.

The physician uses a programmer to communicate with the

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neurostimulator via wireless telemetry. The patient holds the RNS wand near the neurostimulator while the physician uploads the data to the programmer. The uploaded data includes battery and impedance measurements, detections, stimulations, and stored electrocorticograms. The program is also used to set detection and stimulation settings. These are started at recommended settings and then adjusted to the needs according to the patient's response.

Data from the programmer is then transmitted to an interactive web-based database, the Patient Data Management System, or PDMS. Physicians can securely review any of the information stored about their own patients remotely from the web.

The patients themselves have a remote monitor at home to upload this information from the neurostimulator to the PDMS through a phone line or the Internet, and we can review this data through the PDMS.

Here are some examples of detections and stimulations in three different patients. This is the type of information that a physician can review on the programmer or the PDMS.

The physician has programmed the neurostimulator to detect and briefly stimulate specific epileptiform patterns that are characteristic of the type of activity preceding his or her patient's seizures. The initial recommended stimulation settings are then programmed into the neurostimulator. The arrows indicate the detection, followed by the

stimulation. The physician reviews these recordings, determines if the stimulation is having the desired effect, and then adjusts detection and stimulation based on the patient's clinical response.

In summary, medically intractable partial epilepsy is a devastating neurologic condition with profound social, psychological, and health consequences, including increased mortality. Current treatments unfortunately do not help all our patients, leaving a considerable number of patients with a pressing and unmet need for additional treatment options. The RNS System is a first-of-its-kind therapy that you will see is safe and effective for a large number of patients who have medically intractable partial onset seizures and have nowhere else to turn.

I'm now going to return the lectern to Dr. Morrell.

DR. MORRELL: Thank you, Dr. Bergey.

Three studies have been conducted. The feasibility and pivotal studies were in newly implanted subjects. When subjects completed the feasibility or pivotal studies, they could enroll in the long-term treatments trial, which follows subjects for up to an additional seven years.

After a successful feasibility study, the pivotal study began in 2006. The pivotal study was a randomized, double-blinded, sham-stimulation controlled study in which 191 subjects were implanted across 32 epilepsy centers in the United States and then followed for two years. This was the study that was powered to show safety and effectiveness for its intended use

and is the study upon which this premarket approval application is based.

The ongoing long-term treatment study started in 2006, when the first subjects completed the feasibility study and enrolled. It allowed subjects to continue to receive treatment with the RNS System for up to an additional seven years, while data is gathered to assess long-term safety and effectiveness. Ninety-seven percent of eligible subjects enrolled.

Subjects were eligible for the pivotal study if they were between 18 to 70 years old and had three or more simple partial motor, complex partial, or secondarily generalized tonic-clonic seizures on average each month. All subjects had been treated and failed at least two different antiepileptic medications and had seizures coming from one or two foci, as identified using the standard procedures for localization at that investigational site.

Potential subjects were excluded if they had an active psychosis, an unstable major depressive disorder, or suicidal ideation in the previous year. However, patients with a prior history of any of these, or with a stable depressive disorder, could be enrolled. This was so that many patients with psychiatric symptoms could participate.

Finally, patients treated with VNS could enroll, but the VNS pulse generator had to be removed before the RNS neurostimulator and leads were implanted.

Subjects enrolled into a baseline screening period. During this

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period, subjects had to meet the eligibility criteria for implant, including having three or more seizures per month. Antiepileptic medications were to be held constant from baseline until the end of the blinded evaluation period. After the implant, detection was turned on in all the subjects for one month. This is the postoperative stabilization period. One month after implant, the subjects were randomized 1:1 to receive responsive stimulation (these subjects will be called the treatment group) or to receive no stimulation (and we'll refer to these subjects as the sham-stimulation group).

Adaptive randomization was based on investigational site and on three clinical characteristics: seizure onset zone, number of seizure foci, and whether the patient had had an epilepsy surgery. These clinical characteristics used in randomization were selected a priori because they predict baseline seizure frequency and could potentially influence the response to treatment.

Responsive stimulation in the treatment group began at randomization and was adjusted weekly throughout the initial stimulation optimization period, then could continue to be adjusted as necessary throughout the study.

The blinded evaluation period, which was used for the primary effectiveness endpoint, included the third through fifth months after implant. The sham group did not have stimulation turned on during the blinded period but did have the same number of physician visits and the same face-to-face

time with the physician as did the subjects in the treatment group.

Five months after implant, all subjects entered the open-label period and received responsive stimulation. However, subjects remained blinded to their treatment group.

To maintain the blind, each patient was cared for by two different investigator teams. The assessment team gathered all the data used for the effectiveness analyses. This team was blinded to the patient's randomization and never managed the device. The treatment team managed the device but didn't collect any of the data used for effectiveness. However, both teams gathered safety data.

The pre-specified effectiveness endpoint was to demonstrate a statistically significant reduction in seizures in the treatment group compared to the sham group. The pre-specified statistical analysis method was generalized estimating equations, which I will describe later.

Support for the primary effectiveness endpoint was to be provided by other measures of seizure frequency and severity, as well as by a validated quality of life inventory for epilepsy.

The primary safety endpoint compared serious adverse event rates over the first three months post-implant to published rates of serious adverse events with comparable procedures. Supportive safety analyses considered the rates of adverse events as well as data from quantitative testing of neuropsychological function and mood.

Another pre-specified safety endpoint was to show that the rate of SUDEP in patients being treated with responsive stimulation was not higher than the expected literature-based rate for a similar patient population, and to begin to collect data from all of the RNS systems so that a confident estimate of the rate of SUDEP in patients being treated with responsive stimulation could eventually be established.

You'll notice that some of the data in our presentation and in FDA's presentation are different. That is because FDA is presenting data from two different data cutoffs. A complete dataset was submitted to FDA with the premarket approval application in June 2010, when all pivotal subjects had completed the blinded evaluation period. An amendment was submitted to FDA in May 2011, when all the pivotal subjects had completed the entire two-year study, with a median follow-up of 3.3 years for all subjects.

A complete set of safety and efficacy tables were provided. All of the data that we will present today is from this May 2011 cutoff. The only exception is for subject death and SUDEPs, for which data is current to October 2012, in order to provide the most recent subject death.

Here are the subject demographics. The average age was about 35, with a more than 20-year history of epilepsy. Despite taking about three different antiepileptic drugs per day, the mean seizure frequency was more than 34 per month, with a median frequency of nearly 10. You can see that the range of seizures was considerable, between 3 to 338 seizures per

month. There were no significant differences between the treatment and sham group subjects in any of the demographics.

Seizure onsets came equally from the mesial temporal lobes and from neocortical regions. About one-third had already been treated with an epilepsy surgery. Nearly 60% had been evaluated for epilepsy surgery with intracranial electrodes, and approximately one-third had been treated with the vagus nerve stimulator. Two characteristics were moderately out of balance: number of seizure foci and prior intracranial monitoring. Sensitivity analyses showed that this imbalance did not affect the results.

Here's more detail on the seizure onsets in these subjects. Most subjects whose seizures began in the mesial temporal lobe or hippocampus were not candidates for epilepsy surgery because they had seizures coming from both left and right. The remaining patients had already failed a surgery or there was risk to memory.

The subjects with seizures arising in the neocortex mostly had onsets in the lateral, temporal, and frontal lobes. These subjects had already failed a surgery or there was too much risk for neurological deficits because the seizures came from areas of the brain important for neurologic function.

At the risk of repeating myself, let me say again, these subjects were not candidates for an epilepsy surgery.

Subject accountability will be shown in this figure: 240 subjects enrolled in a baseline screening period to determine whether they were

eligible for implant; 49 subjects were not eligible; 20 didn't want to continue for reasons such as stress or anxiety about the procedure or they pursued another treatment; 15 subjects were withdrawn because the physician-investigator felt the subject was no longer a candidate or should consider other treatments; 6 subjects couldn't fulfill the study requirements; and 4 did not have enough seizures to be eligible for the implant; 3 subjects didn't meet eligibility criteria; and 1 was withdrawn because the investigational site was being closed for low enrollment.

191 subjects were implanted with the RNS neurostimulator and leads. All were randomized. After randomization, one subject no longer wished to continue in the trial, and one subject died of SUDEP. Every death across all the studies will be described later.

189 subjects entered the blinded evaluation period. Two subjects withdrew during the blinded evaluation period because the neurostimulator was explanted due to implant site infection. And Dr. Gross will discuss all implant site infections later.

Ninety-eight percent of the subjects completed the blinded evaluation period and entered the open-label period. In the open-label period, two subjects withdrew because of implant site infections, five subjects didn't want to continue, and five subjects died, one of suicide, one of lymphoma, and three of SUDEP.

175 subjects completed the entire study, providing 379 years of

implant experience and over 328 patient-years of experience with the responsive stimulation enabled.

Every subject who was implanted with the device was randomized, and all of the effectiveness analyses were performed using the intent-to-treat population.

Ninety-eight percent of the more than 32,000 possible daily seizure observations were captured for the primary effectiveness endpoint, and 92% of the implanted subjects completed the entire study.

FDA has examined the effectiveness data in a number of ways. NeuroPace and FDA agree that the treatment effect with responsive stimulation is consistent across the pre-specified analyses. However, FDA will raise their concern that the effect of treatment with responsive stimulation is not robust across all their post hoc statistical analyses, particularly their descriptive analyses of means and medians of raw seizure counts and additional GEE models.

We do not agree. Therefore, we will show you some of FDA's analyses as well as our response. You will see that subjects treated with responsive stimulation consistently have a greater reduction in seizures than do the implanted sham subjects.

FDA will present a number of post hoc analyses using raw, mean, and median seizure counts. Medians are insensitive to change in a population, and a presentation of raw means is not adequate to explain

seizure variability. Neither FDA nor NeuroPace thought that these were appropriate endpoints.

Here is why medians and raw means of seizure counts do not accurately represent what is happening in these patients. This is the baseline seizure data from the subjects participating in the pivotal study. As is no surprise, there is a wide range of seizure frequencies.

Now here is the mean. More than three-quarters of the subjects are below the mean. Here is the median, which represents a single point in the population and doesn't tell you what is going on with the subjects above or below. These issues are precisely why FDA requested an endpoint that does not depend on median counts or raw means.

In contrast, the median percent change and responder rates are familiar ways to represent changes in seizures in epilepsy therapy trials. They account for subjects on baseline, but neither account for variability across a population. In fact, in 2005, FDA specifically recommended that NeuroPace not use responder rate as the primary endpoint because of the potential that there would be significant variations in seizures rates both within and across subjects. Nevertheless, these are clinically useful ways to depict the data.

Here is the observed median percent change for the first month of the blinded evolution period, which is the third month after implant. This is compared to baseline. Treatment is in blue and sham in gold. Seizures are

reduced in both groups. This shows the effect of the implant procedure, which caused a reduction in seizures of about 30% in all subjects. This implant effect was anticipated and is known to occur in patients with epilepsy after anesthesia and neurosurgical procedures, although how long it lasts wasn't known before.

In the second and third months there's an additional reduction in the treatment group. However, the seizure reduction is waning in the implanted sham group subjects, so that by the final month, the median percent reduction in the treatment subjects was 34% compared to 18.9% in the implanted sham subjects.

At six months, subjects in the sham-stimulation group received responsive stimulation for the first time, and their seizure frequency drops. This is the effect of stimulation. As you will see, this response to stimulation is not only sustained through the open-label period, it improves.

We've looked at a number of ways to describe the data, and now we'll look at the primary effectiveness endpoint chosen by FDA and NeuroPace.

Generalized estimating equations, or GEE, was agreed upon precisely because it is an excellent method to analyze data over time, especially longitudinal data for which there are multiple counts that are correlated within an individual, but variable across individuals, such as the seizure count data. A properly specified GEE provides the most accurate,

robust estimate of the effect of treatment.

In order to provide context for the primary effectiveness analysis and its post hoc modifications, we'll show a timeline.

The statistical analysis plan pre-specified that GEE would be the method used to determine the magnitude and the significance of the treatment effect. The intent was to demonstrate a significantly greater reduction in seizure frequency in the treatment group compared to the sham during the blinded evaluation period compared to the pre-implant period. Seizure diaries were used to measure seizure frequency.

The primary GEE model evaluates the effect of the subject group, treatment versus sham, and time, the blinded evaluation period versus the pre-implant baseline.

GEE requires that you make an assumption about what the mean and variance will be in your dataset. In our pre-specified model, we used a variance function called the over-dispersed Poisson, which assumes that the mean and variance are proportional to each other.

When the GEE is run, the statistical software generates two sets of standard errors, the model based and the empirical. Our investigational plan said -- and I'm going to use the statistical language here -- the scale parameter, which is also known as the over-dispersion parameter, would be allowed to vary. By definition, this means that model-based standard errors were pre-specified.

The primary effectiveness analysis was performed in October 2009, after the last subject completed the blinded evaluation period. Statisticians approached the data blinded as Groups A and B. Prior to the blind being broken, a significant difference was seen between the groups, with a p-value of less than .0001 using the model-based standard errors that we had described in the statistical analysis plan.

However, it was immediately apparent that there was tremendous variability in the daily seizure count data and that the GEE model as pre-specified did not fit the data. Therefore, NeuroPace was concerned that this analysis was not appropriate.

This is a Forest plot that presents the results of the GEE analysis using the pre-specified model. The rate ratio is shown on the X-axis. A rate ratio of less than one means that the treatment group had fewer seizures than the sham group. Here the rate ratio is .78, indicating that there is a 22% greater reduction in seizures in the treatment subjects, relative to the reduction in seizures in the sham subjects, that occurred after implant.

There are two confidence intervals, the empirical in gold and the model-based in blue. These come from standard errors generated by the statistical software. Although the pre-specified model-based results are highly significant, in an adequate model the model-based and empirical confidence intervals should be quite similar, and they are not.

In the column to the right, you'll see the symbol phi, which is

the over-dispersion parameter that's also provided as part of the GEE results. This tells you how much variability there is in the data beyond what your GEE model assumes. A phi much greater than 1 tells you that the variability in your data is more than what was expected. In this case phi was nearly 9, indicating that this is a poor model.

There was a third indicator that this model couldn't deal with: the variability in the seizure data. In this graph each dot represents the actual mean and variance of a group of seizure counts in the study, described by covariates, and the line is the fit based on the Poisson variance function. Remember, the Poisson requires that the mean and variance be strictly proportional, so you can't make this fit the data.

There was such huge dispersion in the seizure counts that the Poisson, even using the over-dispersion parameter, couldn't handle it. Using this Poisson model is like disregarding 70% of the information in the seizure data, compared to an efficient analysis.

So although the GEE model as pre-specified was significant, it couldn't deal with the variability in the data, so we had to identify modifications that would reduce both within- and across-subject variability. Only the blinded data could be tested for goodness of fit. The treatment effect was evident, so we followed statistical principles and clinical common sense.

Within-subject variability was reduced by grouping seizure

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counts by month rather than day. Across-subject variability was addressed by including the clinical randomization characteristics as covariates. We randomized on these precisely because we knew that these could be correlated with the baseline seizure counts, and they were.

For example, one of these characteristics was onset zone. Subjects with frontal lobe seizures had three times more frequent seizures at baseline than those with mesial temporal onsets. And subjects with one focus had three times more seizures at baseline than those with two. So all of the clinical randomization characteristics were included as covariates.

These two modifications were recommended to us by FDA, are completely supported by the statistical literature, and were advised by the statistical experts from whom we sought guidance.

When these clinically evident modifications were applied, there was still variability in the seizure count data that could not be addressed by the Poisson, even with the over-dispersion parameter. The negative binomial is the more general case of the over-dispersed Poisson and can deal with greater variability. Objective metrics showed that this variance function fits the data.

As you will see, these modifications do not change the magnitude of the treatment effect, which you can think of as the signal. They simply account for the variability or, in other words, the noise.

Here again is the actual seizure data plotted with the negative

binomial variance function, which does not require that the mean and variance are proportional. The negative binomial distribution more closely fits the data and therefore provides three and one-half times more information from the seizure data than does the over-dispersed Poisson.

The objective output from the GEE analysis shows that the model with these modifications is appropriate, efficient, and precise.

Here is the GEE analysis using the model as pre-specified, and below that the GEE model with the required modifications. The rate ratio stays the same, 0.75, indicating that there is an additional 25% seizure reduction with stimulation above and beyond the implant effect. The model-based and empirical confidence intervals are similar, and the over-dispersion parameter, ϕ , is close to 1. The signal isn't changed, but the noise is reduced by appropriately handling the variance.

FDA agreed that the GEE as pre-specified was not appropriate and that this modified analysis was appropriate and efficient. They requested that we submit both in our premarket approval application.

Here are the actual clinical results from the primary effectiveness analysis. The GEE with the post hoc model modifications is used. Over the three-month blinded evaluation period, the treatment group had a 37.9% reduction in seizures compared to a 17.3% reduction in the sham group. This difference is significant, at p equals 0.012.

In a pre-PMA meeting, FDA asked us to look at month-to-month

differences throughout the study, similar to what you saw depicted in the median percent change. The effect of responsive stimulation is sustained in the treatment group, and the effect of the implant procedure, which you see in the sham subjects, wanes over each month of the blinded evaluation period. Initially, the effect of the implant procedure obscures the effect of stimulation. By the last month, the reduction in the treatment group subjects reached 41.5% and dropped to 9.4% in the sham subjects.

Just to show you again that these modifications have no impact on the treatment effect, here are the results using the GEE model as pre-specified. There's very little difference in the change in seizure frequency using either model.

Here's another Forest plot which shows the GEE as pre-specified and with the post hoc modifications that were required. You have already seen these. We pre-specified sensitivity analyses to confirm that the treatment effect was consistent and robust.

First, there was a per-protocol analysis that excludes nine subjects with potentially significant protocol deviations. The treatment effect is not changed and remained significant.

Missing data imputations were also pre-specified: intermittent missing, last observation carried forward, and multiple imputations. In every case the treatment effect was statistically significant, indicating that missing data, which was only 2%, do not bias the results.

We also pre-specified that we'd assess whether the results were sensitive to clinical characteristics that were out of balance. The number of seizure foci and whether the subject had prior intracranial monitoring were slightly out of balance, but adjusting for these covariates did not change the treatment effect.

Across all of these GEE models, the rate ratio is consistently about .75, which tells us that there is an additional seizure reduction of 25% in the treatment subjects, relative to the reduction the implanted sham subjects had. Again, this is the effect of stimulation above and beyond the implant effect.

The statistical software output shows that these models fit the data. The model-based and empirical confidence intervals are quite similar, as are the over-dispersion parameters or phi. All of these pre-specified analyses support a robust treatment effect.

Beginning in November 2011, FDA presented NeuroPace with a number of post hoc analyses. These included more GEE analyses, analyses of baseline seizure frequency, analyses excluding potentially influential subjects or subjects identified as influential by FDA, and a bootstrap analysis.

This is a Forest plot prepared by FDA of additional post hoc GEE analyses for the entire blinded evaluation period. This is in your briefing materials and will be presented by FDA. The top row is the primary endpoint using the modified analysis.

Please note that across all of these GEE models, the treatment effect size or the signal is consistent. What is different is the way that each handles the variability in the seizure count data or the noise. We've agreed that our pre-specified model could not account for the variability. You will see that all the other models here that do not appropriately handle the variability in seizure count data also don't fit the data.

The GEE analysis highlighted at the bottom is the pre-specified analysis that FDA and NeuroPace agree is not appropriate. This uses the Poisson variance function, daily seizure counts, and no randomization covariates. These models use the Poisson variance function, and we already know the Poisson doesn't fit.

Two additional models used daily seizure counts, which are highly variable and cause widely different confidence intervals.

The next model uses a negative binomial distribution and monthly seizure counts, but doesn't include randomization covariates. The confidence intervals are large and the phi is over two, indicating that the analysis is not efficient, including the clinical randomization covariates necessary because they are so highly correlated with baseline seizure frequencies and because this makes the analysis match the study design. If these are not included, the clinical differences in baseline seizure frequencies are treated by the model as noise, and in fact, information is lost.

We're left with a modified analysis provided to FDA in 2010. It

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includes the more appropriate variance function, addresses within-subject variability by using monthly seizure counts and across-subject variability by including the randomization covariates. The confidence intervals are small and similar, and the phi is close to 1. Note again that the treatment effect remains consistent.

When FDA showed this Forest plot to NeuroPace and expressed their concern that not every one of their post hoc analyses was significant, we sought additional expert statistical input from Dr. Patrick Heagerty, Professor of Biostatistics at the University of Washington and an expert in GEE.

Based on statistical principles and without looking at the data in the study, he independently concluded that the modified analysis was the most appropriate and efficient analysis and that these other analyses were not equally plausible or equally appropriate. Dr. Heagerty is here today to answer questions.

Another recent FDA post hoc analysis, shown in this figure, placed subjects into one of four groups based on baseline seizure frequencies grouped in increments of 28, whether there were 0 to 28 seizures a month, 29 to 56, 57 to 84, or more than 84. FDA will express their concern that there might be a differential response to treatment, depending on the baseline seizure frequency, and specifically that subjects with more frequent seizures at baseline had a larger reduction in seizures than did subjects who had a lower baseline seizure frequency.

This analysis simply looks at actual raw means, not at the percentage or proportional change. Also three of these four groups had 20 or fewer subjects, and in every group the treated subjects did better than the sham.

This analysis by FDA is not a formal statistical analysis. It is descriptive. NeuroPace performed the formal statistical test to determine whether baseline seizure frequency predicted the response to treatment. When this formal analysis is performed, there is no evidence that the response to treatment varies according to the baseline seizure count.

This figure will be shown by FDA in their presentation as another post hoc sensitivity analysis examining the effect of excluding potentially influential subjects.

I must begin by saying there were no outliers in the study based on seizure frequency, data collection, clinical attributes, or any other metric.

The two subjects indicated by the orange lines are the subjects that were excluded in FDA's analysis. They are both sham subjects. These subjects are not those with the overall highest seizure frequencies or the highest percent change in seizure frequency. There are 20 other subjects with similar percent changes in seizure frequency. However, it's apparent by visual inspection that one of these subjects had a high seizure count in the final month of the blinded evaluation period.

Here are the actual raw data for that subject. These are daily seizure counts. This subject had only simple partial motor seizures with a quick head turn to the left and speech arrest, but no alteration in awareness. As you see, there is a lot of day-to-day variability, but the variability is consistent in the baseline, which is in the lighter gray, and in the blinded evaluation period shown in the blue. This sham subject was not receiving stimulation in the blinded period. Although we do not consider this subject an outlier, an analysis excluding this subject showed that the treatment effect was largely unchanged and remained statistically significant.

This figure is also in FDA's briefing materials and will be shown in FDA's presentation. These are the mean seizure counts for the intent-to-treat population for the pre-implant period and for each month of the blinded evaluation period. The treatment group is in red and the sham group in a dashed blue line.

The implant effect is seen in the first month and wanes during the blinded evaluation period, whereas the treatment effect persists. To the right is the same representation of mean seizures per month, but with the exclusion of two sham subjects identified by FDA as influential, using a statistical method called Cook's distance.

As you can see, when these two sham subjects are removed, the mean seizure count for the sham group doesn't return to baseline. Of course, there is no change in the treatment subjects. FDA is therefore

concerned that the magnitude of the difference between treatment and sham may be sensitive to these two subjects.

Let me remind you that the representation of the data you see here, using raw means of seizure counts, doesn't account for changes within individuals or the longitudinal properties of the data.

This continues FDA's post hoc analysis excluding the two subjects identified by FDA and then more. This is median percent change. And the effect of treatment remains consistent when the data are viewed with this more robust measure. This is reduction from the pre-implant period through each month of the blinded evaluation period. It's clear that the seizure reduction in the treatment subjects is consistently higher than for the sham subjects and that there is general consistency in the plots. If this post hoc exercise is carried further by excluding additional subjects, the treatment effect remains consistent and is significant.

We then performed post hoc sensitivity analyses using Cook's distance. And we applied this by identifying the most influential subject, removing that subject, reapplying the model to identify the next most influential subject, removing that subject, and so on.

This first plot shows the result as each influential subject is removed. Results remain statistically significant with the removal of the first most influential subject, the top three, four, five, six, seven, and eight. The empirical p-value, but not the model-based p-value, loses significance only

when the top two subjects are removed. This simply reflects variability in patient data. And importantly the analyses that exclude all the other subjects also exclude Subjects 1 and 2.

Finally, FDA suggested that we perform a bootstrap analysis to assess the likelihood that the results in the pivotal trial could have occurred by chance. In other words, how often would you see a difference this big?

The bootstrap analysis was conducted by creating five sets of 2500 simulated clinical trial datasets. For each simulated dataset, 97 subjects were chosen randomly from the entire population of 191 subjects and assigned to the treatment group, and another 94 subjects were chosen randomly and assigned to the sham. Each set was analyzed using modified GEE.

If the result observed in the pivotal trial was no different than chance, then this result would occur commonly in the random datasets. However, this result demonstrated that there was less than a 2% chance that the results of the pivotal trial could have occurred by chance under the null hypothesis. This analysis also supports the robustness of the treatment effect.

To summarize, what we have shown you is that even though seizures are reduced in both groups after the implant, responsive stimulation reduces seizure frequency no matter how the data is shown or analyzed. Using the pre-specified GEE, whether using the model as pre-specified in

2005 or with the post hoc modifications that NeuroPace and FDA agreed represent the data efficiently, appropriately, and accurately, there is a significantly greater reduction in seizures in the treatment group compared to the implanted sham subjects.

With the modified model, the reduction in seizures in the treatment subjects is 37.9% compared to 17.3% in the sham subjects. The treatment effect size is consistent across pre-specified sensitivity analyses and the post hoc analyses performed by FDA.

Finally, bootstrap analyses suggested by FDA show that there is less than 2% probability that these results could've occurred by chance. These analyses confirm that the treatment effect is robust.

Now we'll move on to pre-specified secondary effectiveness results as well as pre-specified and post hoc additional analyses.

Here are the secondary effectiveness analyses. We'll show results for each of the pre-specified secondaries over the entire blinded evaluation period, as well as post hoc analyses requested by FDA showing each month of the blinded evaluation period.

However, I will briefly mention the Liverpool Seizure Severity Scale here. The Liverpool relies on a patient's report of their single-most severe seizure. This was statistically significantly improved for both groups compared to baseline, at the end of the blinded evaluation period, and was not different between groups.

Here is the responder rate, which considers the percent of subjects with a reduction in seizures of 50% or greater. This is a binary measure (yes or no) and is not sensitive to within- and across-subject variability. There was not a significant difference in the responder rate between treatment and sham. And for each individual month of the blinded evaluation period, the responder rate in the treatment group ranged from 34% to 39%. The sham group, due to the implant effect, also had a comparably high responder rate.

This is change in mean seizures per month. Over the entire blinded evaluation period, the treatment subjects had a reduction of 11 seizures per month, which was not significantly different than the reduction of five seizures in the sham subjects by t-test.

When looking at the data month by month, the treatment group clearly has a progressive reduction in seizures over each month of the blinded evaluation period, and the sham group is gradually returning to baseline. The reduction in the treatment group compared to their own baseline is significant, while the reduction in the sham group is not.

Another secondary endpoint was the proportion of seizure-free days. Over the entire blinded evaluation period, there was not a statistically significant difference between the treatment and sham groups. However, over each individual month, the treatment subjects continued to have more seizure-free days. By the end of the blinded evaluation period, the difference

between the treatment and sham groups achieved statistical significance.

That was a post hoc analysis.

Subset analyses were pre-specified to evaluate whether treatment was more likely to benefit particular types of patients. I want to clarify. This was not an analysis to show whether the treatment group does better than the sham in any one of these subsets. This was an analysis to see whether there was any difference in the treatment effect across subsets with different seizure onset zones, number of seizure foci, and prior epilepsy surgery. The formal analysis shows that the interaction term is not significant.

Clinically, these analyses show that patients benefit from treatment, regardless of where the seizures start, mesial temporal lobe or other regions, whether there are one or two foci, and whether or not they've had a prior epilepsy surgery.

FDA will show you a post hoc analysis of these subsets as responder rates, and it will appear as if there is little difference between the treatment and sham subjects. Responder rates are not an accurate method for this type of analysis, which is why FDA and NeuroPace agreed that this analysis would be performed by GEE with formal testing of an interaction term.

Long-term effectiveness of responsive stimulation was assessed using the effectiveness data obtained in the open-label period of the pivotal

trial, which includes data up to two years after implant. Responsive stimulation becomes more effective over time. FDA will show you this data as mean seizure frequency.

Here is the pre-specified analysis, which presents this data as responder rate. The treatment group is in blue, and the sham group is in gold. As stimulation is turned on in the open-label period, the sham subjects improve and continue to do so, as does the treatment group. The slope of improvement is statistically significant at $p < .0001$, and the responder rates exceed 50%.

You may notice that in this plot, which shows time since implant, there is a lag in the sham group. In a moment I will show you a figure of time since stimulation started, and you will see this early difference goes away.

But first let me show you that this continued improvement is not because subjects dropped out if they weren't doing well. This plot overlays the previous plot, showing a constant cohort group which includes subjects for whom data were available at every time point, the line superimposed indicating that the results are not due to selective withdrawal of subjects. Also you'll note there was a very low dropout rate. In fact, as you'll recall, 92% of the implanted subjects completed the entire study.

This plot shows the responder rate based on months of stimulation, and you can see the progressively favorable effect of stimulation

over time in all of the subjects.

This shows the responder rate in all of the subjects, and a responder rate in subjects who had no changes in their antiepileptic drugs at any time in the open-label period, and those subjects who did have antiepileptic drug changes. There is really no difference, indicating that the favorable effect of treatment with responsive stimulation is not because antiepileptic medications were changed during the open-label period.

Quality of life was an additional pre-specified effectiveness analysis measured by the QOLIE-89, which is validated in widely used inventory in epilepsy therapy trials. Both treatment and sham group subjects had improvements in the QOLIE at the end of the three-month blinded evaluation period, and there was no difference between the two groups.

Changes in quality of life are typically not considered reliable until about one year, so this was the pre-specified endpoint. This plot shows significant group improvements in quality of life at one and two years.

This next plot shows the mean change from the QOLIE baseline group overall score at the very top, and all the group subset scores two years after implant. There were statistically significant improvements in 9 of the 17 subscales. These include improvements in aspects of health, including seizure worry, health discouragement, physical role limitations, energy and fatigue, and in cognitive functions such as attention, concentration, language, and memory, which are often impacted by seizures and also by antiepileptic

medications.

Data were combined from the feasibility, pivotal, and long-term treatment studies to look at effectiveness over the longer term. This figure shows that the effectiveness of responsive stimulation is sustained over years of follow-up. The responder rate is in dark blue. This is the percentage of subjects with a 50% or greater reduction in seizures. And the median percent reduction is shown in light blue. The retention rate is 83%. The numbers of subjects gets smaller over the years, as seen along the X-axis, primarily because subjects hadn't reached that time point as of the data cutoff.

For both metrics, subjects treated with responsive stimulation continued to experience seizure reductions in the 50% range, even out to five years for some.

Some subjects had periods of seizure freedom. Twenty-seven percent had at least one period of three months or more with no seizures, and 14.5% had at least one period of seizure freedom that lasted six months or more.

To summarize, treatment with responsive stimulation is effective in a significant number of these patients with severe epilepsy who have had multiple treatment failures.

The primary effectiveness endpoint was met with a GEE, whether using the pre-specified model-based p-value or with the modifications to the model agreed upon with FDA.

Over the blinded evaluation period, the reduction in seizures in the treatment group was 37.9% and 17.3% percent in the sham subjects.

An implant effect reduced seizures in the sham group over the early part of the blinded evaluation period and then began to wane, so that by the end of the blinded evaluation period, seizure frequency was reduced by 41.5% in the treatment group and 9.4% in the sham.

We appreciate that FDA, in addition to independently checking the pre-specified primary endpoints and planned secondary endpoints, also conducts exploratory analyses to assess the robustness of the results. However, regardless of the analysis, the treated group consistently does better than the sham group, and the magnitude of the benefit for these patients with few alternatives is clinically significant and similar to the benefit seen by new drugs for epilepsy.

We agree that the patients with many seizures per day have large reductions in the mean number of seizures per month. But patients with fewer seizures, who of course don't have as much impact on mean seizure counts, also benefited proportionately.

As FDA's and NeuroPace's baseline seizure frequency analyses showed, the subjects receiving stimulation had a greater reduction than the implanted sham subjects.

The likelihood of a favorable response to treatment with responsive stimulation did not depend on where the seizure started, whether

there are one or two seizure foci, or whether the subject had already had an epilepsy surgery. We showed this with pre-specified formal statistical analyses. We've also shown there is less than a 2% chance the overall results could've occurred by chance.

The secondary endpoints all showed an improvement in the treatment subjects. The ability to show a statistically significant difference between the subject groups was impacted by the implant-related reduction in seizures in the sham group. However, the month-to-month data showed that the difference between the two subject groups became greater over each month of the blinded evaluation period as the implant effect waned.

During the open-label periods of the pivotal study, there was a progressive and statistically significant reduction in seizure frequency that was sustained over years of follow-up in the long-term treatment study. These effects were not due to subject dropouts or changes in antiepileptic medications.

In addition, there were progressive and significant improvements in overall quality of life, and in domains of quality of life, they're often impaired in people with epilepsy, including perceptions of health and cognition. The subjects' perception that this treatment is of benefit is evident by the high subject retention rates.

Dr. Robert Gross will now present safety findings from the RNS System studies.

DR. GROSS: Thank you, Dr. Morrell.

My name is Robert Gross. I'm an Associate Professor of Neurosurgery and the Director of Functional and Epilepsy Surgery at Emory University School of Medicine.

I've been performing epilepsy surgery as well as implantation of deep brain stimulators for movement disorders and other conditions for more than 15 years, and I am an investigator in the RNS System trial. NeuroPace is reimbursing me for my travel expenses to be at the meeting, and I am receiving compensation for my time spent here today.

The pre-specified pivotal study primary safety endpoint required that we demonstrate that the safety of the RNS System compared favorably to the safety of comparable procedures, as measured by serious adverse event rates, whether related to the device or not. Serious adverse events were any events that were life threatening or resulted in a hospital admission or a surgical procedure.

Two periods were specified. The first was the acute period, which was the implant through the first four postoperative weeks. The SAE rate for the RNS System of 12% did not exceed the literature-derived rate for SAEs of 15%, which was associated with implantation of intracranial electrodes for purposes of localization of seizures and epilepsy resective surgery.

The second period was the short-term chronic period, defined

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as implant through the first 12 weeks. The RNS System SAE rate of 18.3% did not exceed the literature-derived three- to four-month SAE rate of 36% for DBS systems implanted for movement disorders.

These data demonstrate that the primary safety endpoint was achieved.

Here's some detail for the SAEs in the first postoperative month. Recall that no subject was receiving stimulation during this period. The only SAEs affecting more than one subject were implant site infection, extradural hematoma, hydrocephalus, and headache related to the procedure. We'll provide more detail about the infections and hemorrhages later.

Overall, the risk for an SAE in the first postoperative month is consistent with comparable procedures, implantation of intracranial electrodes, and epilepsy surgery.

This slide presents the rates of all adverse events during the blinded period, which includes non-device related adverse events. There were no differences in the overall rate of serious or mild adverse events between the treatment and sham subjects. The only statistically significant difference in any specific adverse event was for AED toxicity. There were six subjects in the sham group who had this mild adverse event, and no subjects in the treatment group.

There were only four serious adverse events that occurred in

more than one subject during the blinded evaluation period, and each of these occurred in one subject from the treatment group and one from the sham group. One subject in each group had a serious adverse event related to an increase in complex partial seizures. One subject in each group had a procedure to change the location of a lead, and one subject in each group had an implant site infection related to head trauma during a seizure.

The medical device removal refers to removal of a vagus nerve stimulator. This was a serious adverse event because the pulse generator was supposed to have been removed prior to the implant of the RNS System neurostimulator and leads.

Treatment with the RNS System had no negative effects on cognitive function. And according to a comprehensive battery of 17 neuropsychological tests administered by Ph.D. neuropsychologists, there was no difference between treatment and sham subjects in neuropsychological function at the end of the blinded evaluation period and no deterioration in any group scores at any point.

Stimulation did not have a negative impact on mood. Three validated inventories of effective status showed that there was no difference in mood between the treatment or sham subjects at the end of the blinded evaluation period and no deterioration in group scores at any point.

To provide the most comprehensive representation of the safety experience with the RNS System, I'll focus the rest of the safety

discussion on data combined from the pivotal, feasibility, and long-term treatment studies. This captures data from 256 subjects, over 903 patient-years of implant experience and 819 patient-years of stimulation experience.

During the implant procedure and the first postop month, four subjects had a serious adverse event related to hemorrhage. Two of these subjects had an epidural hematoma that were evacuated during the first hours after surgery. One had a subdural hematoma after prolonged intraoperative electrocorticography at implantation that was evacuated. One subject was observed for one day because of a cerebral hemorrhage that was detected incidentally on CT. There were no consequences of any of these hemorrhages.

Eight subjects had an SAE related to hemorrhage after the first month. Five of these were attributed by the investigator to head trauma incurred during a seizure. Two subjects had a subdural hematoma evacuated, and the other three, overall, briefly observed in the hospital, one with a subdural hematoma, one with an intracerebral hematoma, and one with a subarachnoid hemorrhage.

Three subjects had cerebral hemorrhages that were not related to seizures. One subject had residual, mild right-hand weakness and was explanted 13 months after the event, the second subject had exacerbation of a preexisting memory deficit, and the third had ongoing headaches. Both of the last two of these subjects continued to be treated with the RNS System.

These rates are not higher than what is reported in the literature for patients implanted with intracranial electrodes or associated with an epilepsy resective procedure, and they are not higher than the one-year rate of hemorrhage in patients treated with DBS for Parkinson's disease, as documented in a recent prospective study by Weaver and colleagues.

Across all the RNS System studies, the rate of serious adverse events due to implant site infection was 2% in the first postoperative month and 7% over the entire 903-year experience with 3.3 years of follow-up; 4.3% of the subjects had an infection that led to explantation of the neurostimulator leads and neurostimulator, and 2.3% of the subjects had an infection that did not require explantation. All of the infections were localized. There were no cases of sepsis and no neurological consequences.

The total subject and event rates of serious adverse events due to implant site infections are comparable to the expected rates of infection seen with acute implantation of intracranial electrodes and epilepsy surgery. And they are not higher than the rates for the first year after an implant of a DBS system for Parkinson's disease.

The RNS System studies used a very conservative definition of what constituted an adverse event related to a change in seizures. Overall, 16% of subjects had a serious adverse event related to a change in seizures across the 903 years of the studies. These were considered serious because the subject was hospitalized for observation or for treatment with IV

antiepileptic medications, or both. About 11% reported a serious adverse event because seizures were more frequent. About 7% reported more adverse events because the seizures were more prolonged. 1.2% reported that they had a new kind of seizure, but none of these were a more severe type of seizure. No subject withdrew from the study because of a change in seizures.

This experience is consistent with changes in seizures reported in recent randomized controlled trials of antiepileptic medications, which indicate that about 10% to 20% of persons on the active treatment have an increase in seizure frequency.

Status epilepticus is a seizure that lasts 30 minutes or more; 3.1% of subjects reported a serious adverse event related to status epilepticus across all of the studies. There were 16 events in total, and 9 of these were in a single subject. Ten of the 16 were nonconvulsive; the remainder were convulsive or, if not known, were classified as convulsive. None of these occurred as stimulation was first enabled.

According to the literature, the rate of status epilepticus with the RNS System is not higher than that expected for persons with intractable partial onset seizures.

There were no differences between the treatment and sham groups during the blinded periods in the overall rate of any specific type of psychiatric adverse event. Over all the studies, 13 of the 256 subjects had

serious adverse events related to depression or suicidality. One subject was hospitalized because of depression, and two subjects committed suicide. Four subjects made suicide attempts, and six subjects had depression with suicidality that required hospitalization. Twelve of these 13 subjects had a history of suicidality.

As you heard earlier, affective disorders are common in persons with epilepsy. These rates of depression and suicidality over the 903 implant years are consistent with what would be expected, given the high prevalence of depression and suicidality in patients with medically intractable partial epilepsy.

All deaths were immediately reviewed by two independent committees, the data monitoring committee and the SUDEP committee, who were charged with determining whether the death was related to SUDEP or if it was related to a cause other than SUDEP.

There were 11 deaths in 256 subjects over 1100 years of follow-up. You will note that these data have a different date from the other safety cutoff data because they have been updated to include the most recent death. Seven were adjudicated to be possibly, probably, or definitely SUDEP. Two of these subjects were not receiving stimulation. Two subjects committed suicide. One was no longer being treated with the RNS System. One subject died of status epilepticus. He had subtherapeutic levels of antiepileptic medications. Another patient died of lymphoma.

A pre-specified objective of the RNS System studies was to demonstrate that the rate for SUDEP in subjects receiving responsive stimulation is not higher than similar patients. FDA suggested that the comparator rate be 9.3 SUDEP events per 1,000 patient-years, based on the rate for patients with partial onset seizures followed in an epilepsy surgery program.

All deaths as of 10/24/2012 are included here. The SUDEP rate for subjects receiving responsive stimulation is 4.5 per 1,000 stimulation years, given the 1,103 years of stimulation experience. This was the pre-specified analysis. The rate for all implanted subjects is 5.9 per 1,000 patient-years. There is no suggestion that the SUDEP rate is elevated in patients treated with the RNS System.

To conclude, the risks of treatment with the RNS System are identifiable, definable, and reasonable over 256 patients, 903 patient implant years, and 819 patient stimulation years in the combined studies.

Adverse events were consistent with the risks inherent with medically intractable epilepsy and its treatments, including antiepileptic medications and surgery.

These patients have endured decades of uncontrolled seizures and are willing to tolerate risk to achieve a possible improvement in seizure control. As you've heard, these patients were being treated with multiple antiepileptic medications. Sixty percent had intracranial electrodes to

determine whether they were candidates for epilepsy surgery, and one-third had undergone an epilepsy surgery that resected some part of their brain. The others were not considered to be candidates for an epilepsy surgery.

The types of adverse events that arose during the studies were managed using standard medical and surgical interventions that are certainly within the experience and skills of neurologists and neurosurgeons.

I'd like now to turn the lectern back over to Dr. Morrell.

DR. YANG: I'd like to remind the Sponsor that there's 12 minutes left.

DR. MORRELL: Yes. Thank you, Dr. Gross.

The RNS System will initially be available only to neurologists and neurosurgeons associated with Level 4 comprehensive epilepsy centers. These centers serve as referral facilities for intractable epilepsy patients, providing neurodiagnostic monitoring, medical and neuropsychological treatment and procedures, including intracranial electrodes and a broad range of surgeries. The neurologists and neurosurgeons at these centers already have the knowledge, experience, and skill to use the RNS System.

NeuroPace will provide extensive training prior to use of the RNS System and will provide ongoing physician support. Training will be required for all healthcare personnel using the device. Neurosurgeons have the opportunity for interaction with a neurosurgeon experienced in implantation of the neurostimulator and leads. Ongoing in-person support is

provided by NeuroPace field clinical engineers, whether at surgeries or at programming visits.

NeuroPace will continue the long-term treatment study. With the additional seven years of follow-up in the long-term treatment trial, there will be nine years of prospective safety and effectiveness data. In addition, NeuroPace will conduct a post-approval study that will be designed in collaboration with FDA.

NeuroPace is committed to monitoring patient safety, not only through existing systems such as FDA's MAUDE database, but also through ongoing follow-up by field and in-house personnel. NeuroPace is also committed to continuing to learn how best to apply this technology and will maintain its active preclinical and clinical research programs.

I'll now turn the lectern back over to Dr. Greg Bergey, who will address the clinical significance of the RNS System as an adjunctive treatment of medically intractable partial onset epilepsy.

DR. BERGEY: Thank you, Dr. Morrell.

According to the Institute of Medicine's 2012 report that I mentioned before, this very important report published in 2012, patients living with medically intractable partial onset seizures have to deal with the profound impact of these uncontrolled seizures on their life and health. Many patients do not achieve acceptable seizure control despite trials of multiple antiepileptic medications, and many may not respond to or be

candidates for the VNS or epilepsy surgery.

The IOM concluded that new treatment options are needed for those whose epilepsy does not respond to available treatment or who have unacceptable treatment side effects. The RNS System is that new treatment option for many of these patients.

When patients come to our epilepsy centers, what options can we offer them? One option is another antiepileptic medication. All of the RNS participants had previously failed multiple antiepileptic medications. And as I've mentioned before, additional trials of AEDs have a less than 5% chance of producing seizure freedom. Also, adding on additional antiepileptic drugs places the patient at greater risk for side effects involving cognition, coordination, and mood. Many patients don't want to try any more antiepileptic medications.

I might add that the seizure reductions with the RNS System are comparable to the drugs that have been already approved as adjunctive treatment of partial onset seizures and that the RNS System does not have the typical side effects that trouble patients taking some antiepileptic medications.

The second option is epilepsy surgery. Two-thirds of the patients in the RNS System had undergone intracranial monitoring evaluations for resective surgery, and one-third had failed to have their seizures controlled by resective surgery. The patients in the RNS trials were

not considered to be surgical candidates.

What about the VNS? One-third of these patients had already tried the VNS, and it didn't work. The VNS has side effects that are related to stimulus of the vagus nerve, and the median percent reduction in seizures in randomized controlled trials was between 24% and 25%, which is less than that seen with the RNS System.

Option Number 4 is to do nothing, but this is not an acceptable option. Our patient doing nothing continues the risks of ongoing seizures, deterioration in cognitive function and mood, quality of life, and overall health, and increased mortality. Reduction in seizures, even without total control, can mitigate these risks. These patients have no reasonable expectation otherwise that their seizure frequency or their quality of life will spontaneously improve.

We've seen that medically intractable epilepsy is a disabling neurologic condition with a clear and unmet clinical need in many of our patients. The RNS System is a first-of-a-kind technology that is safe and effective in patients with this treatment-resistant partial onset epilepsy.

In a well-controlled, randomized, controlled clinical trial, seizure frequency was reduced by 38% short term and over 58% longer term. In addition, there were progressive improvements in quality of life and no adverse effects on cognition or mood.

The benefit has been demonstrated, and the safety is

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acceptable. In these patients without other reasonable treatment options, the benefits clearly outweigh the risks.

The approval of this device will expand the treatment options for a patient population in need and allow the additional clinical experience that will continue to improve the application of this technology.

I certainly appreciate that the FDA's role is to look at data in different ways and in the most critical light. But at the end of the day, the clinical data do demonstrate that the RNS System has met the FDA's evidentiary standard for approval.

Most importantly, NeuroPace has provided valid scientific data that demonstrate that the probable benefits to health from the use of this RNS System outweigh any probable risks, and the evidence demonstrate that a significant portion of the target population achieved clinically meaningful results.

There's compelling evidence from these studies to allow us to talk to our patients and, together with our patients, weigh the risks and potential benefits of the RNS System so that they can make an informed choice.

I want to thank you all for your thoughtful review and your attention this morning.

DR. MORRELL: We would be delighted to answer any questions.

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DR. YANG: So first I'd like to thank the Sponsor's representatives for their presentation.

Does anyone on the Panel have a brief clarifying question for the Sponsor? Please remember that the Panel may also ask the Sponsor questions during the Panel deliberations in the afternoon.

Sure, Dr. Afifi.

DR. AFIFI: Yes, I actually have two brief questions. The first one is what was the statistical software that you used for the analysis?

DR. MORRELL: SAS.

DR. AFIFI: Okay. The second has to do with the post hoc analysis that was done. It's understandable that when the study was being planned, that GEE was appropriate. But there's a large segment of statisticians that believe that a mixed effects model that includes a random effect for the individual patient could be better than the GEE analysis.

Did you ever consider such a model?

DR. MORRELL: I am definitely out of my area of expertise now and I'm going to turn around and see if, Tammy, do you feel -- oh, Patrick, are you prepared to -- okay, I'm going to ask Dr. Heagerty to address that. I'm just proud of myself for understanding GEE.

(Laughter.)

DR. HEAGERTY: Good morning. She's learned a lot of statistics.

My name's Patrick Heagerty. I'm Professor and Associate Chair

of Biostatistics at the University of Washington in Seattle.

So the question was basically why GEE and why not a mixed model approach for these data. And I think that the primary answer that I would offer is, with long series such as these, specifying a mixed model that captures both patient heterogeneity and serial correlation would be very challenging, just computationally challenging at a minimum.

And GEE then, as an alternative, provides again a model-based and an empirical standard error. So it provides inference that does rely on the model, and inference that can relax reliance on the model.

So I would say those are the two reasons to think about GEE as a primary choice.

DR. AFIFI: But there is now a number of quite powerful software programs that can handle that.

DR. HEAGERTY: Sure.

DR. AFIFI: So why not give it a try?

DR. HEAGERTY: Sure, I think it's a fair point; you could give it a try.

DR. YANG: Thank you.

Dr. Cavazos.

DR. CAVAZOS: The primary outcomes were reported seizure diaries.

DR. MORRELL: That's correct.

DR. CAVAZOS: Okay. However, you were obtaining data from EEG that show electrographic seizures. Was any analysis performed using electrographic seizures as a secondary endpoint?

DR. MORRELL: The RNS System records the electrocorticographic data and the numbers of detections that are made, but it does not record clinical seizures. So there's no way, from the electrographic data, of knowing whether a clinical seizure has occurred.

As far as electrographic seizures -- and we know that there's a range of what would be considered an electrocorticographic seizure or not -- we did not consider those as an outcome.

I'll also say that what the physician-investigators did was to identify, initially, what the typical patterns were that preceded that patient's electrocorticographic signature and electrographic seizures. And as you know, this is typically fairly consistent in individual patients. And so the stimulation was delivered very early into the discharge.

I'll just show this slide from your Panel materials. There's no way, when delivering a stimulation, to know whether that discharge would've evolved into a seizure or not.

DR. CAVAZOS: That is correct. But the issue here is you had a baseline period. And so in the baseline period, you could learn particular patterns in regards to correlations between seizures or validations of the seizure diaries with those events.

DR. MORRELL: Well, because, of course, the neurostimulator wasn't implanted until the time of implant, we have no electrographic data for the pre-implant period.

DR. CAVAZOS: Correct.

DR. MORRELL: The only data that we would have during that would be the first month --

DR. CAVAZOS: Correct.

DR. MORRELL: -- after implant, before people were randomized. And I think it might be fair to argue that the data during that first month could be atypical because of the implant procedure. But the short answer to your question is we did not.

DR. CAVAZOS: The other group is the sham group during the blinded period. You could also have validated that data in regards to validating the seizure diaries.

The other side of the question is you had 60% or 65% in the treatment arm of individuals who had been monitored with intracranial electrodes. Therefore, leads or stimulating leads were placed in locations that were clearly involved with seizure onset.

What about the other 35%? How did you determine where to put these electrodes if you had not done monitoring with intracranial electrodes?

DR. MORRELL: Well, we had the benefit of, on purpose,

working with highly experienced epileptologists and functional neurosurgeons in epilepsy centers, and we asked each site to localize these patients based on their standard procedure, which is typically fairly consistent but may vary depending on the experience at the individual site and their access to technology.

The majority of patients, I would say, who did not have intracranial electrodes were those with mesial temporal onsets, and most of those, of course, were bilateral mesial temporal. And those patients typically can be reliably localized without intracranial monitoring.

DR. CAVAZOS: And the last observation is that NAEC Level 4 is a self-designated designation. So you know, there might be a flurry of individuals self-designating as experts.

DR. YANG: We'll take a question from Dr. Nikhar and then Drs. Engel, Balish, and Petrucci.

DR. NIKHAR: Nirjal Nikhar.

These are two database questions. One is, in those patients who had committed suicide or attempted suicide, in the safety, do we know how many of them had attempted suicide pre-implant? The prevalence of depression was high. That's given. But how many of these patients who committed or attempted suicide had actually attempted these pre-implant?

DR. MORRELL: Well, I can provide you that information. I'll also ask Dr. Kantor to come forward if you have any additional questions

about this.

There were, as we mentioned, 12 subjects who had suicidality; 11 out of 12 had a history of depression or suicidality, and 5 of the 12 endorsed passive suicidality at the time they enrolled. This was determined on the Beck Depression Inventory. There's a question that endorses that. None of them had active suicidality.

As far as the history of suicidality, about 5% of the total patient population had that. One of the patients who committed suicide did have a history of prior suicide attempts.

DR. NIKHAR: I have separate question, actually, on data. In the data that you presented, there were 27% and 14.5% that you mentioned who'd actually gained three months and six months seizure free in the two-year data that you had.

You may not have this data, but do you know if there was any patient who had sustained a seizure-free period like this before the implant?

DR. MORRELL: Yes, I can show you that data. While they're retrieving that slide, I would say that we are not going to make a claim that we had achieved seizure freedom. We will confidently state that we reduced seizures. But I will show you this.

There were 37 subjects who had, all together, 55 periods of seizure freedom lasting more than six months. And you'll see that many of those -- the majority of those, it was a six-month period or less than one year.

But there are some patients who have had extended periods of seizure freedom.

Of course, we are continuing to get this information through the long-term treatment trial. We don't have many patients who are in this dataset who have been out four years. But this will obviously be an important piece of information that -- or a dataset that will continue to be contributed to through the long-term treatment trial.

DR. NIKHAR: But do you have the data for pre-implant? I mean, do you know that?

DR. MORRELL: They would not have been eligible to be enrolled if they didn't have the requisite seizures. But perhaps what you're asking me is, in their lifetime, had they experienced --

DR. NIKHAR: Well, no. Actually the question was the criteria of three months at baseline, that they had to have three seizures or thereabouts. I was talking of, historically, two years pre-randomization or pre even the baseline period.

DR. MORRELL: Yeah.

DR. NIKHAR: Do you have that data?

DR. MORRELL: In order to enroll into the baseline screening period, they had to have had three or more seizures during those three preceding months. We did not try to go back further in time.

DR. NIKHAR: Thank you.

DR. YANG: Thank you.

Dr. Engel.

DR. ENGEL: Yeah, I'd like to follow up on that question and then ask you another one.

For patients that had prolonged periods of seizure freedom, were there any characteristics that identified them? You looked at all the different characteristics for other parameters. Did you look at it for prolonged seizure freedom?

DR. MORRELL: Yeah. It is not a large group. We have looked at the demographic characteristics and the randomization characteristics, and we do not see anything that stands out as distinguishing.

DR. ENGEL: And I recall that you had mentioned previously that in the open-label period, the actual stimulations become less frequent over time, suggesting that this process may actually change the epileptogenic mechanism somehow, not just be doing the same thing continuously. Is that still true?

DR. MORRELL: During this presentation, we didn't provide any information about numbers of stimulations, and I don't think this is not something that FDA has said, so I think probably best not to discuss that.

I think I can simply say that there were iterative programmings, and that may be one of the reasons why the patients continued to get better over time. We also believe there's a possibility that the fundamental effects

of stimulation on the brain may have an effect over time. And I think that would be supported by the experience with the vagus nerve stimulator, which clearly shows improvement over a much longer period of time than what we're used to seeing with antiepileptic medications.

DR. YANG: Thank you.

Dr. Balish, followed by Dr. Petrucci and then Rogawski.

DR. BALISH: Actually one of my comments or questions was very similarly related and follows up on Dr. Cavazos, in that if the stimulations had increased over time, it might be that you see less seizures because the stimulation is effective, but still there's a change in the epileptogenesis. So there's a process going on that's important and might be a safety issue. So that was one comment.

The other question is there's a huge variety of parameters, and this is a complex feedback system. What are the controls on preventing that feedback from getting out of control?

DR. MORRELL: Well, as far as safety measures -- and you'll let me know if I'm answering your question -- there's a feature in it called prescribed therapy limit, so that the physician programs the device with what the maximum number of stimulations delivered per day can be. And that's the physician's discretion, and when it reaches that point, it will not deliver any more stimulation in that 24-hour period. The other safety measure is a limitation on charge density.

So typically, the way this is programmed is there are initial settings. And then the variable that is typically changed is the amplitude or the stimulation current, usually in .5 mA increments, similar to what is done with VNS.

The neurostimulator does not allow the charge density, which is a function of the current and the pulse width, to exceed $25 \mu\text{C}/\text{cm}^2$, which is well within the range that is considered to be safe. So there is that intrinsic safeguard.

DR. BALISH: That's a charge issue, but not -- temporally, you could have accumulation or you could have stimulation actually triggering seizures. There's an issue if you ran into a process that included feedback. So that's a different question.

But you do have this maximum number of stimulations that could be set. But what are the right guidelines for that?

DR. MORRELL: You know, certainly there is a learning process when you're dealing with a first-of-a-kind technology. I will say that the total amount of stimulation that is being delivered for patients is typically less than five minutes, and there are many patients who are receiving two or three minutes, in aggregate, over the day. So this is obviously far less than what is provided in deep brain stimulation for Parkinson's disease, which is a different disease. But the total daily delivery of stimulation is relatively small.

DR. YANG: Dr. Petrucci.

DR. PETRUCCI: An easy question. Absent in your demographics was the education level of the patients and the range.

DR. MORRELL: I'm going to ask Dr. David Loring, who is the neuropsychologist who analyzed our data, to come up and answer that.

DR. LORING: Thank you.

I'm David Loring. I'm a Professor of Neurology and Pediatrics at Emory University, and also director of the neuropsychology program there. I'm a consultant for NeuroPace, and they're reimbursing me for my travel expenses.

With that long introduction, those data have not been presented, and I don't know the answers to them off the top of my head. All the neuropsychology tests scores, however, were appropriately adjusted for age and education when available.

DR. YANG: Sponsor, I'll remind you that you can come back with responses after lunch, during the Panel deliberations.

DR. MORRELL: Yes. So as Dr. Loring said, they were all adjusted for age and educational level. Would you like us to provide you information on the educational level for this cohort of patients?

DR. PETRUCCI: Please.

DR. MORRELL: Okay, we will see if we are able to do that during the break.

DR. YANG: Dr. Rogawski.

DR. ROGAWSKI: Yes. All of the data that we've seen so far has been aggregated, and I'm wondering whether the Sponsor can show us examples of patients who showed what would be considered good responses or excellent responses to the stimulator and maybe those that wouldn't have shown such good responses.

Is there a sense that you can categorize patients into those that do show what you would consider to be good responses, and what fraction of the patients fall into that category?

DR. MORRELL: So I believe you're asking about characteristics or demographics that would distinguish those who have a good response compared to those who do not.

DR. ROGAWSKI: Not so much asking that specific analytical question. But if you look at all of the patients individually rather than aggregating them in those statistical methods you described, does it seem as if there are groups of patients within that that had good responses, that stand above and beyond the large number of patients that were enrolled in the study and received the stimulation during the blind period? And if so, can you show those to us?

DR. MORRELL: Well, we have looked at those who have any increase compared to those who have any decrease, and in those who have a more than 50% increase versus those who have a 50% decrease, and the differences that we see is that subjects who did not do as well were

somewhat more likely to be younger.

But I want to do a caveat there, because the only way that we could group this is above 35 and below 35, and we did not have pediatric patients in this study. We did have patients who were between the ages 18 and 22, but they were relatively small.

I actually will show you a slide that perhaps provides some -- now this is grouped. The issue is there were only 13 patients in the pivotal study, who completed the pivotal study, who had any kind of significant increase. And here are the characteristics. And then the 99 patients who had a 50% or greater decrease are shown to the right. Statistically, there is a difference between the ages at .05. There is not a statistically significant difference in any of these other characteristics.

So the short answer is there is nothing that has come forward to help us understand how to identify those who would be the best responders and those who would be the worst.

DR. ROGAWSKI: Well, I guess what I'm asking is can you show us some longitudinal data during the course of the trial with patients that showed what would be considered -- that you might consider looking back at it as good responses to the treatment?

DR. MORRELL: The type of longitudinal data you're talking about is seizures?

DR. ROGAWSKI: In other words, just kind of plot over time with

each visit, in terms of how many seizure counts did the patients have with respect to baseline.

DR. MORRELL: Right. By each individual subject?

DR. ROGAWSKI: Yeah, just by individual patient, to give us a sense of what you can expect with this device under the best conditions.

DR. MORRELL: We will make every attempt to do that analysis during the break.

DR. YANG: One last question from Dr. Connor.

DR. CONNOR: Yeah. So a quick follow-up to that. Like, for instance, there's this patient that FDA excluded in the one analysis with a huge spike in one spot.

How did that guy do once you turned on the device?

DR. MORRELL: Yeah, that patient is a responder.

DR. CONNOR: Okay. So I mean like, for instance, if you could show us that, how this huge spike thing goes down once it's on, that's compelling. I think that's what Dr. Rogawski is asking for.

DR. CAVAZOS: There was one patient that they showed.

DR. MORRELL: Pardon me?

DR. CAVAZOS: Wasn't there one patient that you showed that you had a case by case?

DR. MORRELL: Perhaps we could bring up the raw data for that one patient.

DR. CAVAZOS: There was one patient that you showed.

DR. CONNOR: So while you're doing that, my question was going to be probably to Professor Heagerty, about if you could explain briefly like what exactly the difference is between the empirical and the model-based standard errors, because we talk about that some and sometimes the empirical goes over 1 and the model-based doesn't. So if you could offer some explanation about that difference, that would be great.

DR. MORRELL: This just answers what was happening with that one patient. This was a sham patient, of course, blind evaluation period and no stimulation.

And now I very happily cede this lectern to Dr. Heagerty.

DR. HEAGERTY: Hi again. Patrick Heagerty, Professor of Biostatistics, University of Washington.

So the question was a brief explanation of the difference between the model-based and the empirical standard errors. And the 30,000-foot view there is the model-based standard errors assume both the variance that you're using and the correlation that you're using to create the estimate are correct and therefore can be used to calculate the variance of that estimate.

The empirical relaxes that assumption in order to calculate the standard error or the variance of the estimate by picking up the absorbed variance in the data and incorporating that into the standard error estimate.

So that's its robustness property. It uses the variance and the correlation to create the estimate, but it relaxes the assumption that those are true when it calculates the standard error.

Thank you.

DR. YANG: Thank you.

Okay, so please remember again that we will have more time for questions from the Panel this afternoon during Panel deliberations. We are now going to take a 10-minute break.

Panel members, please do not discuss the meeting topic during the break amongst yourselves or with any other member of the audience. We will resume at 10:15.

(Off the record.)

(On the record.)

DR. YANG: It is now 10:15, and I would like to call this meeting back to order. We'll take a second and let everybody get seated.

Okay, FDA will now give their presentation on this issue.

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

I would now like to ask the FDA to approach the podium and begin their presentation.

DR. BOWSHER: Thank you. Good morning, Panel members, members of NeuroPace, and audience members. My name is Kristen Bowsher. I'm the engineering reviewer for the NeuroPace RNS System for epilepsy PMA.

The members of the multidisciplinary review team involved in the review of this PMA are shown here.

NeuroPace has submitted a premarket approval application, P100026, to the FDA for the RNS System for epilepsy. NeuroPace conducted a clinical trial under an Investigational Device Exemption, IDE G030126, to assess the safety and effectiveness of the RNS System in reducing seizures in adult patients with partial onset epilepsy.

The PMA describes the safety and effectiveness data collected for the RNS System. FDA has reviewed the PMA and now is seeking the Panel members' expertise and input at an open public meeting of the Neurological Devices Panel.

This slide provides the outline for today's FDA presentation.

Since the Sponsor gave a detailed description in their presentation, I will only give a brief overview of the system.

The RNS System includes both implanted and external components. The implanted system, as shown in this figure, includes the RNS stimulator, intraparenchymal depth leads with electrodes, leads with subdural cortical strip electrodes, and lead extensions.

The primary external components include a clinician program and a patient remote monitor. The detection algorithm is configurable with three detection tools (area, line-length, and bandpass) which can be adjusted by the physician to optimize the detection for each individual patient. Modifying the configuration by adjusting the detection tools impacts the sensitivity and specificity of the algorithm.

Note that the feasibility and pivotal trials were not designed to assess the accuracy, that is, the sensitivity and specificity, of the algorithm for detecting epileptiform activity or seizures, but rather were designed to assess the safety and effectiveness of the RNS System as a whole in decreasing seizures.

Data on the detection algorithm were provided in the form of software verification and also validation data which used data from retrospective patients. Additionally, the algorithm was used in an open-label study of an externalized version of the device. However, again, these studies were not designed to assess the sensitivity and specificity of the algorithm.

The user can program various stimulation output settings, including pulse duration, output current, and pulse repetition rate, to create one or more stimulation paradigms that are applied upon the detection of a clinician-defined electrocorticographic pattern for that patient.

It should also be noted that adequate data with respect to MRI compatibility has not been provided at this time, and thus, MRIs should not

be performed on patients implanted with the device.

Dr. Rodichok will now present a brief overview of the epilepsy study design and safety results.

DR. RODICHOK: Good morning, members of the Panel, NeuroPace team, and audience members. I'm Larry Rodichok. I am a neurologist, a former epileptologist, and one of the medical reviewers for the NeuroPace device.

The Sponsor, Dr. Bergey in particular, has presented an overview of epilepsy that is more than adequate. FDA would therefore like to highlight some specific aspects of partial epilepsy that we believe are relevant to the discussion of the clinical studies of the NeuroPace device. First, we would like to review the important differences in the two major types of partial seizures included in the NeuroPace trials.

Partial seizures most often originate in the mesial temporal cortex. These seizures have somewhat recognizable clinical features and typically occur 5 to 15 times per month when poorly controlled. Other studies such as scalp EEG, intracranial EEG, and when necessary other studies such as imaging studies are often concordant in pointing to a mesial temporal focus.

Partial seizures that do not originate in the mesial temporal cortex usually have less predictable clinical features. Patients with this type of partial seizure can have many seizures per day and are likely to account for

the majority of subjects in the trial with high seizure frequencies.

The distinction between mesial temporal epilepsy and non-mesial temporal epilepsy is important in considering the wide range of seizure frequencies and results seen in the pivotal NeuroPace study.

As already pointed out, the goal of treatment is seizure freedom without significant adverse effects. Failure to achieve complete seizure freedom is not ideal, in that even an occasional seizure will make a patient ineligible for a driver's license, will often lead to loss of their job, and can lead to the psychological and social consequences of not knowing when the next seizure could occur.

With pharmacologic treatment, seizure freedom is achieved in 60% to 70% of partial epilepsy patients. This is most often with one or a combination of two drugs. The standard option for patients with inadequately controlled seizures is yet another trial of anti-seizure medication, usually as an adjunct to existing therapy. It is important to balance the risks and potential benefits of such trials when considering alternatives to pharmacologic treatment.

In trials of four recently approved drugs for partial epilepsy, the addition of the new drug to one to three concomitant anti-epilepsy drugs resulted in a 15% to 24% median seizure reduction compared to placebo. The 50% responder rate, meaning the proportion of patients with a 50% or greater reduction in seizures, is commonly used as a measure of a reduction

in seizures that would be clinically relevant and meaningful to patients.

In these four studies, the 50% responder rate ranged from 35% to 47% of the treated group compared to 18% to 26% in the placebo group, for a difference of 12% to 25%. Only 1.5% to 3.6% of patients achieved seizure freedom compared to placebo in these four trials.

As Dr. Bergey has already pointed out, vagus nerve stimulation results in a 13% to 17% difference in the mean reduction in seizure frequency compared to ineffective stimulation.

Failure to inadequately control seizures is associated with some serious consequences. Mortality and injuries are two of these consequences that are worth highlighting.

First, patients with poorly controlled epilepsy have an overall increased mortality compared to otherwise healthy subjects. Most of the increased risk is accounted for by what has been termed Sudden Unexpected Death in Epilepsy patients, or SUDEP.

It is important to note that effective treatment of the epilepsy, either through successful pharmacologic treatment or successful epilepsy surgery, has been reported to be associated with a reduction in the SUDEP rate.

Injuries, usually seizure related, are common, although in prospective studies of poorly controlled epilepsy patients, serious injuries are not common. In one such study of over 25,000 seizures in 298 epilepsy

patients in a special epilepsy hospital, 2.7% of seizures resulted in a head injury, and approximately 1 seizure in 15,000 resulted in a subdural or epidural hemorrhage. Other injuries, not all seizure related, also occur with increased frequency in poorly controlled epilepsy patients.

Regarding SUDEP specifically, there are generally accepted criteria used to identify SUDEP. And as pointed out, a committee of experts adjudicated all of the deaths in the NeuroPace trial so that SUDEP could be properly identified. The lowest rates of SUDEP are seen in studies of well-controlled epilepsy patients. Unfortunately, that rate is not zero but rather around 1 to 3 per 1,000 patient-years. The highest rates are seen in poorly controlled seizure patients, where it may be as high as 6 to 9 per 1,000 patient-years for the medically refractory patients such as those who are considered candidates for resective surgery. When a treatment is effective, a reduction in the SUDEP rate has been reported.

We will now present a brief overview of the clinical trials of the NeuroPace device.

The clinical studies of the NeuroPace device include a feasibility study, as Dr. Morrell pointed out, and a subsequent pivotal trial. The primary purposes of the feasibility study were to assess safety and to evaluate effectiveness to determine the futility of proceeding to a pivotal trial.

The pivotal trial blinded phase ended at 20 weeks after implantation and was followed by an open-label phase which continued to

104 weeks after implantation.

The long-term treatment study includes subjects from both the feasibility and the pivotal trials who were eligible and chose to participate in continued follow-up for an additional seven years after implantation.

The inclusion and exclusion criteria for the feasibility trial were comparable to those in the pivotal trial, which have already been reviewed in detail by Dr. Morrell.

The feasibility design provided that the first four subjects at any site be entered into an open-label protocol, all of whom received responsive stimulation, and that subsequent subjects enter a double-blinded protocol and be randomized in a 1:1 fashion to the active treatment group or to a sham stimulation group. In that study, stimulation was initiated within 28 days after implantation. Evaluation for effectiveness was for the last 84 days, or days 28 to 111 post-implantation.

The primary endpoint as noted was safety, that is, the incidence of serious adverse events compared to that of implantation of an electrode for deep brain stimulation.

To assess for futility, a 50% responder rate of more than 13% over the last 84 days was considered adequate to justify proceeding to a pivotal trial.

The safety results of the feasibility trial are shown here. The responder rate was highest, at 36%, for those randomized to sham

stimulation. It was 24% for those with active stimulation in the open or in the randomized active groups, and 27% for those in the open group. The trial met the pre-specified futility assessment to proceed to a pivotal trial.

The pivotal trial was a randomized, double-blind trial. As Dr. Morrell pointed out, the assessment clinician and subject were blinded. The treatment clinician was not blinded. The sham group received the implant, but no stimulation. There are some design changes noted on this slide that Dr. Morrell has reviewed that came from lessons learned in the feasibility trial.

The sample size for the trial was based on the 50% responder rate. Assuming the rate of 40% in the treated group, 20% in the sham group, or an effect size of 20%, it was estimated a minimum of 180 subjects completing the blinded evaluation period would be needed for 80% power to detect the estimated treatment effect. Trial endpoints and analysis methods will be discussed in the effectiveness and safety presentations.

The key inclusion criteria have been reviewed by Dr. Morrell. We believe it is important to note that although patients were required to have undergone a previous diagnostic localization of no more than two epileptogenic foci as part of standard care, no specific types of testing or concordance of localization testing results were required for entry into the trial.

The key exclusion criteria were not unusual for this type of

trial, as shown here, and have been reviewed by Dr. Morrell. Please note that since subjects with the implant may not have an MRI scan, those expected to require an MRI scan of the head during the trial were excluded.

As a reminder, this is the pertinent study periods, as shown in this diagram.

Subjects were implanted with either subdural strip electrodes or intraparenchymal depth leads that would serve both to detect electrocorticographic, or what we call ECOG, activity and also to deliver stimulation. Up to four leads were permitted, only two of which could be depth leads. Only two of the leads were connected at any given time. There were no protocol-defined criteria for the choice of electrode placement location or for the accuracy of the placement.

The detection parameters could be modified based on the review of stored ECOG data at all visits following implantation. Storage of ECOG could be programmed to be triggered by the detection of a specific event, by a delivery of the responsive stimulation, by the time of day, or by a magnet swipe. The physician was able to view these ECOG recordings and could assess the correlation of detections with reported clinical seizures and the effects of stimulation on the ECOG.

From the start of the stimulation optimization period, the stimulation parameters could be modified by the unblinded treatment protocol clinician based on the review of the stored ECOG activity. There was

not a protocol-defined method for modification of the recommended initial stimulation parameters.

The sensitivity and specificity of the detection and stimulation systems during the trial have not been reported.

The relationship of selected detection parameters to any change in seizure frequency have not been reported.

240 subjects were enrolled in the pivotal trial, and 191 were implanted, all of whom were subsequently randomized. Dr. Morrell has well reviewed the disposition of the enrolled and implanted subjects.

The treatment groups, as she pointed out, were well balanced for age, gender, epilepsy duration, and the number of concomitant anti-epilepsy drugs, or AEDs, being taken at baseline.

Baseline seizure frequency per month is seen in this table. Drs. Costello and Miller will comment further on the difference between mean and median rates and the range of rates in their presentations. The groups were not significantly different in the mean daily or monthly rates at baseline.

The two treatment arms were balanced for characteristics listed in this table, which are of interest because of their potential influence on outcome. These include mesial temporal focus versus all others; prior therapeutic surgery versus no prior therapeutic surgery; prior therapy with the vagal nerve stimulator, or VNS; the presence of a structural abnormality

on imaging; and the acute use of benzodiazepines for seizure control during the baseline period.

There were more sham subjects with two foci and more treatment subjects with prior intracranial monitoring, although these two differences did not reach statistical significance.

Also note that the first three characteristics in the table were used as strata in the adaptive randomization method used.

There were a number of important characteristics that were related to seizure frequency at baseline. The large difference in seizure frequency by mesial versus non-mesial temporal origin is not unexpected. The two groups were well balanced for this characteristic.

Subjects with unifocal seizures had a much higher seizure frequency than those with bifocal ones had. Subjects with prior surgery had twice as many seizures at baseline as those with no prior surgery. There was no major difference in the two groups for these characteristics.

All subjects had more than one lead implanted, slightly over half had two leads, and about 30% had four. About equal numbers of subjects had subdural strip leads only, depth leads only, or a combination of the two. The two treatment groups were well balanced for the number and types of leads implanted.

I will now give an overview of the safety results.

As already noted, the primary safety endpoint was the

proportion of subjects who experienced a serious adverse event, as defined in the protocol, during the 28 days following implantation, termed the acute post-implantation phase, and the proportion during the 12 weeks following implantation, termed the short-term chronic post-implantation phase.

In order to demonstrate that the acute post-implantation safety of the procedure was not worse than that for implantation of intracranial electrodes, the upper limit of the one-sided 95% confidence bound was not to exceed 20% for the acute phase.

In order to demonstrate that the short-term chronic safety was not worse than that following implantation of electrodes for deep brain stimulation for movement disorders, the upper limit was not to exceed 42% for the short-term chronic phase.

The study met both of these endpoints.

The incidence of serious adverse events in the first four weeks after surgery was 12% with an upper 95% confidence bound of 16.5% in the pivotal trial and 10.5% with an upper bound of 14.9% in the pooled safety population, both below the target upper limit of 20%.

The incidence of serious adverse events in the first 12 weeks after surgery was 18.3% with an upper 95% confidence bound of 23.4% in the pivotal trial and 16.0% with an upper bound of 21% in the pooled safety population, again, both below the target limit of 42%.

For the full 20 weeks of the blinded assessment, 16.5% of

subjects in the treatment arm and 23.4% of those in the sham arm had serious adverse events. Most subjects in both arms experienced non-serious events.

During the post-implantation stabilization period, neither group received stimulation. During this time there were 27 serious adverse events in 23 subjects. The most notable SAEs are the following. There were seven SAEs that were related to the implant site, and as pointed out, five of these were implant site infections, one was a subgaleal effusion, and there was one implant site discharge treated with incision and drainage and antibiotics.

Four serious intracranial hemorrhages occurred during this period: two extradural, one subdural, and one intraparenchymal. There were also two hemorrhages considered by the investigator to be non-serious, or termed mild in the study, during this period. Hemorrhages will be presented as a group in a later slide.

Bacterial meningitis was detected in one subject at the time of implantation, and there was good reason to believe that this probably preceded the procedure.

As seen in this table, following the randomization to the treatment or sham group, there was no difference in the incidence of SAEs between the two groups, suggesting that stimulation itself was not associated with any apparent short-term increase in serious adverse events.

During the four-week stimulation optimization period, 10 SAEs

occurred in six treatment subjects, including one subdural hematoma. In the sham group there were seven SAEs in six subjects. There was one death due to SUDEP in the sham group during this four-week period.

During the subsequent 12-week blinded evaluation period, four subjects in the treatment group had one SAE each. In the sham group, five subjects had seven SAEs. The types of SAEs during this period was unremarkable, and there were no deaths during that period.

As already presented, there were a total of 11 deaths in the combined NeuroPace studies, so this is the most up-to-date dataset. There were nine deaths as of June the 4th, 2010, six due to SUDEP, two due to suicide, and one due to lymphoma. Since that time NeuroPace has reported two further deaths that have been adjudicated, one due to SUDEP and one due to status epilepticus. Stimulation was enabled in six of the seven subjects who died of SUDEP, in one of the two who died of suicide, and in one subject who died in status epilepticus.

The SUDEP rate, both at the June the 4th, 2010 cutoff and at the update as of December 17th, 2012, are not worse than most rates reported in comparable populations of adults with intractable partial epilepsy, and that is, they are in the range of 6 to 9 per 1,000 patient-years. It is higher than in some reports, however, of medically intractable patients, such as a study by Leetsma from a lamotrigine AED development program.

The pooled safety population, as pointed out, does provide a

larger sample for safety, both short and long term. It includes both the feasibility and pivotal trial populations. Data are included for up to the time of subject discontinuation or completion of the study.

At the time of this dataset, 59 of 65 implanted subjects from the feasibility study had completed the trial to 52 weeks. Six had discontinued. As of the submission cutoff date of June the 4th, 2010, 98 of 191 pivotal subjects had completed the trial, 15 had discontinued prior to completion, and 78 were being followed but had not completed the pivotal trial. Thus, the pooled safety population includes 256 subjects, over 708 implant years, and 632 stimulation years.

The most complete safety dataset is that for the first year after implantation. During that time, 34% of subjects had 161 SAEs. The specific SAEs occurring in 2% or more of subjects are listed on the slide. Overall, the two most common SAEs are those related to increases or exacerbation of the individual seizure types. SAEs due to implantation site infection and device lead damage are the most prominent serious adverse events related to the investigational device and/or the procedure.

As noted, intracranial hemorrhage was identified as an event of special interest. Thirteen intracranial hemorrhages occurred over all trials and all periods. Eleven were considered serious. Six of these hemorrhages, four of them considered serious, occurred in the 28-day acute postoperative period. Two were considered by the investigator to be mild or non-serious

because no intervention was required. One of these was an extradural hematoma associated with aphasia and headache, and the other an occipital intracerebral hemorrhage associated with a visual field defect. One subdural hematoma in the stimulus optimization period was considered due to a seizure.

Of the remaining six hemorrhages, they were not considered seizure related, and all were in the third postoperative year. One resulted in explantation. Three hemorrhages were considered secondary to a seizure. Two were subdural hematomas and one intraparenchymal. One resulted in withdrawal from the study.

Infections related to the procedure and/or the device were also of special interest: 26 infections related to the implant or incision site occurred in 22 subjects; 17 of the 26 events were considered serious; 9 of the device explantations and 2 device replacements were due to infections or skin erosions.

Other SAEs of interest are listed on this table. SAEs related to a change in seizures occurred in 14.8% of subjects, seizure-related injuries in 8.2%, psychiatric SAEs in 7.4%, and status epilepticus in 3.5%; 38 subjects had 64 SAEs related to change in seizures.

Adverse events related to changes in seizures were usually considered serious, simply because hospitalization was required for medication change or further video EEG monitoring. The change was typically

a change in existing complex partial seizures, which occurred in 6.3% of the subjects, or an existing generalized tonic-clonic seizure, which occurred in 5.9% of the subjects.

Seizure-related injuries seemed common. 46.1% of subjects had 343 adverse events, and 8.2% of subjects had 28 serious adverse events, all reported as a seizure-related injury.

The incidence of non-serious and serious contusions, skin lacerations, and head injuries are shown on the slide. These were the three most common injuries. These included four intracranial hemorrhages, as described earlier. Seventeen subjects sustained skeletal bone fractures due to a seizure; six were considered serious.

Of the 28 psychiatric SAEs that occurred in 17 subjects, 10 subjects had 15 SAEs related to suicidality. There were two subjects with completed suicide, as already presented. There were four episodes of acute psychosis occurring in two subjects. Most other serious psychiatric adverse events occurred in only one or two subjects.

Eighteen adverse events of status epilepticus occurred in 3.9% of the subjects. Seventeen events in nine subjects, 3.5% of the subjects, were considered serious. One subject accounted for nine of the episodes.

To conclude the safety presentation, the safety results of the pivotal and feasibility trials indicate that the adverse events occurring in the first 4- and 12-week intervals are no worse than those reported for

comparable intracranial implantation procedures.

The blinded phase results support that neurostimulation of the depth or subdural leads does not appear to be associated with an overall short-term increase in serious adverse events.

The long-term safety results suggest no difference in the pattern of adverse events expected in a poorly controlled partial epilepsy population.

We do believe that the incidence of injuries, especially intracranial hemorrhages due to seizures, would merit continued surveillance.

Dr. Costello will now present the effectiveness results.

DR. COSTELLO: Good morning. My name is Ann Costello, and I will be presenting the effectiveness data, based on the 191 subjects implanted in the pivotal study.

The pre-specified primary effectiveness endpoint was to demonstrate superiority of the treatment group over the sham group in reducing the frequency of total disabling seizures, including simple partial motor, complex partial, and generalized tonic-clonic seizures, during the blinded evaluation period of the investigation; the pre-specified analysis method modeled seizure count data using generalized estimating equations, GEE. Seizure data was collected using patient diaries.

One month following implant, subjects were randomized 1:1 to treatment or sham stimulation. An adaptive randomization approach was

used to balance variables that might influence the clinical response to stimulation. These variables included investigational site, seizure onset zone location, number of seizure foci, and previous resection.

A total of 97 subjects were randomized to the treatment group, and 94 were randomized to the sham group. Over the baseline period, the mean and median seizure frequencies in the treatment group were 33.5 and 8.7, respectively, with a range from 3 to 294.7. The mean and median pre-implant seizure frequencies in the sham group during the pre-implant period were 34.9 and 11.6, respectively, with a range from 3 to 338.

During the blinded phase, the mean reduction in the treatment group was 11.5, and the median reduction was 2.7. The mean reduction of the sham group was 5, and the median was 4.6.

Because of variability in seizure counts between subjects and within subjects, there is a large difference between mean and median seizure rates. This difference was also noted in the feasibility study, and the Sponsor noted at that time that because of high seizure rates in certain subjects, medians were a better representation of the seizure rates.

This table provides the range of seizure counts during the baseline and the blinded evaluation period for subjects in the treatment and sham groups. As can be seen, the range of seizure counts during the blinded evaluation period for the treatment group did not vary widely. In contrast, the maximum seizure frequency during the last month of the blinded

evaluation period for subjects in the sham group increased to 799 seizures.

This slide demonstrates the observed mean seizure counts from baseline through the end of the blinded evaluation period. The red line represents the treatment group, and the blue line represents the sham group. All subjects had reduction in observed mean seizures following implant. The seizure reduction post-implant, but prior to initiation of stimulation, is referred to as the surgical effect. It is unclear whether the surgical effect is due to a placebo response, regression to the mean, or some aspect of the surgical procedure.

It is important to note that initiation of stimulation in the treatment group does not result in a significant reduction in mean seizure count as compared to that resulting from the surgical effect.

The mean seizure count for subjects in the sham group appears to return to baseline. However, as will be discussed by Dr. Miller, this return to baseline is driven by two highly influential subjects. Furthermore, the difference between the treatment and sham groups at month 4-5 is not apparent for median seizure frequency, as seen on the next slide.

This slide summarizes the observed mean and median seizure counts from the baseline period through the end of the blinded evaluation period. The upper graph of observed mean seizure counts was discussed on the previous slide. The lower graph compares the observed median seizure counts from baseline through the end of the blinded evaluation period.

As noted previously, for mean seizure count, there is a reduction in median seizure counts following implant. That is the surgical effect. However, in contrast to the graph of mean seizure frequency, the median seizure frequency does not return to baseline for subjects in the sham group.

The difference in mean and median seizure reduction at month 4-5 may be due to the increased range of seizures, i.e., 0 to 799, seen in the last month of the blinded evaluation period for subjects in the sham group. Dr. Miller will discuss this further.

The pre-specified primary effectiveness endpoint was the generalized estimating equation model using a Poisson distribution. The dependent variable was each subject's daily seizure frequency during the baseline and blinded evaluation periods. The primary and second efficacy analyses used seizure data from the 84 days of the baseline period compared to the 84 days of the blinded evaluation period.

There were two standard error estimation methods for the pre-specified analysis: the empirical and model-based method. The Sponsor did not explicitly state in the protocol which method would be used.

The model-based p-value achieved statistical significance, but the more robust empirical p-value did not achieve statistical significance. Because of the difference in the model-based and empirical-based p-values, NeuroPace contacted FDA to discuss a post hoc analysis to support device

effectiveness.

The Sponsor contacted FDA following unblinding of the data and analysis of the pre-specified primary effectiveness endpoint. The Sponsor stated, and FDA agreed, that the difference in p-values is indicative of a poor fit of the model to the data. The Sponsor and FDA agreed that an alternative analysis was needed and that the PMA could include both the pre-specified and alternative models.

Please note that there has been a clarification to this slide.

NeuroPace's post hoc GEE analysis of the primary effectiveness endpoint used monthly seizure count data, the negative binomial distribution, and included the clinical covariates used in the adaptive randomization.

NeuroPace's post hoc GEE model did achieve statistical significance.

Based on the post hoc GEE analysis, the model predicts a percent change of seizure frequency from baseline in the treatment group of -37.9% versus -17.3% in the sham group, resulting in a difference of -20.6%. However, there are uncertainties regarding this result.

Please note that there have been changes to this slide for clarification purposes.

This slide summarizes uncertainties with NeuroPace's post hoc primary effectiveness analysis. The model-based p-value for the pre-specified effectiveness endpoint did achieve statistical significance, but the more robust empirical p-value did not. Both the model-based and the empirical

p-values for the post hoc analysis achieved statistical significance. Some alternative GEE models do not achieve statistical significance, as will be discussed by Dr. Miller.

None of the pre-specified secondary endpoints achieve statistical significance, including the responder rate, which is used to assess the clinical meaningfulness of an epilepsy treatment.

In addition, mean seizure counts, responder rate, and median seizure counts, which are based on the observed data rather than assumptions as in model data, do not achieve statistical significance.

The pre-specified secondary effectiveness endpoints were intended to support the primary effectiveness endpoint. The pre-specified secondary effectiveness endpoints were the responder rate, defined as a 50% reduction in seizure counts from baseline, change in mean seizure frequency, proportion of seizure-free days, and self-reported seizure severity according to the Liverpool Seizure Severity Scale.

This table provides the results of the secondary effectiveness endpoint analyses. The study was powered based on the expectation of a 20% difference in responder rates between the treatment and sham groups. The treatment difference in responder rate was only 2%, i.e., 29% for the treatment group and 27% for the sham group, which was not statistically significant.

It is important to note that responder rates were also used to

determine futility in the feasibility study, as previously discussed by Dr. Rodichok. Despite the results of the feasibility study, the Sponsor decided not to perform the pre-specified interim analysis.

In addition to the responder rate, the difference in mean seizure frequency, percent days with seizures, and seizure severity between the treatment and sham groups were not statistically significant.

It is important to note that although the difference in seizure severity was not statistically significantly different, the difference did favor the sham group.

NeuroPace has performed monthly analyses of the secondary endpoints. It is important to note that monthly analyses were not pre-specified due to variation in seizure counts.

In addition, FDA has focused on analyses of observed responder rates, since responder rates are easy to interpret and less subject to large variations in seizure counts.

This table provides a post hoc analysis of responder rates during baseline compared to each month of the blinded evaluation period. As previously discussed, the Sponsor expected a 20% difference in responder rates during the blinded phase. However, the difference was only 2%.

During month 2-3, the responder rate was greater in the sham group than in the treatment group. During month 3-4, the difference was greater in the treatment group, that is, 8%, and during month 4-5 the

difference was also greater in the treatment group, that is, 4%, which is less than the previous month.

Thus, as expected, seizure variability, both between subjects and within subjects, from month to month make interpretation of monthly data difficult, and therefore a comparison of the 84 days of the blinded phase to 84 -- I'm sorry -- therefore, a comparison of the 84 days of the pre-implant phase to 84 days of the blinded evaluation period was considered preferable.

This slide contains an analysis of median percent change. Because of the observed variation in seizure counts, FDA requested this analysis of the median percent change in seizure frequency. The median percent change in the treatment group was -28% versus -19% in the sham group, with a difference of only -9%.

This table provides a summary of individual seizure counts during the blinded evaluation period: 24% of treatment subjects had no change or an increase in seizures, compared to 30% in the sham group; 47% of subjects in the treatment group and 43% of subjects in the sham group had a greater than 0 to less than 50% reduction in seizures; 29 of subjects in the treatment group were responders, including 5% who had greater than a 90% reduction in seizures; likewise, 27% of subjects in the sham group were responders, including 4% who had greater than a 90% reduction in seizures.

This slide summarizes the pre-specified additional analyses. These include subset analyses of subjects by the clinical covariates used for

adaptive randomization, and quality of life using the Quality of Life in Epilepsy-89 assessment.

The following three tables provide the responder rates by clinical characteristics used in the adaptive randomization process. It is important to note that the study was not powered to demonstrate differences in any of these subgroups. However, it is important to assess whether the effect of stimulation was similar in each of these subgroups.

For subjects with seizure onset in the mesial temporal lobe, more subjects in the treatment group, as compared to the sham group, were responders. In contrast, the subjects with seizure onset in areas other than the mesial temporal lobe, more subjects in the sham group than the treatment group were responders.

For subjects with one seizure focus or two seizure foci, there were slightly more responders in the treatment group as compared to the sham group. For subjects who had not had a prior resective surgery, more subjects in the treatment group than the sham group were responders. In contrast, for subjects who did have a prior resective surgery, more subjects in the sham group, as compared to the treatment group, were responders.

A significant clinical improvement in the quality assessment is defined as an improvement of five or more points. This slide represents the proportion of subjects who achieved a greater than or equal to a five-point increase in the QOLIE-89 scores. The upper table represents the results at

the end of the blinded evaluation period. Both groups had a similar proportion of subjects who achieved a five-point improvement. The proportion of subjects who had a greater than or equal to a five-point improvement at one year did not increase, as compared to the end of the blinded evaluation period.

This table provides an analysis of responder rates for the various seizure subtypes during the blinded evaluation period. The study was not powered to show a difference on the seizure subtypes. However, it is important to determine whether stimulation has a similar effect on all seizure types.

As seen in the table, the largest difference was in simple partial motor seizures. Furthermore, more subjects with complex partial seizures in the sham group were responders, as compared to the treatment group.

This figure shows the observed mean seizure counts for subjects in the sham group from baseline through month 9. Data is provided through month 9 to allow a comparison of seizure counts during the 84 days of the blinded evaluation period, when sham subjects did not achieve stimulation, to the first 84 days of the open-label period, when subjects in the sham group received stimulation for the first time. As previously discussed, following implant, sham subjects had a reduction in seizures.

In addition, as previously discussed, during the last month of the blinded phase, the mean, but not median, seizure counts appear to return

to baseline. At month 5, when sham subjects have stimulation initiated, there is a reduction in observed mean seizure counts. However, it is important to note that the observed mean seizure count in the sham group, following initiation of stimulation at month 5, is similar to that post-implant, i.e., prior to initiation of stimulation.

This table provides a comparison of seizure counts during months 6 to 9 to seizure counts during the baseline and blinded evaluation period for subjects in the sham group. Compared to the baseline, subjects in the sham group had a reduction of 7.8 seizures during months 6 to 9. The p-value was statistically significant. However, compared to the blinded evaluation period, subjects in the sham group had a reduction of only 2.5 seizures. The p-value was not statistically significant.

This figure represents the observed mean seizure counts with 95% confidence intervals from baseline through 26 months post-implant. The red line represents subjects who had received treatment during the blinded phase, and the blue line represents subjects who received sham stimulation during the blinded evaluation period.

Although all subjects knew at month 5 that they were receiving stimulation, they were not informed as to their treatment allocation during the blinded evaluation period. Therefore, the data for the treatment and sham groups was analyzed separately.

As is seen in this figure, the observed mean seizure count in the

sham group is much less than that in the treatment group through the two-year follow-up period. This is difficult to interpret, since the treatment group only received three additional months of optimal stimulation, as compared to the sham group. In other words, it would be expected that the two groups would eventually overlap.

Considering the difference in the observed mean seizure counts during the open-label period, there is concern regarding the comparability of the two groups. However, interpretation of this open-label data is difficult, since during the open-label phase of the study, subjects knew they were receiving active stimulation, which may cause them to overestimate the benefit. There may also be regression to the mean over time, and subjects were able to change their antiepileptic drugs. In addition, there is missing data, and subjects who were not receiving benefit dropped out of the study.

Subjects were able to change their antiepileptic drugs during the open-label phase. This table summarizes the subjects' use of AEDs during this period. It is important to note that all subjects continue to use AEDs, and only 7.7% of subjects were able to decrease their AEDs. Furthermore, 21.9% of subjects increased their AEDs, and 16.4% had both an increase and decrease in AEDs.

Please note that this slide has also been updated for clarity.

Missing data may also confound interpretation of the open-label data. This slide summarizes the reason for the 43 subjects from the

combined feasibility and pivotal trials who had discontinued RNS therapy. Dr. Rodichok has previously discussed the 17 subjects who discontinued due to infection, hemorrhage, or death. In addition, three subjects were lost to follow-up, and 23 subjects chose to discontinue the study. Fourteen of the elective withdrawals chose to pursue other treatments. Four withdrew because the reduction in seizures was not sufficient, and three withdrew because the subjects did not want to undergo neurostimulator replacement when the battery reached the end of service. The reasons for withdrawal of the two additional subjects are included on this slide.

Dr. Miller will now discuss the statistical issues.

DR. MILLER: Good morning. My name is Scott Miller, and I am the statistical reviewer for this submission. I'll be discussing several statistical issues related to the primary effectiveness analysis, and these issues concern sources of uncertainty in the clinical data which you'll be asked to discuss in Panel Question 2.

This slide presents an overview of the topics I'll be discussing. After a brief synopsis of the trial, I'll walk through what the GEE model is measuring and how the improvement metrics are derived. I'll next discuss three sources of uncertainty regarding the primary effectiveness endpoint: first, the Sponsor's proposed post hoc model is one of several alternative GEE models; second, there's a potential differential response by baseline seizure count; and third, the magnitude of the effect size is sensitive to the impact of

two influential sham subjects.

As previously noted by the Sponsor, as well as by Dr. Rodichok, the clinical trial was a two-arm, randomized, concurrent, sham-controlled, double-blind clinical trial. The primary effectiveness outcome was seizure count over three months of blinded evaluation. The primary effectiveness analysis was a generalized estimating equation (GEE) model for longitudinal count data. Essentially, this approach analyzes the mean response over time on the same subjects.

This table presents the observed mean seizure counts per month over time for each treatment group, and the GEE model is attempting to fit the best line to these means over time, as explained in the following slide.

This figure shows the mean seizure counts per month over time for the treatment and sham groups. The GEE model used by the Sponsor collected 84 days of seizure count data at baseline and a subsequent 84 days during the blinded evaluation period. This model did not incorporate the post-implant recovery data, so for clarity, it's not provided here. And note that while these are presenting the overall means, the model itself actually averages over each subject's profile. So this is just for clarity.

Although 84 days were collected at baseline, the model determines the average seizure count at baseline, as shown. First, the three baseline values are averaged. Then this average is used in lieu of the three

monthly estimates at baseline.

Similarly, although 84 days were collected during the blinded evaluation period, the model determined the average seizure count over the blinded evaluation period as well, although these three particular time points were still used in the model to estimate the mean more precisely.

The GEE models the mean response over time. Starting at baseline, the model then looks at the mean response over the entire blinded evaluation period. This is represented by the time portion of the model. And similarly, the group by time interaction term represents the additional effect of active stimulation beyond the effect of treatment. Or time. Excuse me.

If the interaction term was zero, then there would be no significant impact for active stimulation. If it's positive, then active stimulation would increase seizures relative to sham. And if it were negative, then the active stimulation decreases seizures. In essence, the model was comparing the slope of the line from baseline to the end of the blinded evaluation period between the treatment and sham arms.

As discussed in the FDA Executive Summary and alluded to earlier by Dr. Costello and also touched on by Dr. Morrell, there are two ways to estimate the standard error from a GEE analysis: a model-based and empirical.

The model-based estimate assumes that the variance of the model is correctly specified, while the empirical estimate does not make this

assumption. The empirical estimate is calculated by calibrating the model-based estimate using the variability observed in the data. As a result, the empirical estimate is sometimes called the robust estimate, because it is robust to model mis-specification of the variance, although at the cost of a potential loss of efficiency.

Recall that the p-values for the primary effectiveness endpoint were quite different. Using the pre-specified GEE model, the model-based p-value was less than .0001, compared to empirical p-value of .15. The Sponsor did not explicitly state whether they would use the model-based or empirical approach in the protocol. FDA typically prefers the empirical estimate due to its robustness property.

The GEE models the mean response over time. However, the output can be expressed in several different ways, and this slide will briefly explain how the two most commonly discussed approaches are derived. The first is a percent reduction from baseline. As seen, this is a function of the relative seizure frequency in the blinded evaluation period relative to baseline. The second is the relative rate ratio. This is the ratio of the rates of seizure frequency reduction in the active and sham groups.

So as discussed before, there are three major sources of uncertainty regarding the magnitude and generalizability of the primary effectiveness outcome in the NeuroPace pivotal trial.

First, the pre-specified statistical GEE model was not a good fit,

so the Sponsor proposed a post hoc GEE model. As discussed in the next slide, the statistical significance of the primary effectiveness outcome depends upon the specific model assumptions used.

Second, the post hoc analysis conducted by FDA suggests that the overall treatment effect may not be uniform across all subjects, but may vary by baseline seizure count.

Third, the magnitude of the overall effect size is sensitive to the impact of two influential sham subjects.

This graph you've seen previously. It compares several alternative GEE models with various combinations of model assumptions: the distribution, either the over-dispersed Poisson or negative binomial, whether or not the model is adjusted for the clinical covariates used in the randomization, and the time scale, whether it's analyzed by day or grouped by month.

The over-dispersion scale parameter is also presented on the far right. And just a note for clarity. The version of this plot presented by the Sponsor differs in terms of those numbers. The difference for that number is because the Sponsor's version shows the over-dispersion parameter. This is the over-dispersion scale, which is obtained by taking the square root of the over-dispersion parameter. So there's a difference. That's why there's a difference. It's not a difference in terms of whether the model was similar or different from what we get.

So the point estimate in the circle there denotes the relative weight from each model, and the solid line denotes the model-based 95% confidence interval, while the dashed line denotes the empirical 95% confidence interval.

The pre-specified model is denoted by Number 1. This is the model that the Sponsor and FDA agreed, after seeing the result, was not an optimal fit to the data. The Sponsor's post hoc model is denoted by Number 8. Models 2 through 7 represent additional models fit by FDA to explore the robustness of the results to the assumptions made in Model 8.

This Forest plot shows that the estimated treatment effect is consistent across GEE models, namely, that the point estimate is not particularly changed by going from model to model, although statistical significance is sensitive to the particular model structure.

The GEE model results predict an expected improvement overall, that is, a 37.9% improvement from baseline with active stimulation. This assumes that all subjects would be expected to show approximately this level of improvement with some variability. If this assumption were valid, for example, if the magnitude of the benefit varies by baseline seizure count, then relying on an overall treatment effect estimate may not be appropriate.

As the Sponsor has noted, statistically, this assessment would typically be performed via testing an interaction term. However, it is known that these tests have much lower power than tests for main effects.

Particularly, with small sample sizes and multiple covariates, the model cannot estimate these interaction terms particularly precisely. And, further, if a significant interaction is found, it can come from a number of different response pattern differences. And as a result, if you found a significant interaction, you would still need to graph it in order to visualize what the actual driving factor is.

Therefore, as a post hoc analysis of the response, FDA grouped subjects into four categories by baseline seizure count, corresponding to 0-1 seizure per day at baseline on average, 1-2, 2-3, or greater than 3 per day. The goal of this analysis was descriptive, in terms of assessing the fit of the model, not a formal statistical test, given the limitations described.

This graph shows the overall mean response over time in the treatment and sham stimulation groups. As seen in the sham group, it shows an apparent return to baseline by the end of the blinded evaluation period.

As a post hoc exploratory analysis by FDA, the graph on the right presents this data broken down by seizure frequency at baseline and increments of 28 seizures per month. These will be added sequentially, starting as seen here, with the 0 to 28 seizures per month at baseline group.

Note, while there are some overlaps on the graph on the right, the average response is shown separately for the treatment and sham groups.

This shows the 29 to 56 seizures per month group, similarly the

57 to 84 seizures per month group, and finally, the greater than 84 seizures per month subgroup.

This graph suggests that the return to baseline in the sham group seen in the overall results may not be consistent across all subjects but may be limited to the subgroup with greater than 84 seizures at baseline.

In additional analyses, there is evidence that this response in the greater than 84 subgroup itself may not be uniform, but may be driven by two influential subjects, which will be discussed later on. However, it does bear noting that the sample sizes shown on the far right are somewhat small in all subgroups other than the 0 to 28 seizures per month subgroup.

This Forest plot suggests that the magnitude of the observed treatment effect, based on all subjects, may be driven by the greater than 84 seizures at baseline subgroup -- the line at the top -- as the estimated relative effect in that group is largest compared to the other three.

In statistical terms, an influential subject is one who has a larger impact on the overall results than other subjects. In a statistical analysis, each observation contributes to the overall results. If the results change if a particular model -- excuse me -- a particular subject is excluded, then that subject has a much larger influence than others, and therefore the overall results may not be generalizable or representative to all subjects.

In a GEE analysis, an influential subject might not only be a single point out of range of the others, but also a subject with a different

response over time than other subjects.

In the NeuroPace trial, the observation seen in the previous slides, that the return to baseline in the overall sham group is only apparent in the subgroup with subjects with the highest seizure frequency at baseline, raise the possibility that there are some subjects in this particular subgroup that may be overly influencing the results of the model. And this is a potential concern because the GEE models the main response over time, and the mean is known to be sensitive to large values.

To follow up on that possibility, the subject-level responses over time are plotted separately for the treatment and sham groups, shown on the left- and right-hand graphs, respectively. And these plots show several things.

First, there's a large variability in baseline seizure frequency in both the treatment and sham groups, although the majority of all subjects in both groups are in the lower portion of the graph.

Second, the general trend for most subjects in both treatment arms is either flat or downward.

In this plot on the right, the two sham-treated subjects with a different response over time are plotted with a dashed purple line. Both of these subjects show an increase in seizure frequency by the end of the blinded evaluation period, contrary to the pattern seen in the majority of the other sham-treated subjects.

It's important to note that these subjects did not return to baseline. They worsened by the end of the blinded evaluation period.

The profile plot suggests that these two sham-treated subjects do not respond the same as other sham-treated subjects. The question would arise of how that would manifest itself in the results, so this plot shows the mean response over time. If we add the response by excluding the two sham-treated subjects noted, we observe that the return to baseline in the sham-treated group effectively disappears.

When the baseline seizure frequency subgroup graphs are examined, the greater than 84 seizures per month at baseline subgroup similarly attenuates the return to baseline if these two subjects are excluded.

This Forest plot shows the overall results based on all subjects at the top. As seen, the estimated rate ratio is attenuated towards one if the two influential sham-treated subjects are excluded. And, similarly, the results are attenuated towards 1 if the subgroup of 19 subjects with greater than 84 seizures per month at baseline are excluded. This suggests that the magnitude of the estimated treatment effect from the primary analysis may be sensitive to a few subjects with atypical response patterns.

Given the statistical issues presented, there are several uncertainties regarding the following. The pre-specified primary effectiveness analysis model was not statistically significant by the empirical estimate, although it was agreed that it is not a good fit to the data. A post

hoc model is appropriate, but it is not the only possible model and was selected after being unblinded to the results of the initially pre-specified model.

Statistical significance of the primary effectiveness outcome was dependent upon the particular GEE model assumptions used. And, further, the overall estimated treatment effect appears to be driven largely by a small subset of subjects with very high seizure frequency at baseline, namely, greater than 84 seizures per month.

The magnitude is also sensitive to two influential sham-treated subjects. If these two subjects are excluded, the return to baseline seen in the sham-treated subjects disappears.

In any submission, FDA examines the totality of the data, not solely the primary effectiveness outcome, for the total picture of the device's safety and effectiveness.

Several secondary and additional effectiveness outcomes were assessed, including median seizure count, responder rate, and median percent change. While these numerically favored active treatment, they were not statistically significant, although the trial was not explicitly powered for outcomes other than the responder rate.

Importantly, these analyses are less sensitive to influential subjects than the GEE analysis of mean seizure counts, since they're not relying on a mean.

And the long-term data also have caveats for interpretation. Specifically, it is open-label with no concurrent control beyond the end of the blinded evaluation period. Subjects could change their antiepileptic drugs, and there was a potential that the dropout over time could be partially attributable to subject non-response, leading to the possibility that effectiveness estimates are upwardly biased over time.

These issues complicate the interpretation of the long-term data, as attributing effectiveness changes to active stimulation is confounded by these issues.

Dr. Federico Soldani will now discuss the post-approval study.

DR. SOLDANI: Thank you, Dr. Miller.

Good morning, distinguished members of the Panel and members of the audience. My name is Federico Soldani, and I am the epidemiologist on the PMA review team. I will now present the post-approval study considerations for NeuroPace Responsive Neurostimulation System.

Before we talk about post-approval studies, we need to clarify a few things.

The discussion of a post-approval study prior to FDA determination of device approvability should not be interpreted to mean FDA is suggesting that the device is safe and effective.

The plan to conduct a post-approval study does not decrease

the threshold of evidence required by FDA for device approval.

The premarket data submitted to the Agency and discussed today must stand on their own in demonstrating a reasonable assurance of safety and effectiveness and an appropriate benefit/risk balance.

There are two general principles for post-approval studies. The main objective of conducting post-approval studies is to evaluate device performance and potential device-related problems in a broader population over an extended period of time after premarket establishment of reasonable evidence of device safety and effectiveness.

Post-approval studies should not be used to evaluate unresolved issues from the premarket phase that are important to the initial establishment of device safety and effectiveness.

The specific reasons for conducting post-approval studies are to gather postmarket information, including long-term performance of the device, including effects of re-treatments and device changes; data on how the device performs in the real world in a broader patient population that is treated by newly trained specialists, as opposed to highly selected patients treated by investigators in the clinical trials; evaluation of the effectiveness of training programs for use of devices; evaluation of device performance in subgroups of patients, since clinical trials tend to have limited numbers of patients or no patients at all in certain vulnerable subgroups of the general patient population.

In addition, post-approval studies are needed to monitor adverse events and outcomes of concern, including effectiveness, especially rare adverse events that were not observed in the clinical trials. Finally, post-approval studies should account for Panel recommendations.

Post-approval studies should contain a fundamental study question or a hypothesis, safety endpoints and methods of assessment, acute and chronic effectiveness endpoints and methods of assessment. Post-approval studies should specify the duration of follow-up.

If the device were to be approved, the FDA review team has identified the following postmarket issues as relevant for NeuroPace Responsive Neurostimulation System: the need to collect safety and effectiveness data on recipients of the RNS System who are being treated by physicians newly trained on implantation and management of the RNS System; the need to gather additional patient-years of data to contribute to the estimate of the rate of sudden unexplained death in epilepsy.

The applicant proposed two post-approval studies: the long-term treatment study that is an extended follow-up of the premarket cohort up to seven additional years, and the new enrollment study. This slide presents an overview of the applicant's ongoing long-term treatment study. This protocol was approved by FDA in 2005.

The study objective is to assess the ongoing safety and continue to evaluate the long-term effectiveness of the RNS System for its

proposed and intended use as an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures from no more than two foci that are refractory to two or more antiepileptic medications.

The study design is that of a prospective, non-randomized, multicenter, seven-year follow-up study; 230 patients who completed the feasibility and pivotal trials are included.

Endpoints are total serious adverse event rate (device related and non-device related) as well as average percentage change in mean frequency of total disabling seizures relative to the pre-implant period.

This slide presents an overview of the applicant's proposed new enrollment study. Study objectives would be to collect one year of safety data on recipients of the RNS System who are being treated by physicians newly trained on implantation and management of the RNS System, and to gather additional patient-years of data to contribute to the estimate of the rate of sudden unexplained death in epilepsy.

The study design would be that of a prospective, non-randomized, multicenter, one-year follow-up study.

The study hypothesis for the primary endpoint would be the following: total serious adverse event rate (device related and non-device related) at one year is not worse than the total serious adverse event rate observed in the first year of the RNS System pivotal trial, which was 39%, or

74 out of 191 patients in the pivotal trial experienced at least one serious adverse event.

Two hundred patients will be enrolled at 20 centers. The study population will include patients 18 to 70 years of age with disabling seizures (simple partial motor, complex partial, and/or generalized tonic-clonic seizures); failed treatment with a minimum of two antiepileptic medications used in appropriate doses with adequate monitoring of compliance and the effects of treatment as determined by the physician-investigator; diagnostic testing as part of standard care that has identified no more than two epileptogenic regions.

Endpoints would be total serious adverse event rate (device related and non-device related) at one year for patients treated by physicians newly trained in implantation and use of the RNS System, and SUDEP rate.

Here I'm going to present issues from the initial FDA assessment of the post-approval studies that we will ask Panel members to discuss during the afternoon deliberations.

FDA has concerns about the new enrollment study as presented by the company and is seeking the Panel's input on the following points:

1. The Sponsor has not proposed a newly enrolled comparison group (for instance, best medical therapy).
A comparison group may indeed be critical to evaluate safety and effectiveness.

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2. Apart from SUDEP rate, no other specific safety endpoint is proposed. Other safety endpoints, in addition to SUDEP (for instance, intracranial hemorrhage and injuries) could be worth measuring in the new enrollment post-approval study.
3. A one-year follow-up is proposed. A longer duration of follow-up (perhaps up to 10 years) may be necessary to estimate the long-term safety and effectiveness of this permanently implanted device.
4. Effectiveness data are not planned to be collected during the new enrollment study. Given that the device is a permanent implant, it would be important to monitor effectiveness in the postmarket setting.

This concludes my presentation. Now Dr. Rodichok will present FDA's summation.

DR. RODICHOK: So I will present a brief summary of FDA's view of the safety and effectiveness data.

First regarding safety. The procedure is associated with significant risks, including intracranial hemorrhage and local infection. These risks appear to be no worse than risks with other comparable intracranial implantation procedures. However, these are risks that would not be seen with continued medical therapy.

Beyond the procedure itself, the pattern of adverse events is not different from that seen in poorly controlled partial epilepsy patients. However, the incidence of some events, such as seizure-related and nonseizure-related intracranial hemorrhage and injuries, may be higher than expected.

We do want to note that the data for the full population is complete to one year after implantation.

Regarding effectiveness, FDA believes that there is significant uncertainty regarding the result of the model-based analysis of the primary effectiveness endpoint, in that the analysis was post hoc. The pre-specified secondary effectiveness endpoints were not statistically significant.

The responder rate and a post hoc analysis of median percent reduction in particular, both of which are commonly used in the assessment of treatments for epilepsy, do not show a clinically meaningful benefit.

The largest change in seizure frequency occurred in both groups prior to start of stimulation, raising doubt about the role of neurostimulation in any change in seizure frequency attributed to the NeuroPace device.

The uncontrolled open-label effectiveness data are confounded by the impact of unblinding, concurrent changes in other treatments, and the use of a remote baseline for comparison, and therefore we consider these results difficult to interpret.

Elements to be considered in a benefit-to-risk comparison are the following: the risks include the added acute risks of the procedure itself and the lower risks of the chronic implant. In addition, there is a concern for added risks of the implanted device and electrodes in a population of poorly controlled seizure patients prone to head injuries. There is a significant uncertainty as to whether the device provides a clinical meaningful benefit.

Alternative treatments are available. The seizure reduction with additional trials of approved drugs is well established. The recorded benefits and risks of chronic vagal nerve stimulation have been presented. And for those appropriate candidates, the benefits of mesial temporal resection have been shown to outweigh the risks.

Thank you very much. That concludes the FDA presentation.

DR. YANG: I would like to thank the FDA speakers for their presentations.

Does anyone on the Panel have a brief clarifying question for the FDA? Also, please remember that the Panel may also ask questions to the FDA during the Panel deliberation session later this afternoon.

So we have Mr. Mueller, followed by Dr. Rogawski.

MR. MUELLER: Yes, David Mueller.

On FDA's presentation Slide Number 85, to get back to it, with the concerns with the open-label data, one of the bullets there states missing data/dropouts. And two slides later, Slide 87, it describes what's probably

known as the dropouts because it's the subject discontinuations. But there's no explanation what FDA means in the presentation by missing data.

What data was missing?

DR. COSTELLO: So here we're talking about the patients who discontinued the study. The missing data refers to they followed the patients for a total of nine years. So the subset of patients that are being followed out to nine years lessens and lessens and lessens.

MR. MUELLER: So it wasn't patients in the trial that they just forgot or missed or lost data. It's that they stopped.

DR. COSTELLO: No, but it's just the average. Right, I think Dr. Morrell said the average was 3.3 years, but data was presented out to nine years.

MR. MUELLER: Okay.

DR. YANG: Dr. Rogawski.

DR. ROGAWSKI: I believe that Dr. Morrell mentioned in her presentation that the Agency asked the Sponsor to conduct a bootstrap study, and she pointed out that that analysis indicated less than a 2% chance that the results would occur by chance. And I'm wondering whether the FDA carried out a similar bootstrap analysis and whether that agrees with the Sponsor's conclusion.

DR. MILLER: This is Scott Miller.

Yes, we did that analysis. The Sponsor replicated it, and we

agree, the result is about 2%. So it's sort of an assessment in the terms of seeing how likely the treatment effect would happen.

Basically, as she mentioned, you're sort of lumping all of this stuff and pretending that they didn't have a treatment assignment and then you're randomly assigning them, so the average effect is zero. And so if the effect were likely to occur under that scenario, the estimated treatment effect that they observed had been likely to occur under that scenario, then you would say there was some concern about how robust the results are. But as that was not the case, as Dr. Morrell has already mentioned, that's a point in their favor, that it's less likely to occur in that particular -- given that's the seizures in the post hoc model.

DR. YANG: All right, Dr. Afifi.

DR. AFIFI: This question is probably for Dr. Miller. Let me ask you the same question I asked the Sponsor.

Have you considered random effect models? And if so, what were the results?

DR. MILLER: So the answer to that is no, we did not fit a model with that. That was something that was discussed at the protocol development stage. But as the model ended up being a GEE, the models that we looked at were looking at variations of the primary effectiveness and basically sort of trying to see how well the GEE model fit. We did not actually conduct any mixed models.

DR. AFIFI: So do you think it's worth it to try to do that model now and before you make a final decision?

DR. MILLER: I think that would probably be something that would help -- if you feel that that would be necessary, that would be helpful input to receive from you.

DR. AFIFI: Thank you.

DR. YANG: Dr. Connor.

DR. CONNOR: I have two questions. The first one sort of on this bootstrap is what -- and we've seen a variety of GEEs that were fit with different model structures and such. The 2%, essentially, p-value that the Sponsor came up with, that you said you replicated, what model was that or does that tend to be insensitive to the model choice?

DR. MILLER: So that was using Model 8, the post hoc model, so the one that they presented after identifying that the primary one was not a good fit.

DR. CONNOR: Okay. So that's the negative binomial done monthly; is that right?

DR. MILLER: Yes.

DR. CONNOR: Okay.

DR. MILLER: Adjusted for covariates. We did not replicate by any of the other additional models.

DR. CONNOR: Okay. So we don't have like a bootstrap p-value

for the other ones?

DR. MILLER: No.

DR. CONNOR: Okay. And then maybe my other question is, so there was a lot of talk -- some talk from FDA about the responder rates being similar between groups, and that sounds like a key secondary outcome. And then there was talk about once the device was turned on in the sham group, how things didn't come together as much as we would've thought if the device was effective. The Sponsor showed responder rates for that variable, and in fact, they do come together. And FDA showed mean seizure frequency, in which case they don't come together. So my guess may be that the Sponsor showed what's best for them, and the FDA showed what's worse for them.

Do we have that question answered with other things like percent change or medians and things like that?

DR. COSTELLO: The Sponsor applied medians, but not broken down by active and sham. They may have it available. FDA requested it, but the Sponsor said in the open-label data the median was not pre-specified, so we do not have it.

DR. CONNOR: Okay. So in your plot, like Figure 81, you showed the mean seizure frequency still being pretty far apart.

So what led FDA to choose to try to answer that question via the mean versus, say, a responder analysis?

DR. COSTELLO: Well, I think what we're really trying to show is the large amount of variation, which we can't really show that well in the responder analyses. So I think that was really one of the points of the slide, although we do agree with the Sponsor's analysis of responder rates. So both are in our Executive Summary. We only had a limited period of time, so we decided to show the open-label data.

DR. CONNOR: Okay. And one of, I think, the interesting things on this plot is the variability, which you just referred to, is way bigger in the sham group. Is there any sense of -- I mean, in part it's because bigger means are always going to have bigger variability for data generated this way. But it's very interesting to me that the variability is dramatically lower in the treatment group than the sham group sort of along the spectrum there.

DR. MILLER: This is Scott Miller.

I would concur. I find the large variability somewhat indicative that there may be something going on. I've not looked into specifically what might be driving that. I don't know whether the Sponsor has or not.

DR. CONNOR: Okay, thanks.

DR. YANG: Okay, then we'll take Dr. Toledano, followed by Mr. Mueller, then Privitera, Nikhar, and Cavazos.

So first, Dr. Toledano.

DR. TOLEDANO: Thank you. So my name is Alicia Toledano, and I also have a question for Scott Miller.

I'm looking through the Sponsor's Executive Summary, and the regulatory history of discussions going back 13 years and the supplement, the IDE supplement on the pivotal study happening in 2005, and then coming in for the pre-PMA meeting on March 15th, 2010.

I'd like to know from Dr. Miller when you personally became involved as a reviewer on this project.

DR. MILLER: Okay. So my involvement came after the pre-PMA meeting and also after the initial PMA review memo was written.

DR. TOLEDANO: And what happened to the person who was involved at that March 15th meeting?

DR. MILLER: There's just personnel issues that come up, that people leave the Agency or are busy when a particular submission comes in. We try to maintain consistency, but we can't always do so. As far as the reviewer, we certainly try to maintain consistency of thought, even if the reviewer changes.

DR. TOLEDANO: And the Sponsor said that Model 8 was agreed to at that meeting, but FDA's slides say, no, it wasn't. Can you help me understand that?

DR. MILLER: I think that's a difference of opinion. My understanding of the meeting was that there was a discussion that the initial model didn't fit well and that they were interested in selecting -- proposing an alternative model. And at the time we told them we'd be interested in

seeing the original results. But if you feel you have a model that would be a better fit, we'd certainly be open to reviewing it.

DR. YANG: Dr. Krauthamer.

DR. KRAUTHAMER: Yeah, I just wanted to say that it wasn't any sort of formal agreement meeting. It was a meeting of colleagues looking at what would be best. And at that point we thought that they should move forward with both models, but we didn't -- certainly it was not a formal kind of agreement or anything like that.

DR. YANG: Thank you for clarifying.

Mr. Mueller.

MR. MUELLER: Yes, Dave Mueller.

I'm on Slide 127 of the FDA presentation. It's discussing the benefit-to-risk comparison, and it describes that alternatives are available, where it states pharmacological, the benefits are known and they have a lower risk.

But my question is that the indications for use for this device are for patients that are refractory to two or more antiepileptic medications. So how could that be an alternative?

DR. RODICHOK: It is an alternative. The four trials, for example, that I described to you were patients who had, in fact, been considered to have failed up to six previous trials of anti-epilepsy drugs.

Nevertheless, those results that I showed you are reasonably

typical of what one gets when one takes a refractory population and tries another drug. It usually doesn't lead to seizure freedom, which is the goal, but it does often lead to a reduction in seizures. Now, it may be over the short term. Some people say anything works for a little while. But that is a reasonable option with a known benefit and relatively low risk.

MR. MUELLER: Right. But the -- of course, says it was told several different places. They also had adverse events. I mean, they have risks, but they also have potential adverse events, too.

DR. RODICHOK: They do. It comes with its potential adverse events as well.

MR. MUELLER: Thank you.

DR. YANG: Dr. Privitera, followed by Nikhar and then Cavazos.

DR. PRIVITERA: One of the major confounders that I see here in the analysis of efficacy is this surgical effect. And obviously that's not a problem that we have to deal with when we look at clinical trials of antiepileptic drugs because we've got a placebo arm that doesn't have any type of intervention.

Does the FDA have any experience in terms of understanding this surgical effect? In other words, as far as I know, there's not any hard data, and it's essentially all anecdotal data from epilepsy surgery or people who had implanted electrodes and then had their electrodes taken out.

Are we aware of any sort of stronger evidence about the

impact of this surgical effect? And does FDA have any experience in other areas with the impact of surgical effect?

DR. COSTELLO: I think we have to be careful whether we call it a surgical effect versus a post-implant effect because, as you say, we don't know whether it's patients have finally gotten into a trial, they don't want to be in another antiepileptic trial, let's try another drug, let's try a device, and there's regression to the mean. We don't know if it's a placebo effect or if it is a surgical effect.

We have presented in 2010, at another Panel meeting, a similar surgical effect for a similar type of a device. Other surgical effects that we have seen, I don't think at this time we're able to discuss in public.

So to answer your question, we really don't know what the surgical effect is. And my personal opinion is to call it a post-implant effect because we really don't know what it's due to.

DR. PRIVITERA: Just a brief follow-up on that. For example, with vagus nerve stimulation, was there a similar kind of effect? Do we know?

DR. COSTELLO: No, there was not. And I was the clinical reviewer of the VNS.

DR. YANG: Dr. Nikhar.

DR. NIKHAR: Nirjal Nikhar.

If we could look at Slide 69, please, we'll try and understand

this. So does the table reflect all of the patients in the trial in the treatment and the sham arms?

DR. COSTELLO: Correct. If you look at the first three lines, no change or increase greater than zero, less than 50, greater than or equal to 50%. Those are the patients who reached the end of the blinded evaluation period for both the treatment and the sham group. The last line is inclusive of the patients who've had a greater than 50% reduction.

So of the 28 patients who had a greater than 50% reduction, five of them in the treatment group and four of them in the sham group also had greater than a 90% reduction.

DR. NIKHAR: So each table should add up to 100%?

DR. COSTELLO: Well, it depends. I mean, there were several patients who dropped out. I think there were four patients who dropped out during the blinded evaluation period. So they do reflect the number of patients who reached the end of the blinded evaluation period. So it wouldn't be 191. I think it was 187 total.

DR. NIKHAR: Because the percentiles come to 105% in the treatment. 104. So I think there's some overlap or maybe somebody else that's being counted.

DR. AFIFI: I think the greater than 90 is included in the greater than or equal to 50.

DR. COSTELLO: Right.

DR. NIKHAR: Yeah. And so there's an overlap. Okay.

DR. AFIFI: Yeah.

DR. NIKHAR: All right, thank you.

DR. YANG: Dr. Cavazos.

DR. CAVAZOS: Two points. The first one is a follow-up from the prior -- can you put up Slide 81? So the question here is that the variability is greater in the sham group for this particular measure of mean.

Did you look at as to whether the effect of -- and we have 53% of the individuals in the sham group had prior intracranial monitoring, so they knew better their seizure onset zone, whereas the treatment zone had 65, meaning perhaps they have less values. Did you look specifically as to whether this covariate was significant?

DR. COSTELLO: I do not think we did that analysis. I don't know if it's possible to do it over lunch.

DR. MILLER: This is Scott Miller.

We did not do that kind of analysis. I don't know, off hand, if we have the data to be able to do that over lunch or not.

DR. CAVAZOS: Okay. The second is, which is a more broader issue and that has been quite troublesome to me, specifically has to do with the black box that we are discussing here.

So we have experimental evidence for many years that stimulation, it doesn't do the same things in the brain. Some parameters at

low frequencies may excite neurons. Some parameters at high frequencies may do some other things. Some parameters, when they are repeated in some particular manner in those seizures, can limit effect. Some parameters actually are inhibitor. So I'm very troubled as to -- that we are asked to evaluate information without knowing what was there in the black box.

I mean, this is obviously beyond just this particular device. I mean, this is one of the main things that, also as postmarketing, we haven't really had any of the devices during neurostimulation proceeding with studies, trying to understand better what are the parameters that have to be used.

DR. COSTELLO: I think it's important, first of all, that there are certain things that FDA can ask the Sponsor to do prior to a pivotal study. And basically we do not disapprove studies for that kind of -- if we have some basic data, which we had from some open-label trials.

We also then did ask the Sponsor to look at patients and to try to evaluate why they did or did not respond, and in terms of was this a seizure detection device, in essence. And it was not studied as a seizure detection device, and the Sponsor did not wish to make that claim. So we do not have that kind of data, although I agree, it would be very helpful.

DR. YANG: Dr. Krauthamer, do you have anything to add?

DR. KRAUTHAMER: Oh, yes. Our mandate is safety and effectiveness. It would be nice, of course, to know how something worked.

But at FDA, we can treat this as a black box. So we don't know, for example, dose response kinds of things and all the issues that you brought up. I am sure the sponsors would love to investigate those things, but I think they're under other pressures as well.

DR. CAVAZOS: I thought that your first statement, opening statement, was the problem is the disease and getting to the truth.

DR. KRAUTHAMER: Yes.

DR. CAVAZOS: So that's the mandate.

DR. KRAUTHAMER: Yes.

DR. CAVAZOS: That's the mandate.

DR. KRAUTHAMER: Right. And NIH has a big program and research that looks at those things. So our role is a little bit more limited.

DR. YANG: Thank you.

Dr. Petrucci.

DR. PETRUCCI: I may have missed this in the presentation, but there's an absence again of psychiatric and cognitive issues related to the study. Can you comment on that?

DR. YANG: Dr. Rodichok, would you like to?

DR. DR. RODICHOK: I don't recall that NeuroPace presented it, but I think they provided us with adequate data to support that there's no adverse cognitive effect in the patients in the trial.

As far as psychiatric issues are concerned, I think it's fair to say

these are pretty common in this population, and I think it's fair to say that the results are no worse than would be expected in a rather poorly controlled population. They're not any better, either.

DR. PETRUCCI: Thank you.

DR. YANG: Dr. Connor.

DR. CONNOR: My question is about the analysis when you removed the two influential subjects. So I guess I was taught in graduate school that we shouldn't throw away outliers. We should study them in part to make sure the data was right, that there wasn't a mistake, but you know, there's something interesting about them. So I think it's actually evidence that both, maybe, poorly behaved ones are in the sham group, not in the treatment group.

But it just seemed strange. Like, if I see a baseball game and the Nationals win five to three, post hoc, to say the most influential inning was the third because Bryce Harper hit a three-run homer and they lose if you throw out the most influential inning, I just don't understand.

(Laughter.)

DR. CONNOR: So along that line, I wondered if there was a similar analysis where you would remove like the two most influential treatment patients so that we still have some kind of more apples-to-apples comparison here.

DR. MILLER: This is Scott Miller.

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So certainly your point is well taken, that it is post hoc. So the issue here is I did not do an analysis excluding subjects that got worse in the treatment arm. The reason for that would be that, by doing that, you're effectively sort of making the two treatment groups more similar, which is -- so you're effectively biasing, you're making them less or more. So you're sort of biasing it towards the alternative, which is returning to prove -- so the reason I looked into these two subjects was sort of twofold.

One was, when looking at the subject-level Cook's distance criterion for sort of measure of influence, they came up as the two most influential in the model. And the other issue was, when we did the subgroup by baseline seizure count, these subjects happened to have been in that group that showed it seems to be driving the results when you see the results. The other groups, they seem like they sort of trend. Both treatment arms and the sham sort of trend in the same general pattern.

So the reason I felt like it was appropriate to look into that -- certainly I'm not saying I agree with the outliers. If you randomize them, you need to have a very good reason for excluding them, the outliers, influential subjects. This was more sort of an assessment of how well the model fits and doesn't fit.

And so we've already got some concerns about whether the model is the most appropriate model or not. We have some concerns about is the GEE appropriate, given some of the exceptions and whatnot. So this

was an assessment of, okay, given the response pattern seems to be different for these subjects, is that something to be worrisome?

And particularly, going back to your part about that they got worse, if they had just stayed the same or gone back to baseline, then I certainly would not have felt comfortable excluding them until they do an assessment of another analysis. The reason I felt it was particularly different in this case is because they got worse, particularly the one that had 799.

DR. CONNOR: Yeah, I wondered if -- and I agree. I mean, this is right, I think, to think how influential is that, because clearly one of these things is not like the other.

Did you maybe put in, you know, or censor that and say 400, just to say it's still bad, but it's not way bad?

DR. MILLER: That's an interesting speculation. I did not do that.

DR. CONNOR: Okay, all right.

DR. MILLER: That would be something that would be interesting, potentially. But no, I didn't.

DR. CONNOR: All right, thank you.

DR. COSTELLO: I would just like to add that I think the reason from a clinical perspective, that we asked Dr. Miller to do that, too, was the difference in the mean and median scores, those graphs that we showed, because we wanted to see why there was such a big difference in return or

not return to baseline at the end of the blinded evaluation period.

DR. YANG: At the moment I think we're going to break for lunch. We will be able to ask more questions of the FDA during the Panel deliberations this afternoon.

Panel members, please go to Room 1506 -- I believe it's behind this door -- for lunch. Panel members, please also do not discuss the meeting topic during lunch amongst yourselves or with any member of the audience. We will reconvene in this room in one hour at 1:00 p.m. I will ask that all Panel members please return on time. Audience members, please remember to take any personal belongings with you at this time.

(Whereupon, at 12:00 p.m., a lunch recess was taken.)

AFTERNOON SESSION

(1:00 p.m.)

DR. YANG: So it is now 1:00 p.m., and I would like to resume this Panel meeting. We will now proceed with the Open Public Hearing portion of the meeting.

Public attendees are given an opportunity to address the Panel, to present data, information, or views relevant to the meeting agenda.

Ms. Facey will now read the Open Public Hearing disclosure process statement.

MS. FACEY: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. YANG: All Panel members have been provided written comments received prior to this meeting and have had an opportunity to review the comments.

For today's meeting, each scheduled speaker will be given seven minutes to address the Panel. Any additional unscheduled speaker will be given three minutes. We ask that you speak clearly to allow the transcriptionist to provide an accurate transcription of the proceedings of this meeting.

The first speaker is Jacqueline French, M.D., President of American Epilepsy Society.

DR. FRENCH: Thank you for the privilege of allowing me to speak to you at this meeting. I wanted to start with my disclosures. I am the President of the Epilepsy Study Consortium, and I work with pretty much every drug and device -- not every one, but many of them, but I receive no personal compensation for that. And my travel here was paid by the American Epilepsy Society.

So the American Epilepsy Society is a society that promotes research and education for professionals dedicated to the prevention, treatment, and cure of epilepsy. Our membership consists primarily of physician-epileptologists or neurologists who specialize in epilepsy, as well as

neurosurgeons who have an interest in epilepsy, nurses, neuropsychologists, pharmacologists, neuroscientists, and allied health professionals. And I'm happy to say several of the members of the Panel here today belong to the American Epilepsy Society.

I want to remind you about how prevalent epilepsy is. The Institute of Medicine recently had a report, and 2.2 million people in the United States suffer from epilepsy, and 150,000 new cases are diagnosed annually.

The most important statistic obviously is the number of people who might need this device were it to be approved, and unfortunately a third of people with epilepsy have continued to have seizures or are treatment resistant despite the best medical therapy and therapy with the available devices on the market. And of those people, the people with focal seizures, those who would be candidates for this device are among the more difficult-to-control patients.

As you've already heard here today, the risk of death is higher for people with epilepsy, and it is estimated that there are 10 years of lost life in people who have no known cause of epilepsy, and 2 years of lost life -- with a known cause of epilepsy, and 2 years of lost life with an unknown cause of epilepsy.

And you've also heard about the scourge of sudden unexplained death in epilepsy, with a risk of .64% per year for patients who

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were unfortunate enough to be in the placebo arm of randomized controlled trials that enrolled patients with treatment-resistant focal epilepsy. In other words, not making any treatment changes, because that's what happens to people in the placebo arm, was associated with .64% per year rate of death from SUDEP.

In addition, as you also heard from Dr. Bergey this morning, the consequences of uncontrolled focal seizures, in addition to a shortened lifespan, include bodily injury, hospitalization, the risk of status epilepticus, neuropsychological and psychiatric impairment, including depression and reduced quality of life, as well as significant social disability, including reduced employment rates and reduced marriage rates.

And I'm only telling you these things to remind you how important it is for people with epilepsy to receive the therapy that is useful for them.

The current options, as you've heard, include 17 marketed antiepileptic drugs. Unfortunately, we know that once two antiepileptic drugs fail, the likelihood of cessation of seizures with any additional antiepileptic drug therapy is less than 10%.

And I also want to remind you that we've been told that drugs are safer than this type of intervention, but these drugs are not, in any sense of the word, benign. They're associated with lots of serious adverse events in their own right, including aplastic anemia, pancreatitis, and Stevens-Johnson

syndrome. And in fact if you look, for example, at valproate, which is one of our more commonly prescribed drugs, it has a 1 in 3,000 rate of pancreatitis.

The vagus nerve stimulator, another option for these patients, also has risks, as we've heard today, including vocal cord paralysis. And the process of just being evaluated for epilepsy surgery, where the likelihood of actually going on to have a resection that is useful to you, is not 100%. The risk of just being evaluated for the surgery is very real and probably as high as the implantation of this device.

So if you're going to have an epilepsy surgery evaluation, you're going to need intracranial monitoring before you go on to have your surgery, and that's necessary 50% of the time. And 25% of the time, curative surgery is not offered after intracranial monitoring, and yet people feel that the risk is worth the potential benefit just in case they are candidates for surgery.

So these people know that they need to undergo risks to potentially gain benefit. All of these risks and all of the benefits have to be assessed by individual patients.

And I also want to remind the Committee that treatment benefits can take many forms, and unfortunately not all of them are highly measurable. And I've spent a lot of my career trying to measure benefits from different therapies.

Decrease in seizure frequency is only one of the things that can be a benefit. It happens to be the one that we're probably the best at

measuring, but it may not be the only one. Severity of seizures, timing of seizures, duration of seizures, these we are not good at measuring, but they may be also benefits to patients. And unfortunately they are not captured in this clinical trial or any clinical trial. But when people talk about improvement, often these are the things that they are talking about.

So, in conclusion, most epilepsy therapies have risks. The risks of the RNS, we believe, are well within those accepted in a population of patients with continuing partial onset seizures despite medical therapy. And clinicians and patients with this very severe and life-threatening disease do need access to as many therapies as possible to treat their epilepsy.

Thank you.

DR. YANG: Thank you.

Next, I'd like to invite Susan and Brian Hogue to the podium.

MS. HOGUE: It's actually Susan and Paul Hogue.

DR. YANG: My apologies. A misprint.

MS. HOGUE: Thank you for allowing us this opportunity to share with you our miraculous story about how NeuroPace has changed our lives.

First of all, we wish to disclose to you while expressing our utmost appreciation to NeuroPace for covering our travel expenses and lodging and allowing us to be here today. I would also like to thank Paul for allowing me to speak openly and specifically about how epilepsy has touched

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all our lives. Paul wrote this.

MR. HOGUE: I want to thank all the people that work on NeuroPace for all the work you have done for me, especially for making this device happen. This device has helped control my seizures better than any medications I have been on.

Before I got this device, I had lots of seizures and was tired most of the time. I even fell asleep standing up with the vacuum running in my hand. Sometimes when I have seizures, I feel like a broken robot. Sometimes I can see but can't control myself when I move.

Since I got the device, I am able to do a lot more sports and make friends because I'm not as sleepy and I'm not having as many seizures anymore. I love playing soccer now with the guys who have played all their life, and I even score goals, but no headers.

(Laughter.)

MR. HOGUE: This device can help a lot of other people with epilepsy. We have told people who have seizures about this device, and they would love to have it. Every time a person would get this device, it would be a miracle to them. It is real amazing how such a device can help so much.

I couldn't pass high school or even get the GED years later. But after NeuroPace, I went to Cabrillo College and was an honor student. I'm learning Espanol now.

I think since the seizure is like an earthquake, and since

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NeuroPace can reduce seizures, it would be great if we could make big ones to stop earthquakes.

Thank you.

MS. HOGUE: A few years ago someone asked, how can you sign a 21-page human research consent form? This is how. Paul began having absence seizures two weeks before his seventh birthday. We were referred to a neurologist to understand the sudden onset of staring spells and head jerks, and he said, don't worry, lots of kids have this. We'll get him on medication and he'll probably grow out of it.

Two weeks later was my second call to 911 with Paul in a tonic-clonic. When I arrived at the hospital behind the paramedic unit, everyone was being paged code blue to my son's room. After 45 minutes, one nurse finally came out and said the paramedics mistakenly administered morphine instead of diazepam. And they were doing everything they could to save him. Hours later he was still lying lifeless in the critical care unit at Children's Hospital, intubated and connected to every machine they could get into his room, waiting for a spinal tap.

Two days later, one of the doctors said, oh, don't worry. With what we've given him, he won't remember any of this. I said could you give me some of that because I really don't want to remember any of this either.

Eighteen painful, heart-wrenching years of ever-changing seizures, medication trials, and tribulations. Episodes of status epilepticus

followed. Generalized tonic-clonic, myoclonic jerking, complex partial, atonic, every AED known to man, experiencing many horrific side effects, hundreds of blood tests, to the extent that Paul would point out to the phlebotomist which vein to use.

Early on, our simple routines changed. I looked down the store aisle and didn't see Paul, ran to the next aisle and found him on the floor in a tonic-clonic, his head banging on the floor, arms, hands, legs curled up tightly, jerking violently, eyes rolled upward, biting his tongue, with blood and saliva running out of his mouth. I threw myself on the floor next to him and placed my hand under his head, gently rubbing his back, tears running down my face. We basically reattached the umbilical cord, knowing we could never leave him alone again, not even for a moment. People in the store shook their heads in horror, whispering their medical diagnoses guesses to one another.

The stigma of epilepsy is often as painful as the epilepsy itself. Fellow students, soccer players, parents of other children with epilepsy whose seizures were under control, even churches ostracized him.

One director of pediatric neurology asked if he could bring Paul into one of his classes to discuss, and with Paul in front of the class, he told him, my finger is a birthday candle, Paul. I want you to blow it out. Paul blew three times and went into seizure. We had no idea he was so close to seizing so easily.

I told one epileptologist, sometimes Paul seizes, stops

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breathing, and turns blue. How do we administer CPR? He said you can't; you have to wait until the seizure stops.

Paul lived with a sweatshirt tied around his waist, pillows surrounding his bed to catch him whenever seizures threw him down. Just before he received the NeuroPace implants, his seizures would throw his 165-pound body, sound asleep, out of his queen size bed.

We spent 15 years in a dysfunctional special education system and were even forced to pay \$2,000 for a conservatorship when the special ed director shook Paul awake at the first meeting after he turned 18 and said we don't have to talk to your parents anymore. You can make your own decisions.

In his twenties, Paul wanted to move out like his younger sister, but required 24-hour care, funded through state and federal programs. Waiting for acceptance in those programs took years, but he finally made it.

Then came the challenge of finding competent staff. At a meeting months later, I asked if Paul lost continence during his latest seizure, and his senior staff member said, I guess so because I looked everywhere and couldn't find it.

We tried the ketogenic diet, holistic nutrition, naturopathic medicine, even flew to New Mexico for craniosacral therapy for a week, and what we were told, he didn't have sufficient blood flow in his brain. Offering this type of input derives an indescribable expression on an epileptologist's

face, but I explained that if I heard of an aborigine in Australia that danced around people and took their seizures away, we'd be on the next plane, because I can only offer you incredibly intelligent medical specialists the fact that you've never helplessly watched your child have a tonic-clonic seizure.

We've been to four comprehensive epilepsy centers, had bouts with aplastic anemia, Rasmussen's encephalitis, considered callosotomy, underwent gammaglobulin plasma exchange, implanting and explanting the extremely excruciatingly painful VNS, drilling of burr holes for implantation of subdural grids and depth electrodes, until 2006 when Paul received his miracle, the NeuroPace implant, when everything changed and Paul got his new lease on life.

To summarize, thanks to our wonderful epileptologist, Dr. King-Stephens, and NeuroPace, instead of debilitating five-minute tonic-clonics that took an entire day to recover from and could've easily ended Paul's life, his seizures now look like this, and people think he's sneezing.

Please consider Paul as one of thousands so similar who so very desperately need this amazing device. NeuroPace has eliminated Paul's need for government assistance programs costing hundreds of thousands dollars annually. Paul moved from Special Olympics athlete to coach, from someone who would seize and sleep most of the day and night, had very little input on his life and no friends, to someone who gets to live wherever he wants now, is respected and loved and says, I'm going down to see my friends at the

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soccer field. See you in a few hours. And we just smile.

Thank you, NeuroPace.

DR. YANG: Thank you.

Next, if Janie and Brett Norman would please approach the podium.

MS. NORMAN: Hi, my name's Janie Norman, and my travel expenses were paid by NeuroPace. Thank you for the opportunity to come here and tell you the changes in my life because of the NeuroPace device.

I have had epilepsy all of my life, and it has affected every part of my life. There were limitations to my life because of epilepsy. I could not play sports as a teenager. I could not be a nurse like I dreamed of because I was scared because of epilepsy. With everything I did, I had to consider the fact that I had epilepsy.

And I've taken many different medicines with many different combinations, and nothing has helped. I have had seizures, multiple seizures. And I even went through intracranial monitoring, and for 49 days, only to find out I was not a candidate for any kind of surgery whatsoever.

Of the many limitations in my life, there were two that affected me the most. First was the safety to myself and others. And there were many instances of danger that I experienced. There were times I would have seizures going up or down the stairs, while cooking or doing everyday activities that most people do. Most of the time I was very fortunate that

someone was nearby to help me. One time I had so many seizures at one time, I was in a state of having an episode, I guess, for about 20 minutes.

I have two wonderful children, a daughter that's eight and a son that's seven. When I was pregnant with Nathan, I had gone into Wal-Mart to get a couple of things while Brett waited in the car. While I was in there, I must've had a really severe seizure because I don't remember anything of it. A really nice lady helped me and took me to the car where Brett was waiting. I don't know how I told her where I needed to go, but somehow I did, but I have absolutely no recollection of that. And this happened when I was pregnant with my son.

Another instance when I was home with my kids alone, Nathan was about three weeks old and Samantha was about 19 months old, I was sitting in the living room on the carpet holding Nathan. Samantha was sitting next to me. I got up to close the sliding glass door to the sunroom, and I don't remember anything else. When I came out of my epilepsy state, I was sweating, I had a headache, I was confused, and I noticed that the sliding glass door was closed, which means I had closed the door while I was holding my son. I could've easily dropped him and hurt him really, really bad.

I would have many, many seizures each month, but I remember those two instances the most because it scared me a lot.

The most obvious aspect of my life affected by my seizure was the fact that I could not drive. I could not be independent and go places on

my own. Not just for myself, but for my kids also. I could not go shopping to a grocery store or go to a bank or even go to a doctor unless I relied on people. I was very fortunate that my mom was able to help most of the time, but I still wanted to do it myself.

I want to tell you several instances that really affected me.

Once when Samantha was about four years old, she asked me if she could go to the park, and I had to tell her no. And then she said, can Gram-Gram, my mother, come and take us there, and I had to tell her no. I tried to explain it to her, but she's four, you know, and then she started crying.

When Samantha was attending pre-K, she was really lucky that there was a teacher that could take her, pick her up, take her, bring her back. But whenever there was a recital, a party, anything like that, I couldn't go because there was no way I could get there. Nobody was able to drive me.

I wanted to be able to do what most people take for granted, which was to drive, to be independent.

In 2008 Dr. Robert Gross asked me to be part of the NeuroPace study, and my life drastically changed. That little device enabled me to have the freedom that I had wanted for a very longer time. From the time of January 2009, and after waiting the time required by the State of Georgia, I was able to drive. For the first time in my life, I had the freedom I longed for. I could go to the bank on my own, I could go Christmas shopping for my kids, and I could take them anywhere with no consideration. I knew it would affect

me, but I did not realize how much it would affect a seven- and an eight-year-old child.

The freedom to drive and go places on my own is wonderful. Samantha is able to go on play days. We can go to the park. We can do all of these things that little kids do. They would not be able to do this and participate if it were not for the fact that I could drive.

I volunteer in Nathan's class and help them and teach them how to read. I teach them to do math. I'm working now; I've become employable. And I help Brett with the finances at the house and for our family finances. And that wouldn't be possible if I did not drive.

The wonderful changes that I mentioned to you about my life would not be possible but for the NeuroPace device. My life has become right side up and I ask -- no, no, I implore you to please approve this device. Please give thousands of people with epilepsy another choice, another chance, and another hope to have a better quality of life. The fact that we could have a life with less seizures, less frequency, less severity of seizures would be a miracle come true.

Thank you.

DR. YANG: Thank you.

Philip Gattone, President and CEO of Epilepsy Foundation.

MR. GATTONE: Good afternoon, distinguished members of the Panel. It's an honor to speak with you this afternoon. My name is

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Phil Gattone. I'm President and CEO of the Epilepsy Foundation, and I have not received any compensation for travel to appear today. My remarks are solely that of the Epilepsy Foundation.

The Epilepsy Foundation is the leading patient voluntary health agency dedicated solely to the welfare of almost three million people with epilepsy in the United States and their families. Our positions are determined by an independent board of medical advisors.

I'm speaking to this Committee because of the urgency that my community feels for new and better treatments. I also offer my remarks as the father of an adult son with epilepsy, who has experienced thousands of seizures in his 26 years of life.

When Philip had brain surgery for his seizures, it was extremely frightening, as his type of surgery was a new and growing treatment option at the time. An epilepsy surgery was what I would've considered an innovative option.

As I mentioned, he has better seizure control now. He's strong, smart, employed, married, living independently, and amazes me with his accomplishments as a young professional.

Not everyone who has epilepsy is so fortunate. I want to share some of the voices I hear every day from our community of affiliates, advocates, and families from across the nation. We're facing a world where it has been over 15 years since a device has been approved for epilepsy

treatment.

The frustration of the foundation and the epilepsy community is that the access to new treatments should keep pace with innovation. It is our hope that work you do today and in the future will not only help pave the way for access to innovative therapies, but also spark the interest and enthusiasm for creating new devices to treat epilepsy.

I'm extremely thankful for this Committee's time and attention to this issue, and I hope that I can shed some light on the stories and concerns I hear every day from across the country.

One-third of individuals with epilepsy live with uncontrolled seizures because no available treatment works for them. The foundation considers this unacceptable, and we look to the FDA to help address unmet needs for seizure control through new epilepsy treatment options.

Epilepsy presents a great unmet need in treatment. We believe that innovation must take into consideration not only the current options but also the difficulties and the complexities that conditions like epilepsy present in achieving ideal data results.

It should also be noted that patients with difficult-to-treat seizures may have different tolerance levels for risk and improvement that may not fit the existing typical FDA model.

While the foundation and the patient community have great respect for the medical device approval process, we are concerned because

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there are so many individuals with uncontrolled seizures who face no viable options with current therapies. This population may have other health factors, so they're not as healthy as a typical clinical trial patient. It's our hope that this Panel and FDA can evaluate those issues and provide a pathway where the severity can be considered and where the patient's individual right to decide to take on a risk can be permitted.

In addition, the impact on someone's professional, educational, or family life are critical issues for treatment options. Unlike psychiatric conditions, epilepsy treatments can be evaluated by an easy-to-track metric: number of seizures. Unfortunately, the strength of this simple quantifier is perhaps also our greatest weakness, and that physicians too often treat the seizures and not the whole person. A dramatic reduction in seizure frequency may be viewed as a clinical success. But if the patient has cognitive, mood, or memory issues resulting in an inability to perform at work or at school, the treatment could be considered a failure for that individual.

So for many people with epilepsy, it isn't just about seizure reduction, although obviously that's critical. It's also about how someone lives with epilepsy day to day. Can they concentrate better at school or at work? Can they avoid uncontrolled weight gain? Are they tired all the time, and do they have the energy to enjoy their day? Does the epilepsy treatment exacerbate an underlying depression or mood disorder? For women planning pregnancy, do the treatments pose a risk to the child? These are all

questions that must be addressed in considering any treatment option, whether it's in the current today with approved treatments or proposed new treatment options.

We urge the FDA Advisory Committees and the device Panel here today to consider this in evaluating approvals.

People with uncontrolled seizures are those who lack the control or side effect profile that permits them to avoid disabilities or maintain independence and stability in their professional and personal life, have a different tolerance for risk avoidance, and someone deciding between multiple treatment options. In addition, if avoiding or delaying disabilities is possible, an individual may take on risks that an average person would not.

For the third of Americans with intractable epilepsy, new treatments are a critical need, just as a single seizure can have devastating results.

The unemployment rate is two and a half times the national norm. Uncontrolled seizures create huge healthcare cost. There are a host of interpersonal issues resulting in an elevated divorce rate for people with uncontrolled seizures. Most frightening of all is the elevated risk of death from an accident related to the seizure or from SUDEP, sudden unexplained death in epilepsy.

The Epilepsy Foundation is always ready to provide FDA and the Advisory Committee help in finding experts in the field or patient views, and

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we would also welcome the opportunity to meet with FDA staff, medical device teams who are evaluating epilepsy treatments and their data, to provide further background on the spectrum of epilepsy patient and caregiver concerns.

I'd like to thank the members of the Committee for facilitating this process and for the opportunity to share comments with you today. The foundation values your time and contribution to this effort. Your expertise is a true asset to the FDA and this process.

Thank you.

DR. YANG: Thank you.

Warren Lammert, Chairman and Co-Founder of the Epilepsy Therapy Project.

MR. LAMMERT: First, I want to thank the FDA and the Panel for the opportunity to share my thoughts. I am a father of a 15-year-old girl, Sylvie, who lives with uncontrolled epilepsy, as well as the co-founder of the Epilepsy Therapy Project and epilepsy.com, and now very happily a board member of the Epilepsy Foundation, with whom we merged at the end of last year.

I have not received any compensation or travel support for my appearance today, and my comments are solely my own.

Sylvie had her first seizure at nine months, a second seizure the same day, and then later that evening an episode of status that lasted more

than 40 minutes. And so Sylvie started on her first seizure drug, phenobarbital. And when that failed, on to another and another, and quickly a cocktail of medicines that still failed to give her control of her seizures.

Over the next 14 years, Sylvie has gone on to try more than a dozen drugs and a range of drug cocktails and combinations, the ketogenic diet, and has had a vagus nerve stimulator implanted. But still, she's found no answer for her daily waves of absence and myoclonic seizures and far too many tonic-clonic seizures.

A few years into this journey, I learned that Sylvie was like probably 30% to 40% of those living with epilepsy and having no therapy that could control her seizures. And also I came to appreciate that drug therapies bring with them very significant side effects, including fatigue and cognitive slowing, that are only really acceptable against the terrible risks, including SUDEP, of ongoing seizures.

I wanted to try to change that reality for Sylvie and for others living with epilepsy. And so in 2000, I came to start epilepsy.com, a leading website for the epilepsy community, and the Epilepsy Therapy Project, whose mission is to accelerate ideas and therapies for people living with epilepsy.

Now, 10 years later, the Epilepsy Therapy Project has provided funding to a broad range of new pharmacological, device, diagnostic, and dietary therapies that are in the epilepsy pipeline, often working in partnership with other leading organizations and in particular the Epilepsy

Foundation, with whom we've now merged.

As a result of my involvement with ETP, I became aware of NeuroPace and the RNS System over a decade ago and have closely followed its progress through clinical trials, including attending scientific conferences, talking to leading epileptologists about it, reviewing the materials made available today. The results of the RNS, with a 38% reduction during its blinded evaluation period, improving to 50%-plus reduction at one and two years, represent very, very meaningful and important contributions to seizure control and to improving people's lives.

Further, the absence of the common side effects of drugs that I've talked about already, but also including ataxia, already an issue for many people with epilepsy, mood, interactions with other drugs besides sedation and the cognitive issues, is also very important.

Epilepsy, as you've heard from many today, needs new, effective therapies. The RNS is one good option. And it is also an approach that itself offers a new window in epilepsy. It will help us improve our understanding and treatment of epilepsy.

All new therapies involve unknowns and risks. But these, again, have to be weighed against the risk and too often devastating, even fatal, reality of uncontrolled seizures. People living with uncontrolled epilepsy, together with their families and doctors, deserve the opportunity to weigh the costs and risks of their epilepsy against the risks and the promise of this

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new therapy, which has been shown to be effective in appropriate clinical trials.

While a number of new drugs have come to market in recent years, we have not made notable headway against the problem of uncontrolled seizures. And as was just mentioned, it's been 15 years since a new device has been made available against epilepsy.

A failure to approve would take away an important new therapy option, and it would have a devastating impact on investment in other new device therapies. For the sake of Sylvie and all of those living with uncontrolled epilepsy, the RNS should be approved and made available as an important new option for therapy.

Thank you.

DR. YANG: Thank you.

Christina Goodman.

MS. GOODMAN: Hi, my name is Christina Goodman, and this is my daughter, Madeline, nine years old, and we're from Concord, New Hampshire. I want to thank NeuroPace for paying for our travel and accommodations to come here and talk about NeuroPace and how it's affected our lives. And I want to thank my neurologist, Dr. Jobst, for helping me get this.

Since I was about eight years old, I've had seizure activity, but my doctor didn't know. He thought it was anxiety, so I've been treated with

Zoloft at eight years old. I was diagnosed with epilepsy when I was 14 after I had my first grand mal seizure. Four months after, I had another grand mal seizure, and that's when they chose to diagnose me.

After trying many different medications to no avail, my life was just repetitive and boring. I would go to school, come right home, go to my doctor's appointments, and come right home. I did not like to be in public. Seizures, for me, are very embarrassing, and I feel like I'm a burden to my family. I still can't drive. I can't do the things that my daughter would like us to do. I try the hardest, but I have a very supporting family, thankfully.

I can't live alone because I still have seizures, grand mal seizures. But my nine-year-old daughter is very mature for her age and knows how and what to do to take care of me if that should happen. So we live with my mother, her grandmother.

But I had my NeuroPace implanted in September of 2007. Madeline was four years old. Since then the number of seizures that I had per month has dramatically decreased. I remember being told, having 18 seizures in one day, going into status epilepticus, having my heart restarted -- it was before you were born, Madeline.

But since 2007, I actually have a new grasp on things, a new feel for life, a new excitement about being a mom. And even though I suffer from short-term memory loss and I still feel like I'm 18 sometimes and I want to go climb trees with my daughter, I'm 31 and can't do that. But I'm actually

excited now to be a mom and actually realize that it's been four months since my last seizure. If I can make it another two, I can get my driver's license and we can do things. We can go to your friend's house. We can go grocery shopping without having to rely on people and pay the extra gas money just because we just don't like taking advantage of people. And it almost felt like a curse to me before I had my stimulator.

But if this goes through, if you could approve this, not only will it help others out there, it will help me and it will help my daughter, to show us that good things do happen while you wait. And it's just a battle that everybody goes through.

And my daughter actually wrote a speech on her own. I'm going to read it for her because she's a tad shy. She wrote this on her own, thinking that she had to talk. So I'm just going to read it for her.

"My speech. My name is Madeline. I am Christina Goodman's daughter. I am nine. When she was pregnant with me, she had seizures almost every day. Luckily I came out healthy.

"When I was about four, my mom had her surgery to reduce her seizures. And although I don't remember how bad things were before her surgery, I do know that the occasional ones she does have are very scary, and I know, without her implant, she would have seizures all the time, and I don't think I could handle that. Having the NeuroPace allows her and I to have the closest thing to a normal life, and I, Madeline Goodman, am very thankful for

that."

She wrote that all by herself. I'll give that right back to you.

Thank you, honey.

When I try to wake her up in the morning to go to school, Madeline, come on, come on, get up, but yet, when she senses I'm having a seizure in the middle of the night, she's up like a firecracker. In fact, if I were to get another place, which I'm hoping, she would still like us to have baby monitors, not for her, but for me, because she loves her mommy.

But I just want to thank NeuroPace, and I want to thank Dr. Jobst. I want to thank everybody that came here today. Thank you for letting us talk about this and hear our cases about the NeuroPace stimulator, and I hope you can approve it.

Thank you.

DR. YANG: Thank you.

Dr. Ashwini Sharan, American Association of Neurological Surgeons, the Congress of Neurological Surgeons, and the American Society for Functional Neurosurgery.

DR. SHARAN: Okay, thank you for the opportunity to come to speak to this very diligent group. And thank you for the opportunity of being part of the process. And today I represent the comments certified by the American Association of Neurological Surgeons, the Congress of Neurological Surgeons, and the American Society for Stereotactic and Functional

Neurosurgery.

As part of the disclosures, the statements that I'm about to give are done by Dr. Peter Konrad, a neurosurgeon at Vanderbilt University, and myself. As part of the disclosures, we were a clinical site in the Phase III RNS study, and I was the implanting neurosurgeon. And I'm also a founder in a company called ICVrx, which is a startup, not-yet clinical company developing drug delivery for intractable epilepsy. And I also serve on advisory boards and consult for Medtronic, Minneapolis.

The major points that I want to make, that we've heard today, is we also believe that there is a large number of patients with medically intractable epilepsy who are in need of treatment options. Neurostimulation provides a reversible and safe treatment option.

The NeuroPace RNS System has performed a respectable trial demonstrating efficacy in both placebo-control and open-label period and showed sustained reduction in seizures during a long-term follow-up period.

I want to remind the Panel and the audience that a prolonged placebo-control period is not practical in this type of surgical trial. The FDA and Panel should consider the limitations of randomized studies and consider the prolonged data when considering adjunct treatment to this type of patient population.

Major points also: we believe that neurostimulation is safe. Neurostimulation has over 20 years of device safety records. There are

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definitive treatment recommendations, algorithms, and experiences in dealing with any of these issues. We heard about these complications that can happen with the surgery. We are truly aware of how to deal with these problems and help our patients through those problems when and if they exist.

The NeuroPace RNS System has demonstrated safety in a group of patients that have previously failed medically and in many cases surgically. And the study is among the largest, if not the largest, study performed in neurosurgery to date for medically intractable epilepsy.

Patients need options. I'm speaking as a doctor. Patients want treatment options that are not more medications. Given the limited options in patients who have failed antiepileptic medications, and have failed or are not candidates for surgery, as physicians, we are often left asking, what can we do? Sometimes the answer is often nothing. However, the practice of medicine, I emphasize, the practice of medicine is not scientific, as everybody would like it to be. It is not parenthetical and should be collaborative with our patients.

As such, given the obvious medical and socioeconomic dangers of intractable epilepsy, most physicians want to treat, most physicians will treat, most patients will want treatment.

There was also a seizure reduction in the sham group when the device was implanted. Seizure reductions were more than 50% after one and

two years. This is one of the features of stimulation that is so exciting to us. It gets better over time. We just need the opportunity to learn more about it. Therefore, we have to recognize that open-label, long-term data is important as part of the adjunctive treatment.

This technology is a first-of-its-kind technology to provide closed-loop feedback neurostimulation, potentially available for U.S. patients. It represents a significant technology upgrade when compared to any presently implantable neurostimulation device available. This technology, like we've heard, will also really help us understand the true burden of chronic medically intractable epilepsy on patients over a long period of time, by allowing us to have access to chronic electrocorticography.

I wanted to just share an example. Patients with identified epileptic focus in an eloquent area of the brain most often will not be offered resective surgery. We implant grid and strip electrodes. They're incredibly brave to undergo the surgery that they go through. And then, at the end of this operation, the only option that we have, as you see on the screen, on the right, is to do what's called multiple subpial transections where we make a rake through the brain. That is the current treatment offered, that we offer some patients who have focal onset seizures from that area.

In this new world, we envision a case where we implanted NeuroPace on a young gentleman who had his epilepsy localized after going to grid and strip implantations, as you see on the upper right, all of those

electrodes and wires put on the brain, being told that we cannot do multiple subpial transections because of the risk of deficit, and that patient was given a NeuroPace device and offered a chance of therapeutic result.

NeuroPace is a real option. A neurostimulation approach offers a reversible, non-damaging approach to a very difficult problem. I want the Panel, the FDA, everyone, to realize that data is important, but it's only one part of the practice of medicine.

Thank you.

DR. YANG: Thank you.

That concludes our scheduled speakers. Does anyone else wish to address the Panel at this time?

(No response.)

DR. YANG: Okay. If not, then I now pronounce the Open Public Hearing to be officially closed.

To the Panel, would any of the Panel members like to ask any Open Public Hearing speakers a question at this time?

(No response.)

DR. YANG: Okay. Then I now pronounce the Open Public Hearing session to be officially closed, and we will proceed with today's agenda. So we will now begin the Panel deliberations.

Although this portion is open to public observers, public attendees may not participate except at the specific request of the Panel

Chair.

Additionally, we request that all persons who are asked to speak identify themselves each time. This helps the transcriptionist identify the speakers.

Is the Sponsor prepared to respond to the Panel's questions posed this morning, specifically from Dr. Petrucci, about the education level, and Dr. Rogawski, about longitudinal data?

DR. MORRELL: Yes, I am. We have a slide that will be coming up for Dr. Petrucci that represents the educational level for the patients in the study.

This shows the years of education for all subjects and also split out between treatment and sham. You can see that the majority of subjects were able to complete high school, and there were some patients who were not.

If there's no additional questions about this slide, then I'll go on. Dr. Rogawski wanted to see examples of patient case subjects, and Dr. Nikhar had wanted to see a profile of the seizure-free patients, so I'll combine my answer for both of those.

I'm going to show you, in the interest of time, three patients. This is a non-responder. This is someone who did not have a response. This was a 53-year-old individual with 31 years of epilepsy who had onsets in both mesial temporal lobes. He entered the study with 5.7 seizures per month at

baseline and experienced only a 59% reduction in the most recent 84 days for which we have data.

To explain the convention of this, which I should've started with, what you are seeing, the arrow indicates when stimulation was begun. Prior to that is the baseline. The red marks represent number of seizures, and what you see on the X-axis are dates. So this spans from 2006 to 2011. The blue lines that you see, the vertical lines, represent when stimulation programming was changed. So in this case there were more frequent stimulation adjustments early on in his course than later.

Here is an example of a patient who has an intermediate response. This is actually one of the subjects that was identified as influential in FDA's analysis. This is a 42-year-old individual that had epilepsy since the age of nine. This person had only simple partial motor seizures that began in the frontal lobe and had very frequent seizures at baseline, as you had heard, 271. This individual had a 62.9% reduction in seizures with treatment.

And, again, you'll see the same convention with stimulation on and then following that the reprogramming. So this individual had a sufficient response, that iterative reprogrammings became much less frequent in the time period spanning from 2008 to 2011.

The final subject, getting to one of Dr. Nikhar's questions, is someone who became seizure free. This is a 23-year-old individual with nine years of epilepsy. This individual also had bilateral mesial temporal sclerosis

with complex partial seizures. There were no medication changes in this individual, four seizures per month at baseline, and from the time of enrollment, 2008, became seizure free in March 2011 and is to this point.

This probably also gets to some comments earlier about how often do people need to have this adjusted. In this case also, with the blue vertical lines, you see that reprograms are more frequent early on, and then as the response improves, they become less frequent.

I also do need to bring to your attention errors on two of FDA's slides. The first is on Slide 64 in the handout we provided. This shows the GEE with the modified model, and the empirical p-value FDA provided in this is listed as .056, but the actual p-value is .0056.

The second concern is that on the handout we have, FDA Slide 66, FDA presents the mean percent change on this slide, which was not a pre-specified secondary endpoint. What was not presented was the mean change, which was a pre-specified secondary endpoint. And the mean reduction in seizures in the treatment group was 11.4, and the mean change in the sham group was 5.3.

Thank you.

DR. YANG: So, also for the Sponsor, we had Dr. Cavazos, Privitera, Engel, and Rogawski, who had some further questions, so I'd like to take those now, in that order.

Dr. Cavazos.

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DR. CAVAZOS: Just a simple observation that nowhere in the Sponsor or the FDA data there was any information about the number or response of race, ethnic, or gender. And there was one slide that said gender was 48%. But this is an important issue, given the fact that there is actually significant disparities of care and access to care, and that was something that should have been expected. I don't think that there's a biological basis necessarily for that, but it is certainly something that should have been included in the materials.

DR. YANG: Would you like to address that?

DR. MORRELL: Yes. We did not collect data on ethnicity or race. We did on gender.

DR. YANG: Dr. Privitera.

DR. PRIVITERA: First, I'd like to see if the NeuroPace people have any comments about my question before, related to the implantation effect or surgical effect, in other words, that this was a major confounder, I think, at least in the analysis of efficacy.

And can you explain to us, in your review of the data, are there any kind of reasonably good evidence-based data about the magnitude or time course of the implantation effect? That's one question. I'll let you answer that first.

DR. MORRELL: There is a small amount of literature which is provided and referenced in your briefing materials that we provided. But

largely, this is observational, the patients who have been evaluated for epilepsy surgery, so there's very little.

I think the most relevant data would be in the Fisher et al. manuscript that came from the SANTE trial, deep brain stimulation with epilepsy, and they did -- our trials were run concurrently. The experience of one could not inform the other. And in that study there was an implant effect, an apparent implant effect that persisted for a similar period of time as what we saw in our study. But that is the best of the data.

This was the first experience with such a device. In retrospect, I think going forward, implant studies and neurostimulation studies might be designed differently. But when we designed the study in 2005, it was based on our best understanding.

DR. PRIVITERA: The second part of the question also relates to or may also relate to that. So one of the things that was a little surprising to me is the discrepancy between the percent reduction in seizure frequency and the responder rate, because in clinical trials usually they are fairly correlated. Like in most of the trials, you see the percent change and see the frequency is relatively close to the responder rate. And FDA has made the point that they consider responder rate a very important measure of effect.

Do you have any comments about the lack of effect that we see on the responder rates?

DR. MORRELL: Yes, let me show the data displayed in four

ways. This represents the mean change, which is to the upper left. To the right of that is median percent change. Then the bottom is the percent change by the GEE model as pre-specified. And then to the bottom right the percent change by the modified GEE. And I think what we see here is that the overall response is very similar no matter how we look at it.

And now your question was specifically to responder rate. And the magnitude of the responder rate in the treated group, not the difference, but the actual magnitude of the reduction in just the treated group, was quite respectable for epilepsy therapy trials. And the lack of an ability to show a difference between the responder rate, I believe, is attributed to the fact that there was a considerable response in the sham groups, particularly early on, and because responder rate is far less sensitive to variability, which we had a great deal of in this trial, than are these other measures of percent change.

DR. YANG: Dr. Engel.

DR. ENGEL: Yeah. I'd like you to speak to one of the criticisms that Dr. Rodichok had, which could be really important, and that's that you didn't provide any information about the specificity and sensitivity of detection.

And I wondered if you had any idea, in patients where this was not effective or in situations where it wasn't effective, how often it was due to the fact that the stimulation didn't stop the seizure, or how often was it due to the fact that the seizure was not detected? Because if it's the latter, it

means that in many of these cases, perhaps you have the electrodes in the wrong place. And that would suggest that in the future, this could be much more effective if you had better localization.

DR. MORRELL: Yes. And as Dr. Bowsler said, we did do sensitivity testing on recording electrocorticograms before. That was not part of this trial. And I think that what I have to speak to is what this technology does and does not do.

So the idea of detection sensitivity and specificity are not applicable to this therapy the way it's being provided and with the technology that's available. We cannot know which treated electrocorticographic patterns would have evolved into seizures, first of all. Patients have many interictal epileptiform discharges that are treated. The average number of individual stimulations delivered in a patient is 600 a day, each of them being 100 ms. But it's considerable.

So how many of those had to be treated, you know, we really don't know. I think we have to start thinking about this less as termination of seizures and more as neuromodulation.

But technologically the limitation is that it does not provide continuous electrocorticographic recording. The neurostimulator has sufficient memory to store 30 minutes of electrocorticographic snapshots. The physician tells the device what it wants it to store, typically samples of 90 seconds apiece, but it doesn't obtain it continuously.

The patient is told to upload their information on a regular basis, and when that memory is cleared, it will restore 30 minutes. But at this point it is not a continuous monitor, and therefore we can't know what happened when we don't see the data.

DR. ENGEL: But you do know when the detection occurred, correct?

DR. MORRELL: We have numeric counters for detections and for stimulations that are never overwritten and are there always.

DR. ENGEL: So when a patient has a seizure, you should know whether that seizure was detected or not.

DR. MORRELL: I see what you're saying. Yes, we can do it from the numeric counter, and actually even probably more precisely, the patients have a magnet, and they're asked to swipe that over the device when a seizure occurs, and that instructs the neurostimulator to store a sample of that.

And I would tell you that I'm not in a situation to provide you a quantitative assessment of that. But certainly, in most individuals, when they have a clinical seizure, we do see an electrographic seizure, and we see that the responsive stimulation has not been able to terminate it.

So does this terminate every discharge that then goes on to be an electrographic or clinical seizure? No.

DR. ENGEL: But how often do patients have seizures where

there's no detection? Does that happen?

DR. MORRELL: I'm not prepared to answer that quantitatively, but I'll say that yes, absolutely, in my experience it does. It doesn't happen terribly often.

There were lead revisions in the trial, and those revisions to change the detection and stimulation, either changing the connection from leads that had been connected to leads that were previously connected or even to implanting new leads. And all together there were 24 patients that had changes in connection to improve detection sensitivity, and there were five patients who, in fact, had new leads implanted because the physician wanted to improve detection sensitivity.

So certainly not in every case did the investigator feel the detection and the stimulation were being delivered to the optimal patient.

DR. ENGEL: What I'm suggesting is that if those data are available, and it sounds like they are, and you were able to determine that there was a subset of patients where the detection didn't occur, then that doesn't speak to the effectiveness of the device. It speaks to your ability to localize the epileptogenic abnormality appropriately. And those patients could be removed from the study, and you would have a different view of how effective the device is when the electrodes are in the right place.

DR. MORRELL: You know, as several comments today have alluded to, this is obviously an extraordinarily rich database that we have.

This is the first experience with chronic ambulatory recording now in over 1100 patient-years.

For purposes of this meeting today, of course, we're addressing the clinical trial. The clinical trial was assessed to determine these clinical outcomes, but certainly we are investigating this database. We will continue to do so. And I think that what we learn from it will only, as you allude, improve our ability to apply this therapy.

DR. YANG: Dr. Rogawski.

DR. ROGAWSKI: I have two sets of questions. The first one relates to a comment that you alluded to, Dr. Morrell, about how it appeared that, over time, the programming physician got to understand perhaps better how to modify the parameters in such a way that the device had better efficacy. And I wonder if you could speak a little bit more to that and whether there's any actual data from the open-label component of the trial that could demonstrate to us how that process would occur.

DR. MORRELL: We are performing those analyses at NeuroPace in collaboration with our physician-investigators. This is ongoing research. We are very interested in understanding whether there are specific stimulation parameters in specific areas that would refine our approach. Again, today I'm not able to speak to that, but we're absolutely committed to do that.

I do want to make one point, though, that within the study,

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although this technology is what I call, as a neurologist, overbuilt by the engineers, it has a lot of capabilities. But in the trial, actually very few of those were -- those that were adjusted were fairly limited. The vast majority of patients were stimulated at 100 Hz or 200 Hz. The pulse width for the majority of patients was 160 μ s. Almost everyone. The burst duration was 100 ms.

What actually was adjusted in most cases was the current amplitude. And typically the practice would be that it would be programmed to the initial stimulation settings, which would be 200 Hz, 160 ms, and 100 μ s. And then they would adjust the stimulation up in 5 mA increments, similar to what we do with the VNS and what's done in DBS with Parkinson's disease. So there is an opportunity to look at adjustment of these other parameters. But within the trial, that is really where the bulk of the experience is, is in adjusting the amplitude.

DR. ROGAWSKI: And that really does lead into my second set of questions, which is based on a concern I have from the proceedings today, which is that I get a sense that we really don't fully understand how to use this device properly. And let me make a hypothesis and see if perhaps you have some data that might speak to this, or some ideas about it. And I'd like to ask the FDA to respond as well.

In listening to the data, I get the sense that what may be going on here is that the device tends to work much better when the seizure

frequency is greater. And in those two examples you showed initially, that hypothesis was borne out because the initial one was .2 seizures per day, which you demonstrated that there was no effect, and then the intermediate effect was a much higher seizure frequency. And then we had the example of the patient who had the very, very high seizure frequency in the sham group that did seem to respond.

So what I'm wondering is, does the total duration of stimulation have a relationship to the efficacy of the product? In other words, five seconds a day might not be enough stimulation on average, but there seems to be some patients who probably are getting a lot more stimulation. Particularly that high-frequency patient might have had much, much greater duration of stimulation. And I'm wondering if that's what's required to demonstrate an effect on behavioral seizure activity.

So I guess the question is, did you do an analysis looking at the total duration of the stimulation?

And then that really raises a question in my mind as to whether we really need to be stimulating in relationship to electrographic activity, but whether sort of a free-running device might be the actual best way to use this system, and you don't really need to have a responsive neurostimulator, and basically use it essentially like the vagal nerve stimulator, where we stimulate continuously.

And that raises a question, I guess, for the FDA, and that is how

would the FDA approach it? What if the best way to use this device is in a much more sort of simple free-running fashion? If we concluded that, how would that change your view on the approvability of the --

DR. YANG: Dr. Rogawski, why don't we let the Sponsor answer your first question, and then we'll go from there.

DR. MORRELL: So I want to clarify. We do not think that baseline seizure frequency predicts the likelihood of response. The figure that was provided by FDA is a descriptive analysis of raw mean scores and not proportional. So it does show that some patients with 200 seizures a day go down to 100. It's a mean drop of 100 and a percentage drop of 50. And it also shows that patients with eight seizures at baseline go down to four.

So, of course, if you're looking at the raw mean, those few patients with very high seizure frequencies are going to completely dominate that analysis. We looked at baseline seizure frequency and did not find that there was any predictive power of baseline seizure frequency as far as response.

As far as the total duration, I mentioned that typically it's less than five minutes. It can be seconds to up to 10 minutes. Rarely more than that. We find that we will continue to do the analysis, but there is a suggestion that patients may actually require less stimulation as they do better. But that is an analysis that will go forward.

And as far as continuous stimulation, this technology, we

cannot deliver continuous stimulation. It's a limitation of the battery. In order to have a cranially implanted device, continuous stimulation is not necessary. And I think that we have shown that this concept of responsive stimulation not only works, but we are not seeing the types of effects that we were concerned we might see when you stimulate the brain, such as cognitive problems or mood or treatment-emergent adverse events in these domains. We do not see that.

So, you know, I think that your theoretical discussion is of great interest, but today, with this technology, we've demonstrated safety and effectiveness.

DR. YANG: Thank you. If you could step --

DR. ROGAWSKI: Let me just clarify it in my mind. So did you do an analysis where you actually looked at the total duration of stimulation during the day, let's say, and try to correlate that with responsiveness?

DR. MORRELL: Yes. You know, I don't think that we can present that today. This is not data that's been provided to FDA, and it's not the data that we submitted our premarket approval application on. This is within the realm of ongoing research that's being done by our investigators and by NeuroPace. But as of today, I'm not prepared to provide you an authoritative answer.

DR. YANG: I'm going to ask the FDA, however, if they would like to comment, just regarding the data that is provided, on the question

that Dr. Rogawski raises about baseline seizure frequency affecting the results.

DR. RODICHOK: I'll try a clinical answer, and if we need one, we'll have a statistical answer.

From my clinical point of view, one of my concerns when I saw the high seizure frequencies was whether or not there was a subgroup of people who were driving the result, that might represent a subpopulation that we might focus on, whether there was more effectiveness in that group. I thought I might know who they were, that they were probably extratemporal, worst fear, non-lesion, intractable partial seizure patients.

So from a clinical point of view, we've been continuing to look at that for that reason, from a clinical point of view. If your question is statistical, I'll leave it to Scott.

DR. MILLER: So I would just reiterate the reason, statistically, I was interested in that sort of an assessment was basically because the GEE model is looking at sort of an average over all the subjects, of their slope from baseline to the end of the blinded phase. If the slope is about similar for all subjects in, say, treatment or sham, were flat or downward improving, then averaging over those seems reasonable.

But if there are folks that are going up, so that you have a potential interaction, a qualitative interaction where some go down and some go up, then averaging it, particularly in that group, the greater than 28,

could lead to basically an attenuation of the estimated treatment effect or overestimating the effect relative to the sham.

That was the motivation I had, was to just get a sense of how well the data fit. I wouldn't be able to comment on whether that had something to do with the amount and duration of stimulation. That was just in terms of motivation --

DR. ROGAWSKI: Right.

DR. MILLER: -- and in terms of the number of baseline seizures.

DR. ROGAWSKI: But, you know, beyond the sort of statistical issue here, if this device is only useful for patients who have high seizure frequencies, then we ought to know that, because if the device is approved, then it's going to be implanted according to the way the Sponsor defines the indications, and a lot of people who it's not going to be useful for in terms of helping reduce their seizure frequency and subjecting them to what are considerable risks.

So is there any sort of comment that the FDA might have on the utility of the device, based upon the data that we have, with respect to different seizure frequencies?

DR. YANG: Dr. Krauthamer.

DR. KRAUTHAMER: Victor Krauthamer.

I would just say, if we start to dissect into subgroups, it's probably not a valid analysis. For example, if we look at a hypothesis of

duration of stimulation versus seizure reduction, that may be a hypothesis that we could look at the data for, and if there's something that bears it out, FDA would normally want a prospective study on something like that.

The same thing on seizure groups. This is one group. The reason Scott subdivided it, as my understanding as a non-statistician, was to test the assumption that all groups behave the same for the model.

DR. ROGAWSKI: Yeah, well, this really worries me. I mean, if this device is not useful for a large proportion of the patients in which it might be implanted for, that is a problem. If it's beneficial for some patients, it's a device that -- it's a product that we would like to have made available. But if there's a large proportion of the patients who it isn't useful -- and you know, looking at Slide Number 107, the FDA Slide Number 107, this kind of gets at the question that I was asking about, looking at each patient individually. And it's hard to read that slide because most of the patients are down sort of near the bottom.

But it looks to me like the vast majority of patients pretty much were unchanged over the course of treatment, and they tended to have very low seizure frequencies, whereas the patients that look like they're responding are up in the 200 to 300 range.

DR. YANG: Just one second. I'm going to ask the statisticians on the Panel to comment on this analysis, this discrepancy.

Dr. Toledano and Dr. Connor.

DR. ROGAWSKI: Yeah, yeah.

DR. TOLEDANO: Let Dr. Connor start.

DR. YANG: All right, Dr. Connor, go ahead.

DR. CONNOR: Okay. So I think a lot of discussion is about FDA Slide 104, which kind of shows the mean trajectories over time for high, medium, low or medium and low. And I think if we saw that like on a log scale, it would be much more clear, because right now that scale is dominated by the high group, so it's hard to discern the ratio of effect. And the models that we're talking about are all essentially a ratio of effect. And when we're looking at means with low counts, that gets obscured. So I think looking at 104 on a log scale would probably be helpful for everyone.

But I think there's also a way that FDA, you know, you could group these into four groups, Scott, and then you look at essentially these basically by the baseline quantiles and see if there was an interaction with treatment effect.

DR. YANG: We're trying to get the slides up.

DR. CONNOR: No, my question was, did you ever, say, group subjects into quantiles based upon baseline number of seizures and then run the model, looking if there was an interaction with that and treatment effect? And that would tell us, for instance, if there was a treatment effect in the high groups, but maybe in the low groups, which is Dr. Rogawski's question.

DR. MILLER: So I did do a follow-up analysis of this by

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quantiles. I have a slide of that, but I just need to preface it. That's not something the Sponsor has previously seen.

DR. CONNOR: Okay.

DR. YANG: One second. Can you hold that question until we're done with the statisticians?

DR. ENGEL: Well, it's to the statisticians.

DR. YANG: It's to the statisticians, okay.

DR. ENGEL: Okay, I'm statistically challenged, but as I understand it, FDA is looking at number of seizures, and the Sponsor is looking at the percent reduction, and it seems to me that the only thing that's relevant here is the percent reduction, and that's what I'd like to see you guys discuss.

DR. CONNOR: Right. And the question I ask about looking at the model in quantiles will do that, and it will essentially ask the question, does the percent reduction differ amongst high, medium, and low groups? And I think that's what Scott said he's done, that he's looking for.

DR. KRAUTHAMER: We are looking at everything. If you look at the Executive Summary, we do cover a percent reduction and everything. So we're looking at all of the endpoints, and I think clinicians look at percent reduction and responder rates as primarily involved.

DR. ENGEL: Percent reduction is not going to be biased by seizure frequency.

DR. KRAUTHAMER: Correct.

DR. ENGEL: Whereas number of seizures is biased by seizure frequency and is meaningless.

DR. YANG: Okay. Sorry, go ahead.

DR. KRAUTHAMER: I was going to say that may have been what was pre-specified.

DR. YANG: Dr. Toledano, do you want to add to this fray?

DR. TOLEDANO: Thanks, Dr. Yang.

Okay. So this is Dr. Toledano.

First of all, I do worry about percent decrease in seizure frequency, because if somebody's got a hugely high frequency, it's much easier for them to get -- we hope it's much easier for them to get that down. If you're already having a low frequency of seizures, it's kind of hard to get that even lower. There's not as much room to move.

One thing that has bothered me as sort of a disconnect during today's deliberations is that it's not just about frequency of seizures. For the physicians and for the patients, it's about the severity of the seizures, and it's about the sequelae after each seizure. So sorting out everything just limited to frequency of seizures is kind of bothersome.

There was one thing that definitely bothers me about the cherry picking and the data dredging. So when people go into this with the best of intentions of helping patients who need an alternative, there's one

group where if they say, you know what, this model didn't work out, this pre-specified model didn't work out, let's sit down and let's talk about it and let's figure out the right analysis to do, let's work on something post hoc, let's see if there are observations that unduly influence the results, they're praised. And there's another group where if they do the same thing, they're lambasted. And that asymmetry, as somebody who loves math and fairness and impartial judgment, really, really bothers me.

If we're trying to get to the answer, we have to get to the answer and not the cherry picking and the data dredging and the lambasting and the praising one side and not praising the other side.

DR. YANG: Let me ask Dr. Afifi, as our other statistician, to comment here.

DR. AFIFI: The last question that was asked, I think Slide 105 of the FDA answers it. These are the four groups by frequency of seizure at baseline, and what's shown there is the ratio, the rate ratio. So I think that answers your question.

But I have another question, but that's fine.

DR. ROGAWSKI: Could I ask Dr. Afifi a question?

DR. YANG: Let me remind you, I understand this an engaging discussion, but our transcriptionist needs to know who you are before you speak. So if you could state your name before you speak.

DR. ROGAWSKI: Sure, sure. This is Dr. Rogawski.

The comment was made that it's easier to show a reduction if you have a higher rate. And is what's seen here on Slide 105, where it does look like with higher rates you get a greater magnitude effect and they're more statistically significant than the lower rates? Is that what's expected based upon the floor effect that was talked about, or is this telling us something about the response to higher rates versus lower rates?

DR. AFIFI: I don't think so, because if you start with a rate of three, half of it is one and a half. If you start with 150, half of it is 75. So if you agree that the rate ratio is what we want to look at, then it doesn't matter what the starting point is.

DR. CONNOR: If I can answer that, too.

DR. ROGAWSKI: Yeah.

DR. CONNOR: In some ways I --

DR. YANG: Dr. Connor, state your name.

DR. CONNOR: Yeah, sorry. Jason Connor -- respectfully disagree a little bit with that. I mean, there is a range, and if you get in with three seizures per month, you know, you can't do a lot better, right? And maybe before that you were a six or a seven, you know, so that if you're down low, you can go down, but it's easier to go up, versus if you were one of the really high ones, you can get a lot lower, and maybe that's a little more likely.

So I think if you ask me, even if this works, what would plot 105

look like, I would say probably like 105, if I were a betting man, which I am. So I'm not surprised that the treatment can be bigger. If you're really bad, we can help you more than if you're just a little bit bad. So I think that's not a surprise.

DR. YANG: Dr. Toledano, do you want to weigh in here?

DR. TOLEDANO: So it's Dr. Toledano.

Can I just agree with Dr. Connor on that one?

DR. YANG: Yes, you may.

Okay, Dr. Engel, back to you. Does that help clarify your question at all?

DR. ENGEL: Yeah. If you're looking at this graph, first of all, there are very few patients in the top three groups. But this clearly shows that there's an effect at the very low levels, too. So I would not conclude at all that this is only effective if they have very frequent seizures.

DR. YANG: Okay, back to --

DR. ENGEL: Is that fair?

DR. YANG: Let me just finish this up. Back to Dr. Rogawski. This all started out with your question. So have we answered that question?

DR. ROGAWSKI: Thank you very much.

DR. YANG: Let me go down the list here because we have a few other people.

Did you have a comment with relation to this question?

(No audible response.)

DR. YANG: Okay, all right. So let's see. Next up is Dr. Connor, actually with his question for, I believe, the Sponsor but maybe FDA as well.

DR. CONNOR: Yeah, I'll warn you that my question is way easier than Dr. Rogawski's question. It stems from something Ms. Hogue said when she described Paul's seizures, what maybe used to be a big or long seizure is something that looked like a sneeze now.

My question is, in the data, is that a seizure?

DR. MORRELL: Yes. Yeah, anything that is observable, that causes any observable change in behavior, would be a seizure.

DR. CONNOR: Okay, so I think that answers the question. So that's very interesting to me now, because if that's still a seizure and that still counts against it, we're not measuring improvement. So it sounds like there's dramatic improvement in what would've been a bad seizure and is now -- you know, we all sneeze and it's no big deal, right? But none of the data we're seeing, we're not being allowed to factor that into the question of does this thing work?

DR. MORRELL: No.

DR. CONNOR: How am I supposed to think about that?

DR. MORRELL: The challenge, of course, with epilepsy trials is you get count data and we count them by simple partial in this study, motor, where there's an alteration in motor function, and complex partial, where

there's an alteration in awareness, and generalized tonic-clonic seizures. There is a range of severity within in each of those categories, and most of the patients who came into the study had more than one type of seizure.

So looking at shifts in severity is really very difficult to do. It's a challenge for all epilepsy therapy trials.

DR. CONNOR: Okay, thank you.

DR. YANG: Dr. Connor, did you want to address that same thing to the FDA, based on the data today, or if so, restate your question.

DR. CONNOR: No. I mean, I think that answers the question, but it's a very interesting thing. It sounds like there's potential improvement that we don't have data to act upon.

DR. YANG: Okay. So next we have Mr. Mueller.

MR. MUELLER: Yes, David Mueller here.

I'd like to go back to earlier in the morning when Dr. Toledano and Dr. Krauthamer, you were discussing the regulatory history of this whole IDE and the changes back in 2005, and Dr. Krauthamer mentioned that the 2005 meeting was not a formal agreement meeting, and I'm sure he's right.

But from a pure regulatory -- and that's kind of my hat, my expertise. In FDA parlance, there are different kinds of meetings, and if you want to have a "formal agreement" meeting, it takes a long time to get set up. There are certain rules you have to do. There are certain things. And once that formal agreement is written, it's in stone, which okay, fine, that's

good.

But from a practical standpoint, as far as getting in to see the FDA, getting some general agreement or a gentleman's agreement or understanding -- and we all know it's not a formal binding agreement, but there are times when you have a meeting just to go in and talk and people will agree in principle. And I know it's not binding, and I acknowledge that. But just to kind of answer what your earlier question was, is there is a distinction of a formal binding agreement meeting. That's a special deal that you have to set up.

So I wanted to just -- and Dr. Krauthamer, can you agree or disagree?

DR. KRAUTHAMER: Well, we don't see that as that relevant. We're getting now into the history of it, and we're looking -- we really want to look at the data. But it was a verbal meeting.

Generally, when we have deficiencies, we send deficiencies and get answers back in writing and then we respond to them. Other than the meeting minutes, there was no follow-up or continuation.

MR. MUELLER: Right. And in a formal binding agreement meeting, then there's the formal --

DR. KRAUTHAMER: Yes.

MR. MUELLER: -- agreements written up and everything.

DR. KRAUTHAMER: Right. Or a protocol is sent by the sponsor

to answer a deficiency where we could respond.

MR. MUELLER: Right. I just was trying to explain.

DR. KRAUTHAMER: I mean, I don't think the history is that relevant, and we have a very good dataset in front of us.

MR. MUELLER: Right. And that's kind of the next point I wanted to get to from, again, a regulatory sense. And that's my hat.

DR. TOLEDANO: So this is Dr. Toledano.

I just wanted to kind of let you know what my question was about when I asked that.

DR. KRAUTHAMER: Sorry to interrupt, but we just really want to focus on the data in the PMA, not --

DR. TOLEDANO: Yeah, that was exactly my question.

DR. KRAUTHAMER: Okay, good.

DR. TOLEDANO: So I was not asking whether it was a binding protocol agreement meeting, and I'm well aware of what those are, and I've been involved in studies that used them.

What I was asking was why is it that the Sponsor says that the FDA agreed to GEE Model 8 and the FDA says no, we didn't. So not in terms of a formally binding agreement, but what is that miscommunication, and what exactly happened at that meeting; that's what I was asking about for this particular application.

DR. KRAUTHAMER: I wouldn't say that's in the data in the PMA.

DR. YANG: I think that's outside of our focus today. Our focus today is really on the data that is presented here.

MR. MUELLER: Right. And as far as our focus today, we are looking at the PMA data, and I agree, and the focus is that the clinical data -- to get a PMA approved, you have to provide valid scientific data for clinical, and in FDA regulations, 21 C.F.R. 860.7, FDA defines what is valid scientific evidence. And that does include randomized, prospective, double-blind, controlled clinical studies, yes. But then it also goes down to the next step, which is non-randomized. And then it goes down to the next step and the next step, all the way down to well-controlled case histories.

Now, these data here are significantly, maybe even statistically -- I'm not that good a statistician, but these data are significantly better than well-controlled case histories to demonstrate valid scientific evidence that the device does work and it is safe and effective.

So now my second question, which is again with the data, is the two outliers that we keep talking about from a statistics viewpoint. In the Sponsor's presentation -- and then that's even on the one we just saw with the red line going way up high -- the Sponsor Slide C-73, where they removed one patient, they removed two subjects, on and on and on down, is different than the FDA's presentation, where they removed the one and the two patients on the data. And since I'm not a statistician, I'm confused by that. So I'd like the Sponsor and FDA to address that.

DR. YANG: Why don't we start with the Sponsor. I believe it's Slide C-73, which is up right now.

DR. MORRELL: Yes. So the way that FDA performed the Cook's distance is somewhat unconventional. It's not conventional to remove two subjects at a single time from the model because every subject has influence. So if you remove one subject, a new subject may be the next influential, which is what we did where the Cook's distance analysis was refitted after the removal of every subject, and it shows the retention of significance, even with removal of considerable subjects.

I would like to highlight in here, I think we have the two subjects that were from FDA's removal, which in our analysis would be -- it's the same first subject. Doing the Cook's distance the way we did and the way FDA it is the first subject is removed. But if we do it using FDA's methodology, which is you would do Cook's distance once and then just go down the list, then it would be removing Subject Number 4 doing it the way that we did it, which is to refit it. And if it's done in this way, removing those two subjects does not take away significance. It retains significance. And, again, no matter whether you do the Cook's distance the conventional way or the less conventional way, the treatment effect remains consistent.

So I think this is a very strong statement about the robustness of the data, that it is able to survive this type of a subject exclusion deviating from the intent-to-treat analysis, which is the one that we provided.

DR. YANG: I'd like to direct that question to the FDA as well, exclusion of patients. If you have a slide number to put up, that would be --

DR. MILLER: So this is Scott Miller again.

The exclusion that the Sponsor has referred to as unconventional, what I did was again the clustered Cook's distance, so at the subject observation level as opposed to what each subject had. In the model, they used four observations. I found that those two had the most influential of all the observations in the study, and then plotted the profiles, that those were in the presentation. I don't have the number in front of me.

The observation was that those two had a distinct pattern different from the majority of the other sham-treated subjects. That's why I felt it was appropriate to take them both out as a sensitivity analysis. I've not referred to a p-value. In terms that the Sponsor has highlighted the p-value aspect of it, I did not highlight the p-value aspect because I'm less concerned about the statistical significance because this is a post hoc thing.

What I'm looking at is, if you take them out, what impact does it have on the rate ratio? And the Sponsor has just covered that it's consistent. It does attenuate towards 1, so the effect gets smaller.

So I'm not arguing about statistical significance here. I'm just pointing out that two subjects that in the sham group got worse after the duration of the blinded evaluation period had a distinctly different pattern. And, again, the GEE model is essentially looking at the slope. So if the slope

goes down versus if those two go up, then it's going to make the overall slope look like it's flat in the sham group, when in fact there was a substantial number of subjects even in the sham group who responded. And that, therefore, results in an overestimation of the estimated relative treatment effect compared to the sham group. And so, again, it's a part of just an assessment of how sensitive the data were to those two subjects.

In terms of just dropping out one subject and then another subject and another subject, to me, I don't see the value in that approach because you're just ignoring the fact of what is causing those subjects to be influential, which I believe my approach did by looking at the profile plots and then choosing to exclude them. So that was the motivation for that approach.

DR. YANG: Does the Sponsor have a response to that?

DR. MORRELL: I don't think I need to show the slides again. Those subjects were not outliers. There were 20 such similar subjects that had the same types of seizure frequencies, except for that one subject in that third month, which we showed you. If we take that subject out, the treatment effect is the same, significance is retained.

The second subject, it is not clear why that subject was removed. It is not the second-most influential subject when the Cook's distance is performed appropriately, and that patient did not visually look like an outlier. Clinically, there was nothing about these two patients that

distinguished them from any of the others. So we will state, there were no outliers.

We stand by the intent-to-treat analysis and by ways of demonstrating the robustness of the treatment effect. We did perform this analysis of exclusion of sequential subjects, prompted by FDA's analysis, and we showed you the statistically most legitimate way of analyzing that data. The treatment effect remains consistent, and significance is not lost.

DR. YANG: Okay, let's move on, then. We have five other questions on the roster here. First, Dr. Afifi.

DR. AFIFI: Thank you.

My questions relate to a point that was raised by the FDA, and I'd like to know whether the Sponsor has some comments to make on it. They have to do with Slide Number 79 that the FDA had, namely, once the stimulation was turned on for the sham group, you would expect, if there is an effect of the stimulation, that the frequency of the seizures would go down, but they did not.

Or another way to see it is from Slide Number 84. You would expect the two lines of frequency for the sham and the treatment group to eventually approach each other, but they don't.

So I'd like know whether the Sponsor has any comments to make on that, what the explanation might be.

DR. YANG: We're trying to pull the -- I believe the slides are

trying to be pulled up. It sounds like --

DR. MORRELL: Perhaps we can show this -- no, please go ahead and then we can show our slide showing that data.

DR. YANG: Well, I don't think we can put up the FDA slide while the Sponsor is commenting.

DR. MORRELL: So I have an answer, and then I'd like to show you a slide.

So the sham group had a statistically significant reduction in total disabling seizures in the first three months after stimulation was turned on, compared to their own baseline, at $p .04$. The difference compared to the blinded evaluation period, when they were not receiving stimulation, was not significant, and I think we can explain that by the sham effect.

As far as the difference in what we showed and what FDA showed, what FDA showed you were the crude means, they were the raw means. And so with that, given the high variability in this, it appeared that the sham group never caught up with the treatment.

But I can show you this by two ways. One is a descriptive way. This is the median percent change by duration of stimulation. So recall that when the blinded evaluation period ended, the treatment group had been receiving four months of stimulation and the sham group was just turned on. So this is apples-to-apples months of stimulation.

And there is a little difference early on. I think that can be

explained by the fact that in the clinical trial, the treatment group, during those first months, came in every week for adjustment, whereas in the open label the visits were once a month. So the sham group, when receiving stimulation, had less opportunity to have adjustment of programming.

But if I can also show the responder rate slide, I'd also like to point out that we did pre-specify an analysis for this, and that analysis was not raw mean scores. It was responder rate. And I believe that's the slide we showed in our presentation and also the slide that is in your briefing materials.

And here is this. This is also five months of stimulation, and you see that after that initial three-month period, the treatment group had been seen more frequently and the sham group less frequent. They really converge after about three months of stimulation and then follow the same pattern, the same slope towards progressive improvement through the blinded evaluation period.

DR. AFIFI: Thank you.

DR. YANG: If I could ask the Sponsor to step away from the podium for a moment and ask the FDA to put up the slides.

DR. KRAUTHAMER: I just want to say that this analysis is something that we haven't seen before, and it's in this form. So it's something we'll certainly be able to look and evaluate.

Could we have the question again?

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DR. YANG: I'm sorry, what's that?

DR. KRAUTHAMER: What was the question again?

DR. YANG: We'll let Dr. Afifi state that, since he asked.

DR. AFIFI: No, I think I got my answer. I wanted the Sponsor to respond. I have no questions of the FDA at this point.

Thank you.

DR. YANG: I think the confusion is that you started out saying the FDA slide. So I think we got it now.

Okay. So we have four more, and that will probably take us to the break. So Dr. Toledano will be next.

DR. TOLEDANO: So it's Dr. Toledano, and I'm going to ask some statistical questions because the detailed statistical analysis plan is just a section of the protocol. We don't seem to have a separate whole document.

So, usually, if I'm starting a fitted GEE model or any multivariate longitudinal model, I look at what the mean structure would be, and I look at what the correlation structure would be. I would have things built in there to look at the modeling assumptions. And when I look at FDA's Slide 98, and I think the Sponsor also has a similar slide, I look at the distribution. So we have this FDA Slide 98 that says there are multiple plausible GEE models. I don't know if it's possible to pull that up. I think Dr. Miller's trying to get that up, so we'll turn there.

And this came up during the discussion of what is proof of

effectiveness. So FDA says there are eight plausible GEE models. The Sponsor, during their presentation, said they're not all plausible. Okay, great. And get the circles, all the animations. Are they all up there? Okay.

So Number 1 everybody agreed doesn't work. And that uses the over-dispersed Poisson. So I don't know why somebody goes and fits a model without checking the assumptions first, but it doesn't seem like the over-dispersed Poisson works. So now I'm ruling out everything in 1 to 4, and we go with the negative binomial.

The next thing that surprised me is that you had covariates that were used in the randomization that were not put into the model. I know you did the adaptive randomization. Usually, when we do stratified randomization, we put the stratification factors in, unless they're clinical site, because sometimes you have very sparse data site by site. So I'd like to see only the covariate-adjusted models. And there we are, there are 6 and 8, and they look fine.

So why should I be looking at Models 1 through 4 or Models 5 through 7, given that we already know the first model doesn't work and we need a better one? Who wants to take it first, FDA or the Sponsor?

DR. YANG: The FDA slide is up. Why don't we do FDA first.

DR. MILLER: All right. So I agree that the Model 8 is an appropriate model. The concerns I have are basically twofold. One, I would agree with you that adjusting for the variables in the stratification would be

something I would sort of -- especially given that it's an adaptive randomization. The issue is that the protocol didn't specify they were going to do that.

The other issue is when you pre-specify a model and don't have a contingency plan and then come in with a model, Number 8, and say here, we have this new model that's not pre-specified, so there's no guarantee where that model came from and if the justifications were beforehand or after the fact. So there's not as tight Type I error control over it. Typically, people just sort of don't think about Type I error inflation looking at multiple models. That's unfortunately not a luxury we have at FDA. We still have worry about that.

DR. TOLEDANO: Okay. So I'm going to pick up on that because that's a great start to an answer.

DR. YANG: Dr. Toledano, can I have the --

DR. TOLEDANO: Oh, sorry. Dr. Toledano.

DR. YANG: Can I ask the Sponsor to respond to that --

DR. TOLEDANO: Go ahead.

DR. YANG: -- with their slide?

DR. MORRELL: I'm going to ask Dr. Heagerty to respond to this because I know about as much as I want to know about the GEE.

(Laughter.)

DR. TOLEDANO: They're beautiful, lovely models.

DR. HEAGERTY: Probably more than she wants. My name is Patrick Heagerty again.

So my role actually was to provide information on exactly this point. I was brought in by the Sponsor in the middle of 2011. I didn't have access to the data. I took as an exercise to really answer the question, how would I have approached pre-specification on this model? How would I have made it flexible, such that it could adapt to the data in hand? And how could I make it robust?

And the questions were nicely summarized by Dr. Toledano. You have to think about the variance form. Not seeing the data, you can favor the negative binomial. It's a more flexible form. So pick that. It will adapt to the data. The Poisson has a restriction imposed upon it, number one.

Number two, if you have randomization covariates, strongly predictive randomization covariates, the rate ratio is about three. There's threefold variation when you consider different subgroups based on those three factors. Of course, you put them in the model because they explain variation. What's the consequence of explaining variation? You tighten your inference to become more precise. That's exactly what we see in this analysis. It's not a change in the effect size. It's a tightening of the precision. How sure are we that the effect size is around a quarter of reduction? If we use that information and measure the covariates on patients, we're

explaining variation and we can gain precision.

So, again, the variance form is a pretty clear one. The covariates is a pretty clear one. External, in the absence of the results, one can nominate those based on statistical literature.

And then again, the choice of monthly or daily, as Dr. Toledano points out, is not as critical. But if you make it monthly, it's much more straightforward statistically to build a model for monthly data. There's really a small number of months to consider as opposed to 180 total days.

So I think there are objective statistical criterion that lead you to the model at the top.

Number two, there's empirical considerations. You can look at the data and say, data, what do you say? And we've shown that, that the data say it's not Poisson. The variance is much bigger than that. It's more like a quadratic variance. And we can ask the data, are those baseline randomization covariates important? Yes, they're very important.

So I think, from two angles, one can identify objectively what is an appropriate model for the data.

DR. YANG: Just one second. Dr. Toledano, I'll get back to you, but Dr. Connor has a question with regard to this.

DR. CONNOR: Yeah. So I just wanted to clarify something you said at the start, which addresses part of Dr. Miller's question about Type I error. Obviously, when we get to pick whichever model we want when

we have data, Type I error doesn't exist. We don't know what it is.

DR. HEAGERTY: Yeah.

DR. CONNOR: But I wanted to clarify that you said you've basically got to understand the clinical situation and what the data looked like, but you didn't have the data --

DR. HEAGERTY: No, I did not.

DR. CONNOR: -- when you recommended Model 8 is --

DR. HEAGERTY: No. Again, I viewed my role being brought in by the Sponsor, but being brought into a dialogue between the Sponsor and FDA on what to do with a very challenging question --

DR. CONNOR: Right. So, then, would you say that given you didn't actually have the data, that Type I error control is still managed then by choosing Model 8, because you didn't know that Model 8 was going to be to the left of that line?

DR. HEAGERTY: Yeah, I would say you always have some concern about Type I error control, but I didn't give recommendations that selected a result. That's the key thing; it was in the absence of data. Based on principles, what should you choose for an appropriate model for this challenging data?

DR. CONNOR: Good, thank you.

DR. YANG: Let me go back to Dr. Toledano.

DR. TOLEDANO: Okay, so that's Dr. Toledano nodding her

head.

Can I just ask Dr. Heagerty one other very quick question? And he will actually understand it, in terms of the GEE. So there are two things, there's a variance function and there's also the correlation structure.

DR. HEAGERTY: Right.

DR. TOLEDANO: And somewhere in the protocol they talked about compound symmetry. Now, what this would do with your choice of correlation structure, for everybody just looking at the slide, you see the solid lines which are model based and the dotted lines which are empirical. If that correlation structure is wrong, that will also make those two lines very different lengths.

DR. HEAGERTY: Right.

DR. TOLEDANO: Did you talk at all about that compound symmetry and other correlation structures?

DR. HEAGERTY: Yeah, a great question. So, again, I did this in the document that I submitted to NeuroPace, which they forwarded to the FDA, and in it I actually said I would pre-specify an unstructured matrix because that's again the most flexible form. That analysis has been done and basically agrees with these data, with the exception of convergence. It's a very flexible covariance, and it's difficult to converge sometimes.

The next backup is then a very simple structure, the compound symmetric, because that picks up that common patient-to-patient variability

and seizure counts. That's the dominant feature of that correlation.

So I presented a more flexible one actually as the first choice, and then as a backup, the compound symmetric. Then empirically, one can look at the data. What do the correlations look like over time? Compound symmetric says they're approximately equal over time, and that's what it looks like in the data.

DR. TOLEDANO: So it's Dr. Toledano saying thank you very much.

DR. HEAGERTY: You're welcome.

DR. YANG: All right, let's move on to Dr. Nikhar.

DR. NIKHAR: I'm fine, thanks.

DR. YANG: Okay. Let's move on to Dr. Engel.

DR. ENGEL: Yeah, I have two unrelated questions. If you could put up Sponsor Slide 80. Again, this has to do with my statistically challenged brain.

As a clinician, this looks very impressive to me, even though it's not statistically significant that there is improvement over time in the treatment group and not in the sham group. And then look at Slide 79 for another secondary effectiveness endpoint. The same thing. And then look at Slide 78 for the responder rate, and it's almost the same thing for the treatment group and certainly not for the sham group.

Is there some way to put these trends together in some

statistical way to show that this is a significant effect?

DR. YANG: Dr. Engel, are you addressing this to the Sponsor?

DR. ENGEL: I'm addressing it to the statisticians on the Panel.

Is it fair to look at the totality of the data rather than each one individually?

DR. CONNOR: This is Jason Connor.

That's a good question. And sometimes on these I remember an incontinence study, and they reduced events by so much. But my point to the Sponsor was, well, you still are not going to be willing to go out of the house, right, if you lower incontinence from 10 to 5. So I think the quality of life stuff is important.

And looking at if a doctor could tell you, I can double the number of days you don't have a seizure, that's amazingly compelling, far more than anything a model says.

In terms of can we combine these all together, I think that's hard. I mean, there are different questions in terms of seizure-free days. Oh, I can go out of the house without worrying about all the things epileptics have to worry about.

So I think the simple answer is no, but I think looking at the totality of the data and looking at important different clinical outcomes like you just did, and the fact that two out of the three tell sort of the same positive story for the device, is compelling.

DR. ENGEL: I think all three do, actually.

DR. YANG: Dr. Afifi.

DR. ENGEL: I had -- oh, yeah.

DR. YANG: Yeah, let's comment on the same question first.

DR. AFIFI: I agree, there is no currently known way to combine them. Maybe some doctor or student one day will do it.

DR. YANG: Dr. Toledano, any comment on that question?

DR. TOLEDANO: Dr. Toledano being agreeable. Three for three.

(Laughter.)

DR. YANG: All right, Dr. Engel, you have another part?

DR. ENGEL: Yeah, a completely different question for the Sponsor. I was intrigued that there was a small percentage of patients whose seizures got worse, and I wondered whether that was directly related to the stimulus or was it some sort of side effect.

DR. MORRELL: There were no subjects that had adverse events related to worsening in seizures within a month of stimulation. There were 13 subjects who had a 50% or greater increase in seizures. We can't draw conclusions from that. We did obviously look at all of the characteristics of these patients. Compared to the entire population, these 13 subjects were younger, at $p < .05$, and that is the only distinguishing characteristic.

DR. ENGEL: Thank you.

DR. YANG: We'll finish off with Dr. Baltuch. But before we do, I wanted to specifically ask Ms. Lane and Ms. Mattivi, as the Patient and Consumer Reps, if you have any comments or any questions for the Sponsor or FDA. Any specific questions?

(No audible response.)

DR. YANG: Okay. All right, Dr. Baltuch.

DR. BALTUCH: Gordon Baltuch.

Dr. Morrell, could you go over that case again, that you showed of the bi-temporal case that became seizure free? You ran through that before quickly, and I'd just like you to run through that case that became seizure free. Again, you showed the slide before. You showed three slides, and the last one became seizure free. And maybe you could just tell us a little bit about this case and how many seizures they were having. It looks like they were having four and then you implanted the patient. And then what happened after that? I assume the implants were subtemporal strips, or were they depth electrodes that were placed?

DR. MORRELL: In the vast majority of patients with bilateral mesial temporal epilepsy, they were implanted with bilateral hippocampal depths with an occipital approach so that we could have one lead in one side and one in the other. This was one of those typical patients.

The red traces the seizure rate, and the stimulation starts where you see the lines. It was some time before that patient became

seizure free. From the time they were implanted with the device, that would've been in --

DR. BALTUCH: So let me just -- I'm sorry to interrupt you. The seizure freedom right here is not an implant effect. We've had patients who we implant and monitor in units who have become seizure free just from the implants. This was not this case.

DR. MORRELL: Oh, no, definitely.

DR. BALTUCH: We've had seizures after we implanted them, but they still had --

DR. MORRELL: There were -- yes.

DR. BALTUCH: They still have seizures after they have depth electrodes, right?

DR. MORRELL: There were only two patients who were seizure free at the end of the blinded evaluation period. One was treatment and one was sham.

DR. BALTUCH: Okay. And now, was this patient sham or was this patient treatment?

DR. MORRELL: I do not know the answer to that. The patient seizure freedom would have occurred -- the patient was implanted in 2009. Seizure freedom was achieved in 2010.

DR. BALTUCH: Right. So it took a full year before you achieved seizure freedom in this patient.

DR. MORRELL: And that is typically the case, that there is some period of time before seizure freedom is obtained.

I might take the liberty of saying that we did show the analysis where we looked at whether seizure onset predicted the likelihood of response, and we looked at mesial temporal, all basal temporal patients, and then we looked at the neocortical patients, and there is no difference. And we also did the interaction term about baseline seizure frequency and did not see a difference. I'll just show you this.

There is a treatment effect. It's evident in both subsets, the mesial temporal lobe patients, like the one we just showed you, and the neocortical patients. The magnitude of the treatment difference according to the GEE, which is the analysis method that I think everyone agrees here is appropriate, it's better than the median percent change, it's better than responder rate. Even though we're used to those, the GEE is better. It's longitudinal. It addresses the variability and seizure counts.

But I would say, based on everything that we have looked at, that where the seizures began doesn't predict the likelihood that a patient is going to have a response, nor does it predict seizure freedom. We have seizure-free patients who are mesial temporal, unilateral, bilateral, and patients who are seizure free who are neocortical.

DR. BALTUCH: Okay. But in this case you had a bi-temporal case, right?

DR. MORRELL: Yes, that's correct.

DR. BALTUCH: And I presume you didn't change medications in the interim that made them seizure free. I'm presuming that the seizure freedom was developed on the basis of accurate placement of these depth electrodes and then working with time and programming in these patients, that this patient is now seizure free.

And do you capture that electrographic result, that you can see those seizures are being effectively stimulated and you can see causality in the treatment of this patient?

Because, again, what we're looking for here, you have, in my mind, a home run patient. So you have created a patient now who you have had treatment effect, which is profound treatment effect. He's an Engel class 1, right --

(Laughter.)

DR. BALTUCH: -- as we would call it in the old days. He's seizure free now coming up on two years. And, you know, you see that. Well, here's the effect that you see, you know, the profound effect of the stimulation in one patient and try to understand why here you have effect. Why isn't it happening in so many other patients who you had that were like this? And you're left wondering, is it a surgical effect? Is it an implant effect, where the electrodes are, as Dr. Engel asked? Is it an effect of programming, or is it the epilepsy that's different that we're looking at, that we think is the

same and isn't the same?

Again, we get back to talk about cases. And here are cases that are illustrative of points, and I think here you have a case that illustrates that you can make someone seizure free for a considerable amount of time with the stimulation.

DR. MORRELL: There are a number of clinical variables and there are electrographic variables, and the trial was designed to best understand the clinical variables and not the electrographic variables. A study to understand the electrographic variables would look different and would of course require approval.

DR. YANG: I'm sorry, Ms. Lane. I must've missed your wave there a while ago. Go ahead.

MS. LANE: Sure. You had a slide that showed 37 patients, I believe, that achieved greater than six months of seizure freedom. I was wondering what percentage of those patients had higher intracranial monitoring.

DR. MORRELL: I don't know if we have the answer to that. The brains on the side of the room will know. Yeah, I'm sorry, I don't think I can tell you what percentage have intracranial monitoring. We could get that answer to you after the break, if you wish.

DR. YANG: Why don't we let the Sponsor answer that question, but can we do that after the break?

UNIDENTIFIED SPEAKER: Yes.

DR. YANG: Okay. So just once, let me get back to Ms. Mattivi here as the Consumer Rep.

MS. MATTIVI: I'm sorry for lying previously, saying I didn't have a question, and I did think of a question, and it gets back to the point Dr. Toledano and Dr. Connor made earlier about the severity and the sequelae of the seizures that are being experienced. And my understanding was that we're just counting seizure activity, you're just counting the seizure activity.

And then, Dr. Morrell, you made a comment just a minute ago about the number of total disabling seizures, and that kind of caught me and confused me a little bit about just what is being counted.

DR. MORRELL: Yes, the seizures that are being counted fall within the broad category of disabling, and within that we included simple partial motor, where there's an alteration in motor function, so it's observable and it interrupts the individual's ability to interact normally with their environment, any seizures with an alteration in awareness, and then, of course, generalized tonic-clonic seizures. So we combined those. There is a range within those, you know, of severity.

And so, clinically, the impact to the patient is going to be a function of the total numbers of these seizures that interrupt their ability to interact normally with their environment, and then also to some extent the

severity, but it is very difficult to get a handle on it. You know, there's not a sliding scale that would allow you to achieve a single severity number for a patient. At least not that I'm aware of.

MS. MATTIVI: It would certainly add a lot of subjectivity to that type of data collection.

DR. MORRELL: There is a lot of subjectivity. You know, we all use seizure counts. Every epilepsy therapy trial uses seizure counts. We're all aware of the limitations. And there hasn't been anything identified, at this point, that is a better clinical representation of how a patient is doing.

DR. YANG: Okay, last question, Dr. Privitera.

DR. PRIVITERA: This is for the Sponsor. So we've talked mostly about efficacy. We haven't really talked about safety. I've been fairly impressed with the safety data that's been provided both for SUDEP and psychiatric.

The one concern that people had was about hemorrhage, and it just brought up to my mind, when you talk about these patients, that some of them had depth electrodes and some of them had subdural electrodes. Was there a difference? I'm not sure. I don't remember the slide, but was there a difference? In other words, were the people who got depth electrodes more likely to have hemorrhage?

And related to that, could you just give me sort of a ballpark estimate, if you don't have the exact number, about how many electrodes

were depth electrodes versus how many were subdurals?

DR. MORRELL: We do have the exact answer for you, and I'm going to ask Dr. Gross to provide it.

DR. GROSS: The data is provided up over here. So when you see the depths and strips and look at cerebral hemorrhage, each one of the hemorrhages is shown here that, I think, were fairly equally distributed, as we were in the trial, as far as depth and strips.

I might also add that I wouldn't expect, a priori, that the depth electrodes implanted here would be any different, as far as their risk for hemorrhage, than those implanted during deep brain stimulation for Parkinson's disease.

And the strip electrodes. There are two small strips that contain four contacts each. They measure about an inch and a half in length or two inches in length, and it's hard for me to conceive, a priori, that those strips in themselves would provide a risk for hemorrhage.

DR. YANG: My apologies, Dr. Cavazos. I missed your hand. The real last question.

DR. CAVAZOS: I'm going back to the Sponsor, and I unfortunately have three separate questions. They are brief each, however. The first is just an observation.

If you still have the open-label study and you're following this data, you still can capture on 92% of the subjects the racial, ethnic, and all of

those kinds of things.

Now, going back to the validation, I was intrigued in your Figure 11 of your Executive Summary. If there's a way that the PDF can be placed that was distributed to the members. It shows the detection of a seizure by your device. It shows a spectrogram recording of an electrographic seizure in four leads of that particular case, exactly.

And so this is back to the question that Pete and I had asked earlier. You know, this data is being acquired, this data is our gold standard for seizures. There's no data that has been analyzed or looked upon as to validate these seizure diaries, for example, which is the pivotal measure that we're using.

DR. MORRELL: We have not done an analysis to see how many clinically reported seizures were accompanied by electrocorticographic events. There is some practical issue with that. Although we instruct patients to swipe the magnet, they are not always able to do so.

DR. CAVAZOS: Okay.

DR. MORRELL: And when they record the information on their seizures in their seizure diary, they place a time, but as you know, that time is often an estimate.

DR. CAVAZOS: Okay.

DR. MORRELL: And we do not have continuous recordings of the electrocorticogram. We have a total of 30 minutes. So we certainly look

back. When I say we, the physician will typically look back and see if they saw a seizure around that time. But that absence of seeing that electrocorticographic event does not mean that it didn't occur.

DR. CAVAZOS: Sure, certainly. But still, it can provide information as to whether you were having seizures being told by the patient in the seizure diary and whether your stimulation was in the -- or electrodes were in the correct place to record them. And that was kind of where we have been trying to get to, as to whether the electrodes were properly placed in those individuals who did not have depth electrodes or Phase II video monitoring.

Now, you have here four leads, and each of those leads has four points, and the stimulation is delivered between two points out of these potential 16. I mean, you can put, obviously, larger leads. So I still am confused as to -- I mean, here is an example with two depth electrode configurations. So you have at least eight points. But you indicated or at least there wasn't data that there were up to four leads implanted in patients. So potentially you had up to 16 points.

So how these leads were changed? When were they changed? What prompted you to say well, I'm going to attach the stimulation to this and this other one? I mean, all of those details were left out of the protocol or at least left out from the Panel to review.

DR. MORRELL: So just to make sure everyone is clear, because I

think this is somewhat confusing, they were able to implant up to four leads, no more than two of them being depth. But the neurostimulator itself can be connected to only two leads.

So the reason that we decided, in consultation with our investigators, that we would have the implantation of three or four, if they wished, was because sometimes they wanted the option, you know, for example, if a patient was temporal and they wanted some additional lateral temporal and mesial temporal coverage in case the detection was not what they wanted with the leads that they originally connected, and that would save the patient from another procedure. In most cases there was no change in positioning, so the investigator was satisfied.

I think that Dr. Sharan got to this earlier, that we're trying to drive this with as much science as possible, but there is an element of judgment and skill and experience that enters into this. And so in a clinical trial we cannot mandate where leads -- nor should we --

DR. CAVAZOS: Sure.

DR. MORRELL: -- where the leads are placed or what types of diagnostic testing is necessary for those expert physicians, the neurosurgeons and the epileptologists, to know where to put the leads and whether they are happy with detection or not.

So there will be skill and experience involved in this, which is why we have such intensive training plans and why we intend to provide this

device to the epilepsy centers, the highest-level epilepsy centers, where these physicians already have these skills.

DR. CAVAZOS: The last question had to do with getting back to the black box, as to the parameters that we have in there. And the reason why I'm going back to this comment is to do with something that you said earlier, that a portion of patients or the majority of patients were only increased in current.

And can you estimate or can you tell us whether that may be the only parameter that is open for clinical use, as compared to having a broad range of -- I mean, you have a huge range for frequency and a huge range for burst duration, pulse width, et cetera.

And so what I'm trying to get to is that we don't understand -- you know, there's a broad range of physiological responses that happened with frequencies. Kindling, for example, takes weeks, months, years sometimes, to develop depending upon who you are, I mean, what species, et cetera.

And so knowing that this was a blinded period for only three months, you know, how can we assure that our patients are having safety and efficacy? And so tell me what was used in this study, if the study was used -- you know, 90% of the patients had, as you said, between 100 Hz and 200 Hz. Perhaps that limit is much smaller than what has been discussed or potential in your device, and perhaps those numbers may be for investigational

purposes.

DR. MORRELL: So we all understand, today, this is a first-of-a-kind device.

DR. CAVAZOS: Um-hum.

DR. MORRELL: There is nothing like this. And we had to go in with certain assumptions of where stimulation should be set, and those were based largely on the experience with deep brain stimulation and movement disorders, that we felt that there was a range of stimulation that could be safe as far as frequency. We certainly knew that there had to be limitations on charge density, which we built into the device.

DR. CAVAZOS: Right.

DR. MORRELL: And we knew that in terms of safety, that it just made sense that you would start at a low frequency and build up according to the patient's tolerance and the patient's clinical response. So that's where we started. We now have 1,000 years of experience. We have some experience with ranges of parameters. These will be studied.

Certainly, what will happen -- and let me use the analogy of cardiac devices 15 years ago. What will happen is that with additional clinical experience, we will be able to refine this and identify which stimulation parameters are most optimal for a particular patient. Are we there right now? Of course not. We're going to need years more experience. But where we are is that we can tell you that we have a device that is safe. We have a

device that has shown effectiveness in the most challenging situation, which is the first-ever human experience.

And so that is what we can offer you today. And what the future can offer you, I think, is fairly exciting, where we can take this whole field in the future. Yes, absolutely.

DR. YANG: Thank you.

All right. So let's in the interest of time take a nine-minute break. We're going to start back promptly at 3:30.

Panel members, once again, please do not discuss the meeting topic during the break amongst yourselves or with any member of the audience.

(Off the record.)

(On the record.)

DR. YANG: All right. So it's 3:30 now, and I want to give the Sponsor a chance to answer Ms. Lane's question, if they're ready to do so.

Dr. Morrell, I'm sorry.

DR. MORRELL: As my papers go flying.

Sixty percent of the patients who had periods of seizure freedom had had intracranial electrodes.

DR. YANG: Thank you.

Okay, so at this time let the Panel focus our discussion on the FDA questions. Copies of the questions are in your folders. I would ask that

each Panel member identify him or herself each time he or she speaks to facilitate transcription.

Please show the first question.

MS. SMITH: Good afternoon. My name is Myra Smith, and I will now present FDA's questions to the Panel.

Panel Question --

DR. YANG: Could you move the microphone a little closer to you?

MS. SMITH: Sure. Is that better?

DR. YANG: Yes.

MS. SMITH: Panel Question 1: Please address the following safety questions:

- a. The sponsor met the pre-specified acute (surgical procedure to 4 weeks) safety endpoint. The risks associated with implantation were experienced by both the treatment and sham groups during the surgical and post-surgical period (0-4 weeks). Do you consider the numbers and types of adverse events that occurred during this period to represent a reasonable safety risk for device implantation?

DR. YANG: In order to get everyone's point of view, I am going to go around the table, and for Question 1, I'm going to start to my far left with Dr. Toledano. As you do so, you may state yes or no to answer the

question, but also, if you have any safety concerns, please concisely state your concern.

DR. TOLEDANO: So this is Dr. Toledano.

Without M.D. after my name, I can't really make a good judgment on that question.

DR. BALISH: Marshall Balish.

I think the types of events and hemorrhages and infections, et cetera, seem comparable to similar procedures. I think that they're reasonable.

DR. CAVAZOS: Jose Cavazos, yes.

DR. ROGAWSKI: Michael Rogawski, yes. It's clear that they've met the pre-specified criteria, but I still am concerned that there is a significant risk of this kind of an approach that far outweighs that of an anti-epileptic drug. And it was very difficult for me to really come to a conclusion on this point, but at the end of the day, I was convinced. But I still have some concerns.

DR. YANG: Dr. Haines.

DR. HAINES: Steve Haines, yes.

DR. YANG: Dr. Nikhar.

DR. NIKHAR: Nirjal Nikhar, yes.

DR. CONNOR: Jason Connor, yes.

DR. YANG: Dr. Engel.

DR. ENGEL: Pete Engel, yes.

DR. FESSLER: Richard Fessler, yes.

DR. PETRUCCI: Ralph Petrucci, yes.

DR. YANG: Dr. Baltuch.

DR. BALTUCH: Yes. You know, I think I find this -- the safety data presented here was terrific, and it was, I think, testament to the work of the surgeons who worked in this study. Certainly, it represents a new therapy and the best surgeons of the country and did well.

I had some concerns about some chronic -- I had some chronic questions -- well, questions about chronicity that I didn't see anything -- it had to do with how often that the battery needed to be changed and what frequency you would need to change the battery.

You see the young man sitting in the front row. Does he need his battery changed every three years? If he's in his 20s now and he's expected to live to 85, that's 60 years. Three years would be 20 battery changes. That would be 20 incisions into the scalp to change batteries. That was one of the concerns I had as to, you know, there was no mention of battery frequency, how many changes, and considering either alternative places to put the IPG or rechargeable technology for that.

The other concern I had with safety, that was only mentioned briefly, was that as with other devices, we've seen a big issue obtaining imaging in patients who have devices. This has become a big problem.

Traditionally, advances in epilepsy surgery have often been made by advances in imaging, which have allowed us to treat people better and improve, whether there had been CT scan, MRI, MEG. Who knows what's going to come in the future?

And we see with this technology an inability to get MRI to the brain already, and again, as I say in existing device technology, we have difficulty getting MRIs of the brain of certain types. 3T MRIs are unavailable in patients with vagal nerve stimulation. Sometimes you can go back. Even if you take the generator out, you have to take the lead out in the neck, you have to take it off the jugular, so it can be very involved. And I didn't see in the document any mention of future MR compatibility as these imagings become more important, not only in epilepsy, but general imaging of the body itself.

DR. YANG: Dr. Afifi.

DR. AFIFI: Abdelmonem Afifi.

Based on both the presentations by the FDA and the Sponsor, I'm persuaded to say yes.

DR. PRIVITERA: Michael Privitera, yes.

DR. YANG: Okay. Go ahead, Ms. Lane.

MS. LANE: As a patient, but definitely without a medical background, I still would support this and say yes.

MS. MATTIVI: Kris Mattivi, yes.

MR. MUELLER: David Mueller, yes.

DR. YANG: So, Dr. Krauthamer, with regard to Question 1, obviously the Panel generally believes that in that pre-specified acute period, the numbers and types of adverse events are reasonable safety risks.

The concerns, though, however, would be comparisons to ADs. A little more chronic but worth mentionable, which is the battery, the potential for needed battery changes, and the question of suitability for imaging technology as it comes along. Okay?

MS. SMITH: Question 1b: The sponsor met the pre-specified "short-term chronic" (surgical procedure and the following 12 weeks) safety endpoint. However, there were serious adverse events that occurred after the acute four-week safety period that were seen in implanted study subjects (both treatment and sham; from both the feasibility and pivotal trials). As of December 17, 2012, these included: *i*) a total of 11 deaths, with 7 from SUDEP, 2 due to suicide, 1 from status epilepticus and 1 from lymphoma; *ii*) intracranial hemorrhages that occurred outside of the acute surgical and post-surgical phases; *iii*) psychiatric events; *iv*) seizure-related injuries; and *v*) changes in seizure frequencies and types. Do you consider the numbers and types of adverse events that occurred during the "short-term chronic" period to represent reasonable risks for the device for the population studied?

DR. YANG: Again, since we're on Question 1, I'm going to start

to my far left with Dr. Toledano.

DR. TOLEDANO: Okay, so it's Dr. Toledano.

Even though I still don't have M.D. after my name, I guess I could say that based on what I've reviewed, I'll say that it's a yes.

DR. YANG: Thank you.

Dr. Balish.

DR. BALISH: Marshall Balish, yes.

DR. CAVAZOS: Jose Cavazos, yes.

DR. ROGAWSKI: Michael Rogawski, yes.

DR. HAINES: Steve Haines, yes.

DR. NIKHAR: Nirjal Nikhar, yes.

DR. CONNOR: Jason Connor, yes.

DR. ENGEL: Pete Engel, yes.

DR. FESSLER: Richard Fessler, yes.

DR. PETRUCCI: Ralph Petrucci, yes.

DR. BALTUCH: Gordon Baltuch, yes.

DR. AFIFI: Abdelmonem Afifi, yes.

DR. PRIVITERA: Michael Privitera, yes.

MS. LANE: Michelle Lane, yes.

MS. MATTIVI: Kris Mattivi, yes.

MR. MUELLER: David Mueller, yes.

DR. YANG: Dr. Krauthamer, with respect to Question 1b,

overwhelmingly yes from the group that these are reasonable risks for the short-term chronic period and no specific concerns voiced.

1c.

MS. SMITH: 1c: Please indicate any additional safety concerns that you believe should be considered in the risk-benefit analysis.

DR. YANG: For this one I'm just going to ask for a raise of hands because we have had some voiced already. So if you have additional safety concerns, if you would raise your hand, please?

Mr. Mueller.

MR. MUELLER: Yes, I would like to address the MRI question. Remember that pacemakers have been around for many, many, many years and there have been trouble -- not trouble, excuse me -- concerns with MRI, but only recently have there now been coming out with MRI-compatible safe pacemakers. So over time, I believe that that will be something taken care of.

DR. YANG: Okay. Dr. Nikhar.

DR. NIKHAR: I have one concern. I think it's worthwhile dividing the total number of adverse events versus injuries resulting specifically from seizures. So you have a set of adverse events that result from the operative procedure, but it's not clear how much of these are -- if there's a true reduction of adverse events from seizure-related events versus the procedure event.

DR. YANG: So Dr. -- oh, I'm sorry. There's a few more.

Dr. Privitera, and then we'll take Rogawski and Cavazos.

DR. PRIVITERA: The only comment I would make is that the post-marketing study would have to look at all these as well, because these adverse events are things that can occur over time, and any trends and increases in, for example, SUDEP or suicidality would need to be followed.

DR. YANG: I'm going to leave that one -- if you'll restate that when we answer the question about the post-approval study, okay?

Go ahead, Dr. Cavazos.

DR. CAVAZOS: I will say that safety data will need to be -- I will wait for post-marketing.

DR. YANG: Thank you.

Dr. Rogawski, something to do with the additional safety concerns in the pre-specified acute and short-term chronic phase?

DR. ROGAWSKI: Well, I just wanted to comment generally that I think this is a device that does have a high degree of risk, and I think that it's clear that the data that we've seen suggests that it likely doesn't prevent SUDEP, it doesn't prevent status epilepticus, it doesn't do a lot of things that we would really like a device like this to do.

I would also point out that the risk, in my mind, is less than -- or the risk/benefit ratio is appropriate for when it's used for patients who can benefit from the device. But I worry that there are many patients for whom the device might be implanted who will not benefit from the device and

therefore would be subjected to the risk without benefit, so I think it's very important for us to continue to try to study this device and understand who are the most appropriate patients and how best to use it.

DR. YANG: Point taken.

So with regard to Question 1c, we're talking about what Dr. Rogawski just stated plus what Dr. Nikhar stated about separating the adverse events from the procedure from the adverse events from the actual seizure activity.

Question -- does that suffice?

DR. KRAUTHAMER: Just have one quick follow-up.

Dr. Rodichok showed, from the literature, a very low rate of intracranial hemorrhages. Among the epileptologists, would you expect the rate that was seen in here, in the study, from a normal epilepsy population?

DR. YANG: Okay, good.

DR. KRAUTHAMER: I would just like to know that.

DR. YANG: Sure. I think -- okay.

No further comments. Let's go on to Question 2.

MS. SMITH: Question 2: FDA has identified the following sources of uncertainty:

- The sponsor's post-hoc model (which made 3 modifications from the pre-specified model) achieved statistical significance (empirical $p=0.012$, model-based $p=0.0056$). Several other

plausible post-hoc models yielded similar treatment effect estimates but not all were statistically significant.

- A "surgical effect" may confound the overall estimated treatment effect. In this study, 2 highly influential subjects appear to account for much of the diminished surgical effect observed at the end of the blinded period in the sham group.
- Between sham and treatment groups, the mean observed difference in responder rate (a secondary endpoint defined as a proportion of patients with a 50% seizure reduction) was 2% (27% sham versus 29% treatment) and no statistically significant difference was observed. The study was powered to detect a 20% difference in the responder rates.
- Heterogeneity (e.g., seizure type, frequency of seizures at baseline) impacted the estimated treatment effect from the GEE Model (which assumes a homogeneous response for all subjects).
 - a. Do you believe these sources of uncertainty impact the interpretation of the magnitude and clinical significance of the primary treatment effect (i.e., reduction of overall seizure rate)? Please explain your answer, and identify each source of uncertainty that concerned you.

DR. YANG: So let me take this one from my far right. If you

would first tell me if it's yes or no, and then, obviously, if it's yes, then explain the sources of uncertainty that concern you.

MR. MUELLER: David Mueller.

I believe we, the Panel in general and the statisticians in particular, discussed this quite in depth, and I don't have any uncertainty.

MS. MATTIVI: Kris Mattivi.

I agree with Mr. Mueller.

MS. LANE: Michelle Lane.

I agree as well.

DR. PRIVITERA: Michael Privitera.

There clearly is more uncertainty than I would like to see in a typical clinical trial. I personally believe that the major source of uncertainty here was this post-implantation or surgical effect, which, most likely, in my opinion, actually narrowed the difference between the treatment and the sham arms and made it more difficult to show an effect. I do believe that we've seen evidence that there is effectiveness, but I do believe there are a number of confounders that make for uncertainty.

DR. YANG: Dr. Afifi.

DR. AFIFI: Thank you.

We talked a lot, yes, about these sources of uncertainty and the various reasons for it. Among the models that were considered, I do agree that the model indicated binomial is better than the others, and the

one that takes the covariates into account is definitely better than not taking them into account. However, as I mentioned earlier, there is one missing model that was not done, and that is the one that includes random effects. We talked about that. And until I see the results of those -- and I still have major questions about the overall conclusion.

I do believe that there are some effects that disappear as we look into it further. The two influential subjects and the various others that were identified by the Sponsor make things -- again, raised some questions. So, overall, I would have liked to have seen some other analysis, in particular the mixed model rather than the effects one before really making up my mind. At this point, I remain quite concerned about the validity of the final conclusions.

DR. YANG: Okay. So you do believe, just to clarify, that there are sources of uncertainty that --

DR. AFIFI: Yes. The answer is yes.

DR. YANG: Dr. Baltuch.

DR. BALTUCH: Like Dr. Engel, I am statistically challenged, but my only concern was -- the degree of discord between all the statisticians at this meeting was a cause for my concern. I would have liked to have seen unanimity, like in epilepsy, when the localization is clear, the epileptologists all seem to agree with each other. When the localization is unclear, they all seem to have disagreements, and that's how I can tell.

DR. YANG: So let me ask the question again directly, if I can clarify. So do you believe that these sources of uncertainty actually impacted the interpretation, then, of the clinical significance? Okay.

DR. PETRUCCI: Ralph Petrucci, no.

DR. FESSLER: Richard Fessler.

I believe there are a variety of sources of uncertainty here, none of which -- all of which affected deliberation but none of which impacted the final decision, so no.

DR. ENGEL: Pete Engel.

I'm convinced by the totality of the data without applying statistics. It looks pretty good to me.

DR. YANG: Okay. Dr. Connor.

DR. CONNOR: Before I get into the statistics, I'll say I agree with that comment. So are there sources of uncertainty here that make it cloudy? Absolutely. But it seems like -- you know, not knowing a lot about epilepsy, it seems like an extremely heterogeneous disease, and I would suspect that's going to happen almost no matter what.

But it seems like we do all these different models, and certainly, I would rule out the bottom four that FDA showed as plausible as implausible. The negative binomials all tell the same story; they tell the same story with the same effect size. Looking at it by different baseline number of seizures, there's an effect on three of the four groups even though they're

very small.

So it seems like no matter how you look at the primary analysis, it's the same story, and the only difference is whether that tail is over zero or not. So to me, it's pretty robust in terms of telling us the same thing, and even then, getting into the different outcomes like the number of seizure-free days and such seems to show that this works in, you know, a good number of people.

DR. NIKHAR: Nirjal Nikhar.

To me, it does not seem questionable that the data is positive and supports efficacy. What appears questionable is the debate that's conducted by the statisticians here, and really, the analysis that should be -- because it seems like we're trying to find the feet that fit the shoe rather than analyze the data here. So I think it's positive, from what I read of this, but I'm not a statistician.

DR. YANG: So Dr. Nikhar, again, to clarify. So do you believe these sources of uncertainty impact the interpretation?

DR. NIKHAR: No.

DR. YANG: Okay. Dr. Haines.

DR. HAINES: Steve Haines.

There are sources of uncertainty. All of them are reasonable things to worry about. But again, taken in totality, while they may reduce the apparent magnitude and strength of the conclusion, I don't think they

overwhelm it.

DR. YANG: Okay. Dr. Rogawski.

DR. ROGAWSKI: In totality, I was convinced that there was a treatment effect here, and the deciding factor for me was the reanalysis that the Sponsor presented of the open-label sham stimulation data once the sham group had been converted to stimulation. The FDA showed that there was a continuing divergence between the sham group and the initial treatment group, and that worried me to a great degree. And when the Sponsor demonstrated that using a different method of analysis you could get superimposable results, I had a greater level of comfort.

And so I would encourage the Sponsor and the FDA to look at those analyses together and make sure that both groups can agree that that's an appropriate approach because, for me, that was a very important piece of information.

DR. YANG: Okay. Dr. Cavazos.

DR. CAVAZOS: The answer is no. And similar to the other clinical epileptologists in the group, Dr. Privitera, Dr. Engel, Dr. Rogawski, we have -- I mean, there are uncertainties in the practice of medicine that, in totality, as a whole, there is overwhelming evidence that there is an effect.

DR. YANG: Thank you. Dr. Balish.

DR. BALISH: Marshall Balish.

I have to agree, no. I think that there are uncertainties, but I don't think they impact the overall.

DR. YANG: Dr. Toledano.

DR. TOLEDANO: Dr. Toledano.

And I also would say no. I would agree with Dr. Connor. I don't think so much we're finding feet to fit the shoe. I think when the Sponsor went out and found Dr. Heagerty and asked him what would be the right way to do it without seeing the data, they just went to a better shoe store.

(Laughter.)

DR. TOLEDANO: I think that was really very, very helpful to me, keeping all the observations in ITT. So you know what? There's always stuff that happens in clinical real-world data, but at the end of the day, I think the effectiveness is really solid.

DR. YANG: Okay. So Dr. Krauthamer --

DR. KRAUTHAMER: Just back to the last --

DR. YANG: Oh, can I save that for --

DR. KRAUTHAMER: Oh, okay.

DR. YANG: Let me finish this off, then.

All right. So with regard to Question 2a, it looks like the majority of our Panel says no, that the sources of uncertainty did not significantly impact the interpretation of the clinical significance of the primary treatment effect. If there were concerns, it was about the post-

implantation effect. Obviously, the statistical disparity that had to do with mixed model random effects and then finding the right shoe. Okay.

So let's do Question 2b, and then we'll go back to Question 1.

I apologize.

MS. SMITH: Okay, 2b: Based on this blinded study, please state why, or why not, you believe the electrical stimulation added benefit beyond the "surgical effect" observed in both treatment and sham groups.

DR. YANG: So for this one, I think, since it's still Question 2, I'll start to my far right with Mr. Mueller.

MR. MUELLER: Yes, David Mueller.

I definitely believe that the blinded study demonstrated that the stimulation did exceed the surgical effect, primarily based on the month-to-month comparison where the sham effect was decreasing while the stimulation was increasing.

So the answer -- I do not believe that there is any effect of the surgical --

DR. YANG: So to clarify, you do believe that there was an effect beyond the surgical effect?

MR. MUELLER: Yes.

DR. YANG: Okay. Ms. Mattivi.

MS. MATTIVI: Kris Mattivi, yes.

As with Dr. Cavazos, when the sham group converted to

treatment, I think that was very telling.

DR. YANG: Ms. Lane.

DR. CAVAZOS: It was Dr. Rogawski, not me.

DR. YANG: Okay.

MS. LANE: Yes, I believe that the data provided by the Sponsor shows that there is evidence that there's a benefit to stimulation far beyond the surgical effect.

DR. YANG: Thank you.

Dr. Privitera.

DR. PRIVITERA: Yes.

DR. YANG: Okay.

DR. AFIFI: To me, it showed clearly in the treatment group; in the sham group, I'm still on the fence.

DR. BALTUCH: Yes.

DR. YANG: Okay.

DR. PETRUCCI: Ralph Petrucci, yes.

DR. FESSLER: Richard Fessler.

Yes for the reasons previously stated.

DR. YANG: Dr. Engel.

DR. ENGEL: Pete Engel.

Although I agree that the open-label data was significant, this is based on the blinded study.

DR. YANG: Um-hum.

DR. ENGEL: Based on the blinded study, I think the statisticians and the FDA agree that the model that was finally used was appropriate and it's statistically significant. But in addition to that, all the other studies that were presented that were not statistically significant were trending in the right direction, so I have no doubts.

DR. YANG: Thank you.

Dr. Connor.

DR. CONNOR: Yeah, I say yes. And I think, you know, beyond -- you know, we can talk about models and p-values and all this, but it frequently comes down to can you show me a picture that goes wow, that looks like it works. And I think the picture of after surgery there's an effect, but that effect keeps going away and away and away in the control group, and it keeps being there and maybe even gets a little bit better in the treatment group really speaks to "there is an effect beyond surgery."

DR. YANG: Dr. Nikhar.

DR. NIKHAR: Just on the blinded study, I think it's a little difficult to say, in those three months, largely because of the surgical effect. That was clear in both groups, in the treatment and the sham groups. I would say yes, but it's not striking. I think it sways to some degree by the long-term data that we have for two years, but I'll still go with yes.

DR. YANG: Dr. Haines.

DR. HAINES: I'll also go with yes. I also agree that if you limit it just to the blinded study, it's a bit problematic. But we know, in general, that the surgical effect of implantation is a short-term effect in other circumstances, so it makes biological sense that it goes away. And the open-label data support that.

DR. YANG: Dr. Rogawski.

DR. ROGAWSKI: Yes, but with a caveat. I'm not convinced that for many patients this is a clinically significant effect. I think there is an effect based upon the statistical considerations that we make during the course of the day, but I'm still concerned about whether how clinically significant the effect is.

DR. YANG: Dr. Cavazos.

DR. CAVAZOS: Yes, but clearly we don't understand why, and understanding why must be part of the post-marketing study.

DR. YANG: Dr. Balish.

DR. BALISH: Yes, I think it's been stated there. Number of reasons.

DR. YANG: Dr. Toledano.

DR. TOLEDANO: Dr. Toledano just says yes.

(Laughter.)

DR. YANG: Okay. Dr. Krauthamer, with respect to Question 2b, you heard all the yeses going around. The concern was the comparison of the

blinded study versus the rest, the sham effect decreasing when we look further out. And then, of course, this question of clinical significance and why, which may come back up again in the post-approval study.

So now my apologies to Dr. Krauthamer. When he made that comment on Question 1, I did not interpret that as being a question to pose to the Panel. Can you repose the question and we'll go back around?

DR. KRAUTHAMER: It was just, from the epileptologists on the Panel, I just wanted to know whether intracranial hemorrhage is a usual finding/rare finding in patients with epilepsy. Dr. Rodichok showed that in one study it was generally pretty rare -- if it popped up in the study.

DR. YANG: Okay. Let me address that to the epileptologists, so -- or the neurologists. So shall we go to Balish and then Cavazos, Rogawski, and then on down?

DR. BALISH: I'd have to say it's pretty rare in my experience.

DR. YANG: Okay. Dr. Cavazos.

DR. CAVAZOS: Given the fact that this is 60-something percent of patients have intracranial monitoring with Phase 2, if you take that particular population, then it's comparable to what this device does.

So the question, we're just back to many of the comments that Mike Rogawski has indicated for people who have significantly intractable epilepsy for whom there are very limited options, for whom you are trying to pursue surgical curative-receptive surgery, pursuing intracranial electrodes.

The safety concerns that were raised are not out of proportion.

In fact, as indicated by Dr. Baltuch, the surgical group was, perhaps, even slightly better than the average individual. So from clinical epileptologists at this particular population of patients, we may talk about where they failed two medications or something else, but the particular population examined in this study is not out of proportion.

DR. YANG: Dr. Cavazos, let me clarify that question. The question was whether or not you found intracranial hemorrhages to be rare or if you want to cite a percentage in epileptic patients.

DR. CAVAZOS: Correct. But it isn't in a particular population of patients, and that's the difference. If you take everybody who has epilepsy who is of very different situation --

DR. YANG: Take -- yeah. Take that, for instance.

DR. CAVAZOS: Pre-surgical case.

DR. YANG: Okay. So you'd say rare.

Dr. Rogawski, same question.

DR. ROGAWSKI: Yeah. I would just like to reinforce the Agency's concern about this issue. I mean, I think we're looking at two different kinds of comparisons with respect to safety. On one hand, we're looking at the safety of the stimulation itself, and on the second hand, we're looking at the safety of implantation of this device in a population that is at risk. And in that sense, you've got to take the whole data together, and you

can't really compare one group versus the other.

We don't have a control group for that question, but it seems logical, to me, that in patients who are having frequent seizures and falling and hitting their head, that having a device that's implanted in the skull could provide substantial risk, and I'm very concerned about it. And that's the reason why I think that yeah, we have to work toward using this device only in those patients who could benefit from it because those patients who were implanted who are not benefiting are being subjected, in my view, to a substantial risk.

DR. YANG: Okay. Let me go to Dr. Petrucci. As a neuropsychologist, do you want to -- oh, Dr. Engel. My apologies. I looked right over you.

DR. ENGEL: There are two answers to that question, in my mind. One is, patients with intractable epilepsy don't have this degree of hemorrhages, as far as we know. This is because the patients in the study have hardware in their head. And so the Sponsors didn't use patients with intractable epilepsy as control; they used patients who have hardware in their head for other reasons. And I don't know whether the degree of hemorrhage in the patients who have hardware in their head for Parkinson's disease have this degree of hemorrhage, but it does seem to be comparable at least.

But the other question, which was addressed, I think, by Mike, is that we don't follow our patients as carefully as they followed these

patients. And for all we know, there are clinically insignificant hemorrhages in our patients that we don't know about. So without a good control group followed the same way, we can't really say anything.

DR. YANG: My apologies. My peripheral vision must be going.

Dr. Nikhar, as an epileptologist, would you like to comment on the question of intracranial hemorrhages in epileptic patients?

DR. NIKHAR: It's not been my experience. I'm not an epileptologist, but in the experience that I have in neurology, unless there's some underlying factor like surgery or some apparatus being used or an AVM or some vascular malformation, I have not found that to be the case.

DR. YANG: Dr. Petrucci, as a neuropsychologist, do you want to comment?

DR. PETRUCCI: What am I addressing?

DR. YANG: The question of intracranial hemorrhages in epileptic patients.

DR. PETRUCCI: Well, obviously they're at a greater risk of not only cognitive dysfunction, but other psychosocial concerns. Memory is a part of that. The more you hemorrhage, the greater the hemorrhage, the more frequency of the hemorrhage, the more concern we have. Earlier the onset of a hemorrhage and the less ability to adapt through demands of life obviously creates an ongoing issue for these patients. That's all I would say about it.

DR. YANG: Okay. Dr. Privitera.

DR. PRIVITERA: In my experience, the hemorrhage rate that wasn't related to implantation is a little bit higher than I would think it would be. It's not something that I think would prevent approval, but it's something that I would put into the long-term study. So I think it's a possible signal that should be followed carefully.

DR. YANG: So, Dr. Krauthamer, that question was a little more difficult to answer than as posed. However, it seems like at baseline, probably, the concerns are whether or not you're comparing to the right group and particular groups of epileptic patients, and in particular those that have hardware that has been implanted. So considerations to be taken.

All right. Dr. Krauthamer, that answers your questions? Yeah.

Okay. So we'll go on to Question 3.

MS. SMITH: Okay. Question 3, Overall Effectiveness: The following results were seen with analysis of the effectiveness data from the baseline period through the end of the blinded evaluation period:

For NeuroPace's post hoc primary endpoint analysis, the model predicted a reduction in GEE mean seizures per month when adjusted for covariates of 37.9% in the treatment group versus 17.3% in the sham group.

NeuroPace's pre-specified secondary effectiveness endpoint results for the 50% responder rate were 29% for the treatment group and 27% for the sham group.

NeuroPace's pre-specified secondary effectiveness endpoint results for the change in mean seizures per month were -11.5 in the treatment group and -5.0 in the sham group.

NeuroPace's pre-specified secondary effectiveness endpoint results for percent change in days with seizures per month were -18.9% in the treatment group and -18.3% in the sham group.

NeuroPace's pre-specified secondary effectiveness endpoint results for change in mean Liverpool Seizure Severity scores were -4.7 in the treatment group and -5.9 in the sham group.

The median % change in seizures per month was -28% in the treatment group versus -19% in the sham group.

The proportion of subjects who achieved a ≥ 5 point increase in the Quality of Life in Epilepsy 89 score at the end of the blinded evaluation period were 36.6% in the treatment group and 39.1% in the sham group.

- i. Do the results from the key endpoint analyses represent a clinically significant treatment effect? If so, please identify which endpoint(s) represent a clinically significant treatment effect. If not, please discuss what you believe would be a clinically significant treatment effect.

DR. YANG: May I ask -- yeah. I was going to ask you to put that table right back up.

All right, for this question, I'm going to start with my immediate

right, with Dr. Engel, and we'll go around the table.

DR. ENGEL: Yeah, I'll just repeat what I said before. I think the answer is yes, that the primary measure is statistically significant. The others trended in the right direction for the treatment group and didn't in the sham group except for the QOLIE, and I don't think quality of life, we should expect any changes in three months.

DR. YANG: Okay. Dr. Fessler.

DR. FESSLER: Just for a point of clarification before I answer. Other than Slide 63, which says it was adjusted for the covariates, were the other slides, 66 through 74, also adjusted for covariates, or was that just the original GEE analysis?

DR. YANG: I'm going to ask the FDA to answer that.

DR. FESSLER: If the answer is we don't know, then I have a two-part answer.

DR. MILLER: Scott Miller.

If I could just have a moment to check this to make sure.

So I believe, with the exception of the primary with the GEE model, the majority of these were not covariate adjusted. The Sponsor could correct that if there --

DR. FESSLER: Okay, thanks.

Then my answer is yes, I believe that these data do represent clinically significant treatment effect. We've all agreed, on our previous

discussion, that the original GEE analysis was flawed and so to give us non-statistical data, then, and ask us if it's a significant treatment effect is not really appropriate.

DR. YANG: Okay.

DR. PETRUCCI: My answer is yes. When we consider the longstanding dysfunction that many of these patients experienced, I'm not persuaded to think otherwise.

Thank you.

DR. YANG: Okay. Dr. Baltuch.

DR. BALTUCH: Yeah, I think there's treatment effect, unfortunately. I think at three months, there's a clinically significant treatment effect. You look at the responder rates, they're not particularly different. And for a big neurosurgical procedure, we sort of live by a standard that Engel 1 was our standard, and if you didn't make the patient seizure-free, you weren't doing that well. And our patients at this level, at three months -- you know, it's a little bit disappointing, the data, at three months, that data. But it's probably magical thinking to think it was going to be better at three months.

If you look further out, you see that you have some terrific patients doing very well over a longer period of time, and there actually are some seizure-free patients in the group out there, so you know, as I said, Dr. Morrell said it was the best that they could do in terms of study design

when they designed it. The retrospective scope always looks at things differently.

DR. YANG: True.

Dr. Afifi.

DR. AFIFI: Since the question is specifically about the clinical significance, I defer to the clinicians.

DR. YANG: Dr. Privitera.

DR. PRIVITERA: I think that the mean reduction in seizure frequency is most likely clinically significant. I would have been happier if the responder rate was also there, but as I mentioned before, I do believe that this post-implantation effect narrowed both the GEE analysis and the responder rate, and I think if we were able to look purely at stimulation or no stimulation without this post-implantation effect, we would see something that would be more clinically relevant.

DR. YANG: Ms. Lane.

MS. LANE: I would say yes and specifically towards the reduction in GEE mean seizures per month.

DR. YANG: Ms. Mattivi.

MS. MATTIVI: Kris Mattivi.

I would also say yes along the lines of how secondary endpoints were not adjusted for covariates. As a consumer looking at this in the light of clinical significance, I would say yes.

DR. YANG: Mr. Mueller.

MR. MUELLER: Dave Mueller, yes.

DR. YANG: Dr. Toledano.

DR. TOLEDANO: So I'm Dr. Toledano, and still no M.D. after my name, but as a person having heard all the testimonies, I'd have to say that this impact on people's lives does seem like it could be clinically significant. So I'm going to say yes.

DR. YANG: Dr. Balish.

DR. BALISH: Marshall Balish.

I'm going to say yes. This is the hardest-of-the-hard group, if you look at who is in the study. So the rule reduction and significant reduction in seizures per month in that group of patients, I think, is clinically significant.

DR. CAVAZOS: Yes.

DR. YANG: Dr. Rogawski.

DR. ROGAWSKI: Yes. But, again, with a caveat. Only for those patients who benefit. For those patients who don't benefit, I think there's a significant risk, and that worries me. But looking at the mean seizure scores, in my view, it's clear that there was an effect of the treatment.

DR. HAINES: Yes. All three methods of measuring seizures per month are clinically significant.

DR. YANG: Okay. Dr. Nikhar.

DR. NIKHAR: Yes.

DR. CONNOR: I think yes to the primary. For the others, being neither a clinician nor a patient or family member of a patient, I don't think I can define "clinically significant."

DR. YANG: So, Dr. Krauthamer, with regard to Question 3a(i), it seems that the majority of the Panel feel that the primary endpoint certainly represents a clinically significant treatment effect. The caveats are, of course, what you've heard regarding the appropriateness of the question without covariates on the others, that "Is the clinical significance at three months in this period adequate?" But most feel that the secondary endpoints all trend in the right direction.

Is that answer -- okay.

How about Question 3a(ii)?

MS. SMITH: Question 3a(ii): Are the results generalizable to a "real world" epilepsy population for the indicated treatment population? If not, do you believe that there is a subgroup for which there is a reasonable assurance that the device is effective (e.g. specific seizure type, specific location of seizure foci, number of foci, baseline seizure count, and history of prior surgery)?

DR. YANG: So, Dr. Engel, let's start with you again.

DR. ENGEL: Yeah. I think clearly there is a subpopulation of patients who do really well with this from the statements that we heard, as

well as from the data, and unfortunately, we don't know what the subpopulation is. So if this is approved, I hope that the post-approval study will be designed to elucidate that.

I just want to make one comment here because I agree with Mike Rogawski, that this is a very invasive procedure, and if there are going to be a lot of patients who are not going to benefit from it, it needs to be used carefully. And the VNS experience taught us that a lot of patients went for VNS who really shouldn't have and who should have been referred for surgery and weren't.

So I really appreciate the fact that the intention, if this is approved, would be to have it used only at Level 4 epilepsy centers that do epilepsy surgery. And I think that ought to be a criterion that it only be done in places that do epilepsy surgery so that this won't be done to people who might be candidates for surgery and don't realize it.

DR. YANG: So, Dr. Engel, I would like to clarify your answer, though. The question, as stated, is are these results generalizable to a real-world epilepsy population for the indicated population?

DR. ENGEL: Yes.

DR. YANG: Okay. Dr. Fessler.

DR. FESSLER: Yes.

DR. YANG: Okay.

DR. PETRUCCI: Ralph Petrucci, yes.

DR. BALUCH: Yes. I'd like to see, in the post-market study, that some -- looking at, you know, being closer to the focus and some sort of correlation between how close you are to the focus with your electrode and how well you do in terms of pickup and stimulation.

DR. AFIFI: Yes, I believe that the results are generalizable for the indicated population.

The other part of the question, are there any subgroups, it seems to me that the group with the very high frequency of seizures would probably benefit more than the rest.

DR. PRIVITERA: Michael Privitera.

I think that there's not a clear subgroup from the data that can be identified. I do agree with the other comments that this is a very small specific subgroup of people who are qualified for this treatment. And looking at the proposed indication, one of the comments I would make, it says "with partial onset seizures from no more than two foci," and I would be concerned that the definition of two foci and the definition of the seizure type may need to be put into the indication a little bit more clearly. I don't know exactly how to do that, but that might be something that could be considered.

DR. YANG: Ms. Lane.

MS. LANE: Michelle Lane, yes.

MS. MATTIVI: Kris Mattivi, and I am so blatantly not qualified to answer this question.

DR. YANG: Okay.

MR. MUELLER: David Mueller.

Yes, I agree. And I think this is demonstrated, as well, by the numerous letters that we were provided and read through, as well as the excellent comments by the patients here today. They are the real world, where they went through multiple drugs, multiple drugs, other treatments, and so this is a real-world experience.

Additionally, this device is a Class III device. It's also a prescription-use only device. Not anybody can get their hands on it; there has to be an M.D. And the company has already discussed about their extensive training program that would be going on with this.

And, lastly, as was stated by many of the patients, these patients have gone through so much that their risk tolerance is much higher than the normal population.

Thank you.

DR. YANG: Thank you.

Dr. Toledano.

DR. TOLEDANO: So it's Dr. Toledano.

Are the results generalizable to a "real world" epilepsy population for the indicated treatment population? I'm going to say absolutely yes, that's the population that was studied in a very real-world -- as close to real world as you could get on this clinical trial, so I like it a lot.

I'm going to say yes.

Regarding the subgroups, I'm sure that there are subpopulations within there that benefit more or less than others and are more or less subject to risk than others, but that's not what we're about today. I'm not prepared to make post hoc limitations to data dredging and subgroups. We studied a group, it worked, yes.

DR. YANG: Dr. Balish.

DR. BALISH: Marshall Balish.

Yes, I think it's generalizable to the appropriate population. I don't have any adequate information about subgroups yet.

DR. YANG: Fair enough.

Dr. Cavazos.

DR. CAVAZOS: It is a yes, but a conditional yes. The way they are indicating the population was based on failure of two medications. That's not exactly what the population was studied. The population is not exactly real world. Failing two medications implies that you go to -- monitoring unit, but it is not the population. I mean, the median of time after surgery -- I mean, after epilepsy onset was considerably long, the number of anticonvulsants used were considerably many more than that. This is the traditional very intractable population, so it's not just real-world epilepsy, everybody with epilepsy.

So the answer is, is it generalizable to a population, a real-

world population? Yes. But it is a population that is with severe epilepsy that has been studied with intracranial electrodes, et cetera.

In regards to the subgroups, there is no question that there are some differences, you know, the variance between -- I mean, there is tremendous variance, and when there is tremendous variance, it's because you don't understand, you know, what the variables are. So, yes, I do believe that there are subgroups.

I think the most powerful piece that convinced me that this is not just the high-frequency seizures was the graph that was presented by the Sponsor where the analysis of the 140 patients that were low seizure frequency numbers, it was still statistically significant. So I do believe that post-marketing studies need to be done very specifically to understand who are these patients who respond.

DR. YANG: Thank you.

Dr. Rogawski.

DR. ROGAWSKI: My answer on this is a definitive no. I don't think that the treatment is generalizable to the indicated population, and the reason for that is I think that the Sponsor has produced an overly expansive set of indications for use. I think there needs to be a discussion between the Sponsor and the Agency to narrow that significantly to account for some of the concerns that we heard from other Panel members with respect to use of this in a general intractable epilepsy population.

In my opinion, I mean, I began to think a little bit about what sorts of things you might want to say in the labeling regarding the indication. Some of the things that occur to me are including a comment about the fact that this is indicated for patients who are not candidates for resective or definitive epilepsy surgery. We heard from many of the people who testified today that epilepsy surgery is actually a curative procedure in a high number of individuals. And for those people who are candidates, I wouldn't want to have this delay a potentially curative procedure.

Other ideas might be to speak about severe or disabling seizures. That was the criterion that was used in the trial. These had to be disabling seizures. I'd like to see that specified in the labeling so that people who do not have -- maybe annoying, but not disabling, seizures are not treated with this particular product.

So I just think we need to narrow the set of indications for this product if it's approved.

DR. YANG: Thank you.

Dr. Haines.

DR. HAINES: Steve Haines.

Yes, they're generalizable to a population that resembles the population that was studied, which sort of goes to that same issue. I believe there is a subgroup or subgroups that benefit more, and I have no idea what they are.

DR. YANG: Thank you.

Dr. Nikhar.

DR. NIKHAR: So I believe there is a subtype that will benefit more, and there's a subtype that will benefit less. And I think this, I expect, will emerge from the long-term data that will naturally follow from this.

You know, I think from the long-term data you not only have a subtype that emerges, but also other pieces of information that may influence the efficacy of this beyond just a seizure reduction. We've talked a lot about how many seizures go down, but we also have testimonial from a patient today who may still have frequent seizures, but is very functional. I'm sure there's going to be more data that will come out that will be positive beyond simply a reduction of seizure-free -- in short, I'd say yes, this generalizes right now.

DR. YANG: Okay, thank you.

Dr. Connor.

DR. CONNOR: Yes, I think it's generalizable. I mean, yes, I think there are definitely subgroups in which it works better than the others. We don't know what it is, but I think we can't let that debilitate us too much. I mean, I think with -- statins work and the number needed for statins is about eight, which means we give seven people pills that do nothing for every heart attack we prevent. And pills are a lot different than brain surgery. I totally get that. But I --

(Laughter.)

DR. CONNOR: Right. But within the premarket setting, I think it's so hard to identify, you know, which ones is this effect for and which ones that aren't. So I guess I don't want to be too restrictive, but I certainly, you know, want to make sure that we do due diligence and figure out where it works. But I just want to say that I don't want to be too restrictive yet or put too much in figuring out in which subgroups it works. It would be too restrictive.

DR. YANG: So, Dr. Krauthamer, with respect to Question 3a(ii), it seems that the majority of the Panel said yes and one very emphatic no, which I will talk about in a second.

For the yeses, there is the feeling that there is likely a subpopulation that will benefit more and maybe a subpopulation that might benefit less, but we can't identify it based on the data presented today. The population that might benefit more, there was one suggestion, high frequency of seizures.

There is also concern that this type of surgery should -- or this device should be limited or offered at epilepsy centers where things like studying the distance from seizure focus and all that later on could take place.

Now, as far as the emphatic no, the concern was the over-expansive set of indications. Perhaps on the labeling there should be

something about disabling seizures or patients that are not qualified, you know, for seizure surgery. And those are amongst the things that you might consider.

Okay, so --

DR. KRAUTHAMER: Thank you. That was an excellent discussion.

DR. YANG: Okay, perfect.

Let's go on to 3b.

MS. SMITH: Question 3b: Seizure frequency was recorded during the open label phase of the study during which both treatment and sham groups received stimulation. During the open label phase:

- Subjects were aware that they were receiving active stimulation.
- Subjects were permitted to change medications.
- The trial no longer had a concurrent control arm.
- There was some evidence that subjects discontinued for perceived lack of improvement.
- There were missing data.

What conclusions can be drawn from the open label study results? Please explain your answer.

DR. YANG: So, Dr. Engel, as we're still on Question 3, I think it would make it clear if you could say if there are conclusions that could be

drawn and then tell us what conclusions could be drawn.

DR. ENGEL: Yeah. With refractory patients who are put on medications and you try new medications, they tend to get worse. In most cases the medications don't work after a while; you keep changing the medications. The stimulation treatments have a different effect with VNS, now TNS, deep brain stimulation. They get better over time. And I think the data that are presented here for the open label study strongly suggests that the same thing is true for RNS, that they continue to improve, and I think that's an important conclusion.

DR. YANG: So just again to clarify, given the concerns that are stated here, can you make any conclusions, then, from this open-label study, or are you saying that you can and it's that the more --

DR. ENGEL: Yeah, I think you can.

DR. YANG: Okay.

DR. ENGEL: I think, despite all these concerns, I think --

DR. YANG: Okay.

DR. ENGEL: -- there is a strong tendency to -- and there's no reason to believe, since it's a stimulation study, it should be different from the other stimulation treatments.

DR. YANG: Okay. Dr. Fessler.

DR. FESSLER: I believe there were two strong conclusions that can be made from this part of the study. The major question was, when you

convert the sham group to a stimulation group, are they going to receive the same kind of beneficial effect, and I think the answer to that was yes.

The other thing that can be concluded is that just like every other medical and every other surgical treatment we have, it doesn't work the same for everybody. Some people get better effects, some people don't, and that's what we saw here.

DR. PETRUCCI: Ralph Petrucci.

It appears as though this was a fair and equitable design in the study and that everybody was an equal opportunity responder. And I don't know that I can draw any other conclusions.

Thank you.

DR. YANG: Okay. Dr. Baltuch.

DR. BALTUCH: The open label stuff looks terrific. It's open label. It is what it is. But it does look pretty good. I've always wondered if you could -- though the statisticians probably have something to say about this -- if you could do a study where you take the people who are great responders and then randomly turn half of them off and see if there's a change, if their seizures go up again or not.

DR. YANG: Okay.

DR. AFIFI: The Sponsor and the FDA reached different conclusions from the open-label study. My answer to the question is I would be happier if they can get together and come to a consensus.

DR. YANG: Okay. All right, Dr. Privitera.

DR. PRIVITERA: I think the conclusions that can be drawn from the open-label study are safety conclusions. I would disagree about making any efficacy conclusions based on open label data. If you look at open-label extension trials of antiepileptic drug trials, they always show improved efficacy in the open label portions. So from my perspective, efficacy data out of an open-label study is always suspect.

DR. YANG: Okay. Ms. Lane.

MS. LANE: I would conclude that the Sponsor's evidence shows that this is effective and safe for a number of the trial participants, and I understand a number of the FDA's concerns, but -- and I'm aware of them, and I would still be supportive.

MS. MATTIVI: Kris Mattivi.

I think it would be overly optimistic to hope for global improvement across a study of this type in all subjects. So it appears that the signals that were seen in the blinded portion of the study were carried through and the study became open label. So I think, you know, yes, there are certainly indications that carries forward.

DR. YANG: Mr. Mueller.

MR. MUELLER: Dave Mueller.

I agree. Yes, there definitely can be conclusions, particularly like Dr. Fessler, there's an explanation and that the conclusions do

demonstrate safety and effectiveness. I also agree that not every patient will get a benefit, and therefore there are going to be some patients dropping out.

The statement about -- which I questioned earlier -- there were missing data, I disagree with that statement in that when a patient drops out, you're not going to get their data, and you can't count data that's not yet gotten for down the road. So I disagree with that statement being missing data. But overall, yes.

DR. YANG: Okay. Dr. Toledano.

DR. TOLEDANO: Dr. Toledano thanks Mr. Mueller for clarifying the definition of missing data versus data that isn't due to come into the system yet. I think the open label phase gets as close to real world as you can pretty much get in the actual real world. A very strong yes on the safety results and yes on the effectiveness as well.

DR. YANG: Dr. Balish.

DR. BALISH: Marshall Balish.

Again, safety I agree on. I'm a little concerned about the efficacy. I was a little bit happier when they showed the slide that patients with or without medication changes had similar improvement over time in the open label. I also have reservations about concluding efficacy from open label.

DR. YANG: Okay.

DR. CAVAZOS: Although I share that reservation, I do believe that this was a very long open-label study that demonstrates that there is no regression to the mean. The efficacy seems to be maintained and, in fact, improve as indicated, but the reason why in antiepileptic drugs, we give those -- I mean, they are -- yes, indeed, they tend to keep getting better is because the drugs work. I mean, that's traditionally the explanation.

So from my standpoint, I do believe that there are some conclusions that can be drawn that are -- the inferences clearly are not as strong, but nevertheless, there is data of efficacy as well as safety.

DR. YANG: Thank you.

Dr. Rogawski.

DR. ROGAWSKI: I agree with Dr. Privitera and others that open-label data are suspect and should be taken with caution. For me, the most important piece of the open-label data was whether there was or was not convergence of the sham group to the treated group. And, therefore, in my mind, it's very important for the FDA and the Sponsor to come together, and since they did have a divergent analysis there, to try to understand whether the Sponsor's statistical approach was valid. Apparently that data hadn't been presented to the FDA, and so hopefully, that will be something that the FDA will be able to address.

DR. YANG: Thank you.

Dr. Haines.

DR. HAINES: Steve Haines.

I think we can conclude that the open-label data suggests the continuing effect and do not suggest that the effect wears off. And it's a good way to monitor for long-term safety.

DR. YANG: Okay. Dr. Nikhar.

DR. NIKHAR: Nirjal Nikhar.

My interpretation from the open-label data is positive, that it's safe, and I do agree with the efficacy. I think it is efficacious, you know, though this caution, I think there is some comparator to the baseline and the historical studies. It may not be as clean as we'd like, but it's what you have, and what you have is good.

DR. YANG: All right.

DR. CONNOR: Jason Connor.

I think that the open label data reassures us of the safety signal, and even though it's a bit ambiguous with FDA's look at the open-label phase in terms of means, I think it's heartening to see, particularly, that the responder analysis shows progressively in statistically significant increases in response rates for both the treatment and sham group once the sham is turned on.

DR. YANG: All right, Dr. Krauthamer. With regard to Question 3b, it seems that from the Panel there is a strong yes for safety conclusions despite the issues that are stated.

However, it's a bit more mixed when it comes to efficacy data. Some of the concerns of the ones that say yes to that, the continuity effect seems to be convincing.

There is disparity on the sham to treatment issue and that this doesn't work the same for everyone.

And the last issue was about the "with or without AEDs" and the changes there.

Okay? Good. Question 4.

MS. SMITH: Question 4: The protocol and study results do not contain specific data regarding electrode placement or selection of detection and stimulation parameters. Please state whether the instructions for electrode placement and device settings are adequate for general use of the device in the indicated population concerning:

- a. Electrode placement - how to choose anatomic location and place the electrodes, including the depth electrodes
- b. Selection of detection and stimulation parameters

Or, please provide the type of information that the sponsor would need to collect to adequately inform the instructions.

DR. YANG: So I'd like to start to my immediate left with Dr. Connor and go around the other way. If you could please answer the question, too, as to whether or not the protocol and study device, the instructions for electrode placement and device settings are adequate, first.

And then tell me the type of information; otherwise, if not.

DR. CONNOR: Jason Connor.

As a non-neurosurgeon, I have no idea.

DR. YANG: Okay. Dr. Nikhar.

DR. NIKHAR: It doesn't contain the data about the electrode placement except that it's -- and I'm not so sure that you can. I think this is going to be a difficult one to mandate that you've got to put it in this place or other place. I think much depends on the patient and the seizure focus. While it would be nice to have some specific guideline, I don't know how you would write that; it's too -- this is exactly where it's going to go. So I don't have an answer to this question. I think it should be left to the neurosurgeon who is going to be placing the electrodes.

DR. YANG: Good. Dr. Haines, you're a neurosurgeon, so --

DR. HAINES: Steve Haines.

Yeah. We can't be prescriptive about this in the labeling at this point because there just isn't enough knowledge. I think the plan, the stated plan, to have this done at advanced epilepsy centers where there is great experience in localizing epileptic foci is necessary, and at this stage, that's --

DR. YANG: As best we can do. Okay, thank you.

Dr. Rogawski.

DR. ROGAWSKI: I agree that it's important to limit this to use in centers that have the expertise to carry out the procedures.

DR. YANG: Okay, thanks.

Dr. Cavazos.

DR. CAVAZOS: I want to make the point that the practice of clinical epileptology is precisely on -- or one of the -- of this particular aspect falls in that purview in location of epileptogenic zone. This is where we have epilepsy surgical conferences where all the members of the team participate.

In my view, as I have indicated through the discussion, I have concerns about the broad range of detection and stimulation parameters. I do believe that the information of what was used in this study needs to be conveyed more properly to the Panel or to the FDA because many of these parameters may have been used once or twice only. I do believe that the Sponsor said that the parameters were used across the board except for two pieces, one second on time frequency or -- I can't remember which one. There were only two parameters out of the large, broad range.

So my concern is that no, there is not enough information provided for detection and stimulation parameters, and in regards to electrode placement, that is epilepsy surgical conference. It's not prescribable based on the indication.

DR. YANG: Okay. Yes, Dr. Krauthamer.

DR. KRAUTHAMER: There's just one thing I want to add about FDA. We can't limit it to a certain level epilepsy center. We can only limit it to prescription by neurosurgeons, but --

DR. CAVAZOS: The issue here is that the detection -- the location of and positioning of strips is part of the -- of what ABPN and the American Board of Medical Specialties agrees that the epileptologists do. That's one of the areas that epileptologists do for medical practice. And so the decision point is actually not done even by a neurosurgeon. A neurosurgeon participates in the conference and, you know, votes in the conference, but this is something that is specific to a medical specialty. And I just want to make that particular point.

DR. YANG: Dr. Rogawski, you wanted to address the same?

DR. ROGAWSKI: Just a question of clarification there. Are you able to require a REMS kind of an approach where the Sponsor would be required to limit the distribution of the product through a specific mechanism, or are there any provisions that the device divisions have for that?

DR. KRAUTHAMER: Let me defer to our Chief Medical Officer, Dr. Brockman.

DR. BROCKMAN: I'm Randy Brockman. I'm the Acting Chief Medical Officer for ODE/CDRH.

So the first part to the answer, and maybe the only answer I can give you, is we can't limit the distribution of the device to a certain level of center, a certain level of expertise. We can make sure the instructions say that it's to be used by someone with a certain type of skill set, but we can't

limit it to a certain level.

Does that answer your question?

DR. ROGAWSKI: Okay.

DR. YANG: Okay, Dr. Balish, with that in mind, do you want to take a crack at the question?

DR. BALISH: I think it would be appropriate to not prescribe where the electrodes are placed, but to say that it should be -- they should be placed by someone with appropriate experience in localization of epileptic foci.

As far as detection and stimulation parameters, I would like to have more information. I think we have a real broad range. But they said, really, that a small range was really used. We'd like to know about that, like to get a little more experience and knowledge about what parameters might be most helpful, if there are some.

DR. YANG: Okay, thanks.

Dr. Toledano.

DR. TOLEDANO: Dr. Toledano still has an Sc.D. and no M.D.
Pass.

DR. YANG: Okay. Mr. Mueller.

MR. MUELLER: David Mueller.

I do not have an M.D. either. However, I do have lots of regulatory experience in dealing with FDA and labeling, and I agree with the

medical officer that FDA can't -- for a prescription device, what FDA rules on is, in the labeling, does the labeling provide adequate instructions for use. That's the key term. And what it keeps on saying is adequate instructions for use for a layperson to use the device. And obviously, no, we're not going to have a layperson using that, therefore it's a prescription device, which is limited by U.S. law to licensed physicians who have the medical experience.

Now, in the labeling of the instructions for use, the IFU, it could say something to the effect of a precaution statement, something to the effect of physicians that are adequately trained and/or experienced or have undergone adequate training, for example, the NeuroPace training program that they described earlier. I mean, there's also -- I know from experience that proctoring goes on where you all are the experts and you would have your young fellows come in and you would train them to do it the right way, so that could also be an adequate training or appropriate training.

So as far as medical degree, no, I don't have that, but labeling, yes, I think you can.

DR. YANG: Thank you.

Ms. Mattivi.

MS. MATTIVI: Kris Mattivi.

No M.D., but I agree. I think it's clear that more information, and the Sponsor has indicated that some of this investigation will be pursued.

DR. YANG: Ms. Lane.

MS. LANE: Michelle Lane.

As a patient, obviously I would be an advocate of appropriate physician training, but I have no idea how to tell you how to attain that.

Thank you.

DR. YANG: Okay. Dr. Privitera.

DR. PRIVITERA: The question of the electrode placement, I think, is a very problematic one. One, especially since we've heard that it's difficult to limit the distribution. One other possible thing would be to add to the indication that the seizure foci are localized using video EEG monitoring, because the proposed indication that the Sponsor has shown would -- says two or more foci. Somebody who is inexperienced could -- a patient comes in the office and says, oh, I have grand mal and petit mal, and they can say well, that's two foci, or have an interictal EG with spikes in two different areas, who doesn't necessarily have seizures from both of them, and say those are two foci.

So I would think, possibly, instead of limiting the physicians who can do it, to say that there are certain procedures that need to precede an indication like this, and at least video EEG monitoring would be one of them.

Selection of detection and stimulation parameters, I think that's an easier one because I think NeuroPace can provide the baseline ones, and then you can change it from there. But if you put the electrode in the

wrong place or implant the wrong kind of patient, then I think you'll have more difficulty.

DR. YANG: Thank you.

Dr. Afifi.

DR. AFIFI: Since I don't want to practice medicine without a license, I'll defer.

DR. YANG: Okay. Dr. Baltuch.

DR. BALTUCH: Yeah, I agree with Dr. Haines. I would just say that I think you'll need -- this will require a multi-disciplinary team of people which may include not only neurologists and neurosurgeons; you may require scientists and neurophysiologists. And I would hope that the industry partners here would also play a huge role in development, as programming parameters and programming goes, as we see in other device technologies.

DR. YANG: Thank you.

Dr. Petrucci.

DR. PETRUCCI: I defer to my neurosurgical and neurologic colleagues.

DR. YANG: Okay.

DR. FESSLER: Two comments. First of all, the mechanisms for training neurologists and neurosurgeons and how to do this and who to do it to and where to do it are in place. We don't have to recreate the wheel.

Secondly, if I'm lucky enough to catch my flight tonight, I have

no intention of telling the pilot how to fly my plane. By the same logic, I think it unwise for any individual group or organization that doesn't do this every day to try and tell the most highly skilled and educated clinicians in this field how to do their job.

DR. ENGEL: This is a very disturbing discussion to me. I think the placement of the electrodes is critical if this device is approved and is going to be useful. And the evaluation is essentially the same as the evaluation we do for epilepsy surgery, and the people who should do it are people who do evaluation for epilepsy surgery. And if there's no way to limit the device to that group of centers and investigators, it would be a disaster if this gets in the hands of people who want to use it in every little hospital around the country. So I would approve this only if there were some way to regulate its use to the people who could use it properly.

DR. YANG: Okay. So for Dr. Krauthamer, with regard to Question 4, as expected, there's a fair bit of abstention, obviously, but the points that are to be made were, as far as electrode placement, my impression from the group is that we don't need to reinvent the wheel, but we need to rely on those people that are qualified, that have the skill sets to localize foci, that already have some requirement to undergo training and proctoring, certain procedures that maybe must be in place before implantation takes place and, you know, with the caveat that yes, we cannot limit this to centers, but we need to be careful as to who to limit it to. So as

far as electrode placement, I think with that one, adequacy is difficult to talk about.

With regard to the selection of detection and stimulation parameters, there is apparently some work to be done there, but it may be an easier question to address. So in that sense, the data, as presented, or the protocol and study results may not yet be quite adequate.

Okay.

DR. KRAUTHAMER: Thank you.

DR. YANG: Now I would like to ask you a question. Should we proceed to Number 5, or should we go to the voting questions?

DR. KRAUTHAMER: I would like to go to 5. We've covered some of the post-approval --

DR. YANG: Okay.

DR. KRAUTHAMER: -- issues already, but I think we can finalize that.

DR. YANG: Okay, if that's the case, then let's proceed with Question 5.

MS. SMITH: Question 5: FDA's inclusion of a question on a post-approval study should not be interpreted to mean that FDA has made a decision on the approvability of this PMA device. The presence of post-approval study plans or commitments does not in any way alter the requirements for premarket approval. The recommendation from the Panel

on whether to approve a device must be based on the premarket data. The premarket data must reach the threshold for providing a reasonable assurance of safety and effectiveness before the device can be found approvable and any post-approval study would be considered. FDA requests your input on the following aspects regarding post-approval studies whether or not the Panel finds there is reasonable assurance of safety, effectiveness, and an appropriate benefit/risk balance (following its discussion and deliberations on the premarket data and analyses).

The applicant has proposed two post-approval studies:

(1) extended follow-up of premarket patients, and (2) a 1-year prospective, non-randomized study to follow up 200 newly enrolled patients at multiple centers.

The following aspects of the new enrollment study are of potential concern:

- a. The sponsor has not proposed a comparison group (e.g., best medical therapy). A comparison group may indeed be critical to evaluate safety and effectiveness. Please discuss whether there is a need for a prospective, concurrently enrolled comparison group or whether historical controls/literature would be sufficient. Please make a recommendation on the most appropriate comparator.

DR. YANG: So with Question 5, Dr. Toledano, I'm afraid we're

back to your side of the table there. If you could first answer the question of whether the historical controls are sufficient or whether you need a prospective concurrently enrolled comparison group, that would help.

DR. TOLEDANO: So this is Dr. Toledano.

I think historical controls and literature might be sufficient without reviewing them; I can't tell for sure. I think using a patient as his or her own control for some baseline period or pre-implant period might be something to look at. I'm not convinced that you need a randomized comparison group or some other prospectively enrolled comparison group.

DR. YANG: Okay. Dr. Balish.

DR. BALISH: Marshall Balish.

I think it would be preferable to have some kind of control group, not a historical control or literature control.

DR. YANG: Okay. And if so, what kind of --

DR. BALISH: So it could be people on a wait list waiting for the procedure, for example.

DR. YANG: Okay. Okay, Dr. Cavazos. Historical or prospective?

DR. CAVAZOS: Well, I'm looking. I'm beginning with the question, and it says two studies. I think the first study has value. The second study has limited value because training 20 epilepsy centers, well, there's 100 epilepsy centers, or so in the country, and it's just repeating this Study Number 1, the people to study.

So in my view, the 1 and 2, the 2 has very limited utility and is a lot of expense for another one that is not useful. Historical controls might be useful in this particular case. But I will highly encourage to have, for post-approval studies, a parameter study. A parameter study is understanding of how to use the stimulation. And so in my view, for that, it will need a prospective component.

DR. YANG: Okay, thank you.

Dr. Rogawski.

DR. ROGAWSKI: Yeah, I agree with Dr. Cavazos. I don't think that the post-marketing studies that have been proposed are adequate. There's a lot we certainly don't know about this device. And in addition to trying to understand exactly what the proper stimulation parameters are, I think we could fairly easily find out whether the device is working in any specific individual, to do exactly what Dr. Baltuch proposes, which is just turn it off for a period of time. And you could do that either in an open label fashion, which would be less desirable, or in some kind of a control fashion.

DR. YANG: Okay.

Dr. Haines, I want to bring you back to the question, whether historical cohorts are sufficient or any new prospective enrolled?

DR. HAINES: Well, I would start by, asking people to go and continue on best medical therapy when the indication for the device is failure of medical therapy is outrageous. It will take some thought, but there are

creative ways, some of which have been mentioned, to come up with comparison groups.

DR. YANG: Like a wait list.

Okay, Dr. Nikhar.

DR. NIKHAR: I think historical controls would be adequate, I agree. I think Dr. Haines raises a good point. If you go to treatment modality, going to ask people just to wait as a comparator group is not fair.

DR. YANG: Dr. Connor.

DR. CONNOR: Yeah, I agree with Dr. Nikhar.

DR. YANG: Okay. Dr. Engel.

DR. ENGEL: I don't think historical controls are appropriate. Historical controls, the clinical trials that show a responder rate of 50%, having 50% seizure reduction, and if we used historical controls, those historical controls as we make it, I think we need to use real-life controls that also are long term, because the historical controls are short term, and we want to know whether this device really has a long-term effect that continues to improve. So I think it's worth the effort to have the comparator group, and there are going to be patients who meet criteria but who don't want to have the device implanted, and they can serve as controls.

DR. YANG: Okay. Dr. Fessler.

DR. FESSLER: I agree with Dr. Haines that it's probably inappropriate to ask these people to continue on best medical therapy when

it's already failed. That being said, the other control groups were really more appropriate for the first study, not for post-market approval studies. And I think the second study proposed is subject to the same criticism. So I think the appropriate post-market approval study is to study the people that have already been done for another 5 to 10 years.

DR. YANG: Okay. Dr. Petrucci.

DR. PETRUCCI: I agree with Dr. Haines as well, for the following reasons. Not relying on the historical approach, but we should design it prospectively for more than two years, and if we want to use a control, why not look at centers that have had experience versus the newly enrolled centers and looking at the results and their outcome?

DR. YANG: Okay. Dr. Baltuch.

DR. BALTUCH: Yeah, I would -- similar convulsion disorders, I think, you do best when you have a best medical therapy arm, and you can accrue it to a best medical therapy arm by asking -- telling the patients that they will eventually get the surgery after a period of 6 to 12 months and they will be followed over that time. That seems to have given the strongest and most powerful evidence, as we saw with CSP #468.

And I think that that allows you to accrue also -- have the data and safety monitoring committee watch that very, very closely as they did with CSP when they closed the medical arm, because the surgical arm was just so much more robust in the Parkinson's disease population.

I still think that the existing patients could serve as their own controls on the overall, but I think I would defer to the statisticians on the amount of contamination that you would see if you did something like that. That would be something beyond my expertise in terms of the validity of having patients serve as their own controls in the overall turn-on/turn-off type scenarios.

DR. YANG: All right. Dr. Afifi.

DR. AFIFI: Afifi.

In a medium- to long-term prospective study, the advantage of a control group is that it shows us what the secular trend is and by definition is unpredictable because we don't know what else is going to become available for such patients. So patients who are eligible for the implant but do not wish to, as Dr. Engel mentioned, could serve as a good control group.

DR. YANG: Dr. Privitera.

DR. PRIVITERA: This is Privitera.

Because an open-label observational study like this would not be used for efficacy, I don't believe a comparison group is necessary. I think the main reason for these follow-on studies is for safety, and you don't need a comparison group for that.

DR. YANG: Ms. Lane.

MS. LANE: This is Michelle Lane.

And I would agree with Dr. Privitera's comments.

DR. YANG: Okay.

MS. MATTIVI: Kris Mattivi.

I defer.

DR. YANG: Okay.

MR. MUELLER: David Mueller.

I agree with many of the physicians so far in that controls where making patients wait, who are already intractable, 6 to 12 months, I think, is extremely inappropriate. Since all you doctors have great medical records, why not just go back into those patients' medical records and you've got their control in history already? So I think the patient could serve as their own control if a control is actually needed. I don't think a control is needed in that the data that's been provided has already demonstrated, in my mind, that the device is safe and effective. And I agree, you don't need controls if you're not going after efficacy.

And once a patient is implanted and then turn them off and see what happens is even more inappropriate, especially if they're trying to go best case, seizure-free for 6 months or 12 months, whatever it is, to get their license back or -- driver's license. I think that's not the kind of thing that we want. So either the patient as their own control if you need a control, or not have any control at all.

Thank you.

DR. YANG: Okay. So, Dr. Krauthamer, with regard to

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Question 5a, certainly the majority said historical, although there was a significant contingent that said prospective.

There are creative ways of doing that prospective one, although for instance, like waiting until you have the implantation and certain patients that met the criteria but don't want the device.

Also a concern about making patients wait when they've already failed the AEDs.

So also a concern about whether or not it's ethical to turn off the stimulator once it's working and it's effective.

So I think overall we're still talking about the Panel feeling more historical, but a few that are very strongly prospective.

Okay, Question 5b.

MS. SMITH: Question 5b: The proposal includes a collection of serious adverse events during the post-approval study, but only includes SUDEP as a specific adverse event among the endpoints. Other safety endpoints in addition to SUDEP (e.g., intracranial hemorrhage and injuries) could be worth measuring in the new enrollment post-approval study. Please discuss what safety endpoints in addition to SUDEP need to be evaluated in this post-approval study.

DR. YANG: So on this question I'm going to ask for a raise of hands if you want to comment, actually. If you feel that there are other endpoints in response to SUDEP, please raise your hand and tell me what

they are, okay?

All right, I'll just go around. Mr. Mueller.

MR. MUELLER: I want to remind the Panel that currently, by law, FDA requires that for a commercial product, when there is a death or serious injury or a device malfunction, the sponsor and the hospital have to submit medical device reports or MDRs. That's already in place; it's not anything that has to be put into a post-approval study. So the SUDEP is a death and would be reported, but if that's the only thing the Sponsor is promoting --

DR. YANG: Okay. Dr. Privitera, did you have your hand up?

DR. PRIVITERA: Yes. Hemorrhage needs to be added.

DR. YANG: Hemorrhage, okay.

I'm sorry, I missed who else on this side of the room?

Dr. Baltuch.

DR. BALTUCH: I think hardware issues should be --

DR. YANG: What?

DR. BALTUCH: Hardware issues need to be included.

DR. YANG: Hardware issues.

Okay. Dr. Engel.

DR. ENGEL: The same. Infections and replacement and hemorrhage.

DR. YANG: Hardware, okay.

All right, on this side of the table. Dr. Nikhar.

DR. NIKHAR: Yeah, the prevalence of depression was very high in this study, the baseline data. And I think in the PAS, suicidal attempts and other forms of death, I think, need to be assessed aside from just SUDEP.

DR. YANG: Okay. Dr. Haines.

DR. HAINES: I'm going to agree with all of the things that have been suggested and respectfully disagree with Mr. Mueller, that the system exists, but it's not used well. And having spent a summer trying to sort through all that data on a specific device, we need to collect it.

DR. YANG: Okay. Dr. Rogawski and then Dr. Cavazos.

DR. ROGAWSKI: Yeah. So I completely agree that data, particularly on hemorrhages, but other kinds of serious side effects like infection should be collected, sure.

DR. YANG: Okay. Dr. Cavazos, do you have anything to add to the list?

DR. CAVAZOS: Yes, I do. Seizure exacerbations are one thing that has been noted and understanding what parameters -- or what covariate characteristics will be important to try to understand how this thing works.

DR. YANG: Okay. Anyone else?

If not, to Question 5b, Dr. Krauthamer, there were obviously a number of people that said there are more than SUDEP, particularly other

forms of death like suicidal ideation or significant depression. But also hemorrhage, hardware issues, infection, and seizure exacerbations.

Okay, Question 5c.

MS. SMITH: Question 5c: The sponsor has proposed a 1-year follow up. A longer duration of follow-up (perhaps up to 10 years) may be necessary to estimate the long-term safety of devices permanently implanted by newly trained specialists in a real world setting. Please discuss what is an appropriate length of follow-up for the newly enrolled patients.

DR. YANG: This one I'm going to have to go around, so Dr. Toledano, let's start with you again.

DR. TOLEDANO: So Dr. Toledano thinks, in light of the fact that we have a seven-year long-term treatment -- right, the LTT -- seven-year study there with the open-label phases and we do have the MDR system and reports can go into the MAUDE, whether they do or not, 10 years is just outrageous. It's not doable. The patients are going to lose interest, they're going to move, you're not going to be able to get them to come back. You're just setting somebody up for failure and wasted effort. I think, really, two years would be the maximum on follow-up.

DR. YANG: Okay. So what's your length of time, Dr. Balish?

DR. BALISH: I think two years is reasonable. I think that there are adjustments, also, in parameters that people will be doing, so is that going to be safe in new hands? Is that going to be --

DR. YANG: Okay.

DR. BALISH: Two years will give you time for that.

DR. YANG: Okay. Dr. Cavazos.

DR. CAVAZOS: Two years.

DR. YANG: Okay. Dr. Rogawski.

DR. ROGAWSKI: I don't know what the appropriate length of time is. The more the better, for sure.

I just wanted to reinforce Dr. Cavazos' point about the possibility that there could be kind of a kindling effect. Now, he's the expert on kindling, so I have to defer to him on that, but that's something I would worry about, if you're stimulating repetitively over a long period of time. There may be a problem there.

DR. YANG: Okay. Dr. Haines.

DR. HAINES: In terms of device issues and infection rates, we've got to have at least two, three -- it depends a little bit on what the battery life is and how often --

DR. YANG: Okay.

DR. HAINES: -- the batteries need to be changed.

DR. YANG: Okay.

DR. NIKHAR: I agree. Nirjal Nikhar.

I agree, two years. I think 1 year is too short; 10 years is too long.

DR. YANG: Okay. Dr. Connor.

DR. CONNOR: Yeah. I think, without exactly knowing what specific clinical questions this is meant to answer, it's hard to answer the length question. But it seems like we have a lot of long-term data, and continuing to follow those patients, if possible, is a good idea.

DR. YANG: Okay. Dr. Engel.

DR. ENGEL: Yeah, the issue of kindling is an interesting one, and if there is a kindling effect, it could take 5 to 10 years. But I don't think that justifies a formal follow-up, but somebody needs to keep an eye on it.

DR. YANG: All right. Dr. Fessler.

DR. FESSLER: I think two years is a reasonable compromise.

DR. PETRUCCI: Ralph Petrucci.

I think, judging a bit on our patients with us today, it should be a two-year minimum given their lifelong readjustment. Five years, probably. Two to five. It takes a long time to readjust after being in such a storm for such a long period of time.

DR. YANG: Dr. Baltuch.

DR. BALTUCH: Yeah, I think that's a reasonable amount. I just want to make sure that all the people with devices are tracked pretty carefully as to where they are and what they're up to, that they're just not lost. We've seen, in the past with other devices, that patients just become lost. They're not necessarily tracked as to when they need a battery change.

Industry is often not on top of their most current addresses and where they are, and I have concerns about these patients that wind up in emergency rooms where people have -- you know, this is a new device. People have no idea what this is, you know, how they're going to be studied, how they're going to be imaged. So I think this is a novel device; this is new, it's never been used before. People don't know about it, they will not know about it widely, so I think industry is going to have to track all these people very carefully over a fairly long period of time. Not necessarily -- just sort of careful. Clinical things, but from demographic issues, definitely.

DR. YANG: Okay. Dr. Afifi.

DR. AFIFI: I would go with three to five years.

DR. YANG: Okay.

DR. PRIVITERA: Privitera.

Two years. I think that would be sufficient to evaluate the hemorrhage question.

DR. YANG: Okay.

MS. LANE: Michelle Lane.

Two to five years.

MS. MATTIVI: Kris Mattivi.

I also agree that 10 years would be unreasonable for the sponsor to have to conduct a study for that period of time.

DR. YANG: Okay.

MR. MUELLER: Dave Mueller.

I agree with Dr. Toledano, that they're already doing a seven-year study of the existing patients, and that's definitely long enough. I do have a concern, a serious concern, on the way the question is phrased in that it says to estimate the long term safety of devices implanted by newly trained specialists. So how many newly trained specialists? How long do you follow the newly trained? When are they no longer new? So in five years, if there's a newly trained doctor, do you now have to follow that doctor's patients for another five years or two years or three years, whatever it ends up with? So that's a very strong point on my end. Otherwise, I -- I'll stop.

(Laughter.)

DR. YANG: Okay. Dr. Krauthamer, 5c, with regard to.

You've heard the latest concern about the newly trained. However, I'll just say that most people were saying that two to three years with a few three to five years, with most feeling that 10 years is probably not reasonable, and that is because of hardware issues, readjustment, and that it's very important that industry track these patients for a while because it is a new device and if they do end up -- I take his point entirely -- if they do end up in the ER, no one's going to know what to do with these things.

DR. KRAUTHAMER: Thank you.

DR. YANG: Okay. Question 5d and last question.

MS. SMITH: Question 5d: Effectiveness data are not planned

to be collected during the new enrollment post-approval study. Given that the device is a permanent implant, it is important to monitor effectiveness in a real world setting. Please discuss what effectiveness questions, if any, should be addressed in the post-approval study.

DR. YANG: All right. Shall we do the quick run around the table? Concise.

DR. TOLEDANO: This is Dr. Toledano starting. No M.D., pass.

DR. YANG: All right.

DR. BALISH: Marshall Balish.

I think it would be nice to know about responders in their real-world setting.

DR. YANG: Okay.

DR. BALISH: Responder rate.

DR. YANG: Okay.

DR. BALISH: Quality of life.

DR. YANG: Okay. Dr. Cavazos, we've got responder rate, quality of life.

DR. CAVAZOS: I understand. But back to parameters.

Effectiveness parameters --

DR. YANG: Okay.

DR. CAVAZOS: -- need to be studied.

DR. YANG: Okay. Dr. Rogawski.

DR. ROGAWSKI: I agree with Dr. Cavazos. And I understand the ethical concerns of asking the patients to shut the device off, but on the other hand, you think that that's a benefit to the patient because they'll find out, you know, whether their device is working for them or whether they need to have it in their head. So I think there's a balance there, and I think you might be able to construct a study that would provide patient benefit and at the same time collect data that would be important medically.

DR. YANG: Okay. So far, Dr. Haines, we have responder rate, quality of life, parameters. Want to add to that?

DR. HAINES: Yes. Some efficacy measures must be collected, and I agree with the ones that have been stated.

DR. YANG: All right, very good.

Dr. Nikhar.

DR. NIKHAR: Nirjal Nikhar.

I think, aside from seizure frequency, which has been the focus of efficacy of this product, I think we can also measure things like functionality. So you may have as many seizures as you had previously, but if you're able to go to work, if you're able to go to school without missing school days, I think these are measures of functionality that should be measured. And I think this is broader than merely numbers.

I think shutting off the device is an unreasonable suggestion, and I don't think any patient who is benefiting would like to have that option

presented to them. And neither do I think it would be, again, a reasonable offer.

But functionality, in some measure, some quality measure should be addressed and followed.

DR. YANG: Okay. Dr. Connor.

DR. CONNOR: Jason Connor.

I think, you know, we're going to vote here on effectiveness today, and FDA will approve it or not based upon that effectiveness. I think beyond that, to me, this is an interesting question but beyond FDA's job, meaning if some study, whether it's this post-approval study or someone, you know, some neurologist does shows that it stops working after five years, what's FDA going to do? They're not going to, I think, say okay, it's not approved anymore because it doesn't work after five years. Neurologists are going to have a conversation with their patients and say this only works for so long, do you want to bother having it. So to me, if it doesn't matter to FDA what they can do by law, what the answer is, then we shouldn't make it part of the regulatory project.

DR. YANG: Okay. Dr. Engel.

DR. ENGEL: This is a very important question for research purposes, and I would like to see it pursued, but maybe FDA regulations are not the right place to do it. But the fact that there is evidence that it becomes more effective over time and an increasing number of patients

become seizure-free would be very important to document. And in order to do that, you really would have to have a comparator group because there are no long-term studies of comparable patients with intractable epilepsy.

Also, if you're going to follow quality of life, most NIH studies, if you do quality of life, you have to do other things because if quality of life improves, you want to know why, so you have to do functionality tests. So I think it would be very important to do this, but hopefully you could get an NIH grant to do it.

DR. YANG: Okay. So, Dr. Fessler, we have responder rate, quality of life, functionality, parameters for effectiveness, and then seizure-free.

DR. FESSLER: Really, I have nothing further to add.

DR. YANG: All right.

DR. PETRUCCI: Again, the storm that these patients have been through, I think, really warrants a closer longer-term follow-up period. This is ripe for research, and it's right for behaviors to be involved. Some of the psychiatric parameters ought to be looked at, certainly the extension of the cognitive parameters over a long period of time. That's all.

DR. YANG: Okay.

DR. PETRUCCI: Thanks.

DR. YANG: Dr. Baltuch.

DR. BALTUCH: Yeah, I think one of the people mentioned, in

the patient advocacy group presentations, that nothing had been approved in 15 years, and it took me back to, you know, E05 vagal nerve stimulation, you know, and then many, many questions that are not answered by E05 that remain, what, 80 to 100 thousand implants later, still unanswered. And I have patients who sit in the office, and they ask me all these questions about seizure type and what their chances are and this or that that were never answered. And after E05 and approval, they probably never will be answered.

I mean, there are many, many papers that have been written on vagal nerve stimulation. Do they really answer any questions in any Class I or Class II fashion beyond E05? So I'm left with a sense that I don't know what the answer should be to the question, but I worry, as a clinician, with device approval, what goes forward afterwards? Are we really going to learn and get these questions answered? Are we going to find ourselves in, sort of, what we see with vagal nerve stimulation?

DR. YANG: Dr. Afifi.

DR. AFIFI: One question that was discussed earlier is what subgroups might benefit more than others, and the post-approval study would be a good opportunity to try to answer that question.

And there are two ways to go about it: to either collect data on everybody and then look at those data and see which subgroups do best, or think ahead which are the potential subgroups and collect more extensive

data about those and then try to answer it that way.

So the answer is yes, I think some effectiveness analysis needs to be done, and I suggested a couple of ways to go about it.

DR. YANG: Okay. Dr. Privitera.

DR. PRIVITERA: Privitera.

I don't think effectiveness is necessary in a post-marketing study like this, but I think a lot of the questions that have been brought up provide wonderful opportunities for investigator-initiated projects, but mostly multi-center to look at some of these questions. But I don't think that that's within the purview of the FDA.

DR. YANG: Ms. Lane.

MS. LANE: Michelle Lane.

I agree. I don't think that the post-marketing studies are the correct opportunity for effectiveness studies.

DR. YANG: Okay. Ms. Mattivi.

MS. MATTIVI: I have nothing further to add.

DR. YANG: Okay. Mr. Mueller.

MR. MUELLER: Dave Mueller.

I agree with Dr. Privitera and Ms. Lane. This is not the place for research. NIH grants, fantastic, great. But the data has shown that it's safe and effective, and the post-approval study is not an FDA research proposal. So that's my answer there.

One other topic, and again, I don't know, you have to talk to the company, but pretty much all the devices that I have dealt with over the years, the patients get patient ID cards to carry with them so if they do end up in the ER and they're unconscious, the doctor has a contact number to call to learn about the device.

Thank you.

DR. YANG: Okay. Dr. Krauthamer, with Question 5d there were at least four voices that questioned whether or not effectiveness should be studied in a post-approval study. The ones that said yes, perhaps the questions can be derived from a subgroup analysis; otherwise, responder rate, quality of life, functionality, psychiatric issues, and parameters for effectiveness are probably the main ones that come to the fore.

Does that answer your --

DR. KRAUTHAMER: Yes, thank you.

And we are a public health agency, and we are concerned once a device is out as well. We look at the whole lifecycle of a device.

Thank you.

DR. YANG: Okay. Thank you very much.

At this time, we're going to move on to the FDA and Sponsor summations, then. The Panel will hear summations, comments, or clarifications from the FDA. You have five minutes, and you may approach the podium, if you like.

MS. HOANG: Good afternoon. I'm Quynh Hoang, Chief of the Neurodiagnostic and Neurosurgical Devices Branch at FDA.

From this morning, you've heard from the FDA review team that there are risks associated with the use of the RNS device and that there is significant uncertainty as to whether the device provides a clinically meaningful benefit. As such, we have requested your input in several key areas.

The comments and suggestions that you have just provided will be included in our assessment of whether the available data support a reasonable assurance of safety and effectiveness for the RNS for the proposed indication. We thank you for your thoughtful comments and suggestions.

In addition, I would like to take this opportunity to thank you, the Open Public presenters, for sharing their experience and assessments.

DR. YANG: Thank you.

Are there any summations, comments, or clarifications from the Sponsor? You have five minutes. You may approach the podium at this time. Please remember this is for summation and clarification, not for presenting new data.

DR. BERGEY: So I think they asked me to talk because, number one, I was involved in some of the pivotal trials and the feasibility trials, but mainly because I treat patients with very severe intractable partial

seizures.

And you've heard, we've had 14 new drugs in the last 20 years, and yet, when the Institute of Medicine put out their report in 2012, they underscored the fact that we have unmet needs. Sure, we're underutilizing resective surgery. We should be doing more resective surgery. But there are patients who are not candidates for that and don't respond to medications. And what we've heard here today is a novel, innovative device that really advances the field of neurostimulation with a closed loop type of paradigm.

Are there unanswered questions? Absolutely. What are the best stimulation parameters? Is there a type of neuromodulation that occurs? Are there subgroups of populations that may benefit more than others? These are the things that we will learn if we have the opportunity, as treating physicians, to apply this to our patients.

When you talk about successful treatment of patients, we've obviously today focused on efficacy and safety. Those are the most important considerations. But I think if you ask any patient, side effect profile is equally important. And one of the benefits of neurostimulation is the side effects are dramatically lower than you see with drug-related applications. There aren't cognitive side effects, there's much less concern about teratogenicity, and there are many unknowns with newly approved drugs that you don't need to consider when you have a device such as the RNS.

And so I would just appeal to the Panel, as a treating physician, that we need this to add to our armamentarium. It's not going to be first line therapy, it's not going to be second line therapy, but we just want to have it available to apply to appropriate patients.

Thank you.

DR. YANG: Thank you.

Before we proceed to vote, I would like to ask our non-voting members, Ms. Mattivi, our Consumer Representative; Ms. Lane, our Patient Representative; and Mr. Mueller, our Industry Representative, if they have any final comments before proceeding to the vote.

Let me just go in line here, Mr. Mueller. Or Ms. Lane, let's go the other way. Any last comments?

MS. LANE: Sure. As a patient, I understand the need. I remember being in college and having a case of epilepsy that was difficult at that time to treat and having a new drug come out that really helped me. And now I'm in a place where I feel, you know, I can speak on behalf of others that find it difficult to speak for themselves. So I understand the need for finding new therapies, but also balancing that need for the risks that come associated with them.

So I thank everyone for being here today and take that in mind when you vote.

DR. YANG: Thank you for your comments.

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Ms. Mattivi.

MS. MATTIVI: First I would like to applaud the patients who came today to share their experiences with us. It was very important and very important testimony that you gave.

I would also like to applaud the Sponsor for a very well presented presentation and the integrity with which you conducted your analyses and especially when difficulties arose. I thought you just did a very good job, and you have presented a device that provides great hope and the opportunity for great clinical significance for this patient population.

DR. YANG: Thank you, Ms. Mattivi.

Mr. Mueller, last comments.

MR. MUELLER: Yes, thank you.

I want to thank the Panel for the very detailed and thorough discussion. I also want to thank the Sponsor, as well as -- especially the patients, very meaningful. And last but certainly not least, the FDA. They did an excellent job going through -- it's a lot of work to go through PMAs and to analyze the data and try to look at all the possibilities, so I want to congratulate them on the great job. And I would hope that we all recommend approval.

And, last, I also want to thank FDA for giving me the opportunity to be the Industry Rep. This will be my last panel meeting after three years, so thank you.

DR. YANG: Thank you very much.

So we are now ready to vote on the Panel's recommendations to FDA for this premarket approval application. The Panel is expected to respond to three question relating to safety, effectiveness, and risk versus benefit.

Ms. Facey will now read the three definitions to assist in the PMA voting process. Ms. Facey will also read the indication statement for this product.

MS. FACEY: The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, allow the Food and Drug Administration to obtain a recommendation from an expert Advisory Panel on designated medical device pre-market 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.

The definitions of safety, effectiveness, and valid scientific evidence are as follows:

Safety, as defined in 21 C.F.R. Section 860.7(d)(1) - There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied

by adequate directions and warnings against unsafe use, outweigh any probable benefits [sic].

Effectiveness, as defined in 21 C.F.R. Section 860.7(e)(1) - There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

Valid Scientific Evidence, as defined in 21 C.F.R. Section 860.7(c)(2) - Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness.

The sponsor has proposed the following indications for use:
The RNS System is an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures from no

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more than two foci that are refractory to two or more antiepileptic medications.

Panel members, please use the buttons on your microphone to place your vote of yes, no, or abstain to the following three questions.

Voting Question 1 reads as follows: Is there reasonable assurance that the NeuroPace RNS System is safe for use in patients who meet the criteria specified in the proposed indication?

Please vote now: yes, no, or abstain.

Voting Question Number 2: Is there reasonable assurance that the NeuroPace RNS System is effective for patients who meet the criteria specified in the proposed indication?

Please vote now: yes, no, or abstain.

The third and final voting question reads as follows: Do the benefits of the NeuroPace RNS System for use in patients who meet the criteria specified in the proposed indication outweigh the risks for use in patients who meet the criteria specified in the proposed indication?

Please vote now: yes, no, or abstain.

The three voting questions have been read, and Panel members have voted. Everyone please give us a few minutes to verify the results.

(Verification of voting.)

MS. FACEY: Okay. Thank you, everyone, for that brief pause.

So the votes have been captured, and I will now read the votes

into the record.

For Question Number 1: Dr. Toledano, yes. Dr. Balish, yes.
Dr. Cavazos, yes. Dr. Rogawski, yes. Dr. Haines, yes. Dr. Nikhar, yes.
Dr. Connor, yes. Dr. Engel, yes. Dr. Fessler, yes. Dr. Petrucci, yes.
Dr. Baltuch, yes. Dr. Afifi, yes. And Dr. Privitera, yes.

On Question 1, the Panel voted 13 yes, 0 no, and 0 abstentions that the data shows that there is reasonable assurance that the NeuroPace RNS System is safe for use in patients who meet the criteria specified in the proposed indication.

Question Number 2, the votes were as follows: Dr. Toledano, yes. Dr. Balish, yes. Dr. Cavazos, yes. Dr. Rogawski, yes. Dr. Haines, yes. Dr. Nikhar, yes. Dr. Connor, yes. Dr. Engel, yes. Dr. Fessler, yes. Dr. Petrucci, yes. Dr. Baltuch, yes. Dr. Afifi, abstain. And Dr. Privitera, yes.

On Question 2, the Panel voted 12 yes, 0 no, and 1 abstention that there is reasonable assurance that the NeuroPace RNS System provides probable benefit for patients who meet the criteria specified in the proposed indication.

The third and final voting question. The votes are as follows:
Dr. Toledano, abstain. Dr. Balish, yes. Dr. Cavazos, yes. Dr. Rogawski, yes.
Dr. Haines, yes. Dr. Nikhar, yes. Dr. Connor, yes. Dr. Engel, yes. Dr. Fessler, yes. Dr. Petrucci, yes. Dr. Baltuch, yes. Dr. Afifi, abstain. Dr. Privitera, yes.

On Question 3, the Panel voted 11 yes, 2 abstentions, and 0 no

that the probable benefits of the NeuroPace RNS System do outweigh the risks for use in patients who meet the criteria specified in the proposed indication.

The three voting questions are now complete.

DR. YANG: Given that there are no "no" votes to any of the questions, I still would like to ask the Panel whether there are any final comments with respect to labeling restrictions on use or other controls.

Dr. Rogawski.

DR. ROGAWSKI: Yes. I would again propose that the labeling be significantly restricted. I mentioned a couple of ideas on how to do that.

Dr. Privitera raised the possibility of limiting it to use in patients who have had video EEG monitoring, and that seems like it's something sensible that could be discussed between the FDA and the Sponsor. And that would have the added advantage of really requiring it to be done in centers that have the expertise to do this device.

DR. YANG: Okay, thank you.

Dr. Cavazos.

DR. CAVAZOS: Yes, but the issue for meeting these parameters, I will say that the FDA needs to review the parameters that were used substantially in the study and the limits, it needs to be limited to those parameters. Certainly, stimulators, for experimental uses, can be available, can be used or can be kept for other more broad examination of parameters.

But for clinical use, the indication has to be more limited to what it was used.

DR. YANG: Great, thank you.

DR. ENGEL: I definitely would not say video EEG monitoring because lots of places do video EEG monitoring that are not epilepsy centers. If possible, I think it should be done in places, only places, that have the facilities to do invasive monitoring, if necessary.

DR. YANG: Okay, thank you.

I would like to thank the Panel, then, and the FDA and the Sponsor for their contributions to today's panel meeting.

Dr. Krauthamer, do you have any final remarks?

DR. KRAUTHAMER: No, but I do want to thank everyone in the audience and the speakers that we had today and especially the Panel for your contribution to this effort.

DR. YANG: Great, thank you.

Therefore, the February 22nd, 2013 meeting of the Neurological Devices Panel is now adjourned. Thank you.

(Whereupon, at 5:42 p.m., the meeting was adjourned.)

CERTIFICATE

This is to certify that the attached proceedings in the matter of:

NEUROLOGICAL DEVICES PANEL

February 22, 2013

Silver Spring, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

CATHY BELKA

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