

SUMMARY MINUTES

MEETING OF THE NEUROLOGICAL DEVICES ADVISORY PANEL

OPEN SESSION

June 15, 2004

**Gaithersburg Holiday Inn
Gaithersburg, MD**

**Neurological Devices Advisory Panel Meeting
June 15, 2004**

Open Session

Attendees

Chairperson

Kyra J. Becker, M.D.
University of Washington
School of Medicine

Philip S. Wang, M.D., M.P.H., Dr. P.H.
Brigham and Women's Hospital

Executive Secretary

Janet L. Scudiero, M.S.

Consumer Representative

Crissy E. Wells, R.T., M.B.A., M.H.S.A.
Western Regional Community Clinical
Oncology Program

Voting Members

Jonas H. Ellenberg, Ph.D.
Westat

Industry Representative

Andrew K. Balo
DexCom, Inc.

Laura J. Fochtmann, M.D.
State University of New York,
Stony Brook

FDA Representatives

Chang Lao, Ph.D.
Division of Biostatistics
Statistical Reviewer

Annapurni Jayam-Trouth, M.D.
Howard University
College of Medicine

Carlos Peña, Ph.D.
Efficacy Reviewer

Mary E. Jensen, M.D.
University of Virginia
Health Sciences Center

Michael Schlosser, M.D.
Safety Reviewer

Richard P. Malone, M.D.
Medical College of Pennsylvania
Hanneman University

Theodore R. Stevens
Chief, Restorative Devices Branch

Irene E. Ortiz, M.D.
University of New Mexico

Celia M. Witten, M.D., Ph.D.
Division Director

CALL TO ORDER

Panel Executive Secretary Janet L. Scudiero, M.S., called the meeting to order at 8:05 a.m. She stated that Laura J. Fochtman, M.D., Richard P. Malone, M.D., Irene E. Ortiz, M.D., and Philip S. Wang, M.D., M.P.H., Dr. P.H. were temporary voting members of the panel for the meeting,

Dr. Becker, panel chair, began by noting that the panel was meeting to discuss and make recommendations to the Food and Drug Administration (FDA) on the pre-market application (PMA) P970003/S50, the Cyberonics, Inc., Vagus Nerve Stimulator (VNS) Therapy System. This device is indicated for adjunctive long-term treatment of chronic or recurrent depression for patients over the age of 18 who are experiencing a major depressive episode with no adequate response to two or more antidepressant treatments. She invited panel members to introduce themselves.

PANEL UPDATE

Theodore R. Stevens, Chief, Restorative Devices Branch, stated that the Concentric Medical MERCI Retriever device remains under review in the General Surgical Devices Branch. FDA has recently published a draft guidance and a reclassification proposed rule for the vascular and neurovascular embolization devices; the comment period ended May 25. Several devices have been cleared that were reviewed under the Orthopedic Devices Panel, including several PMMA cements used for pathological fracture of the vertebral body. These 510(k)s were cleared based on the reclassification of bone cements.

OPEN PUBLIC HEARING

Colleen Kelly, a patient in the D-01 Cyberonics study, asked the panel to approve VNS because it offers a viable alternative to those suffering from treatment resistant depression (TRD). She said that she had exhausted all treatment options for her depression, including drugs, yoga, and 33 consecutive treatments of electric convulsive therapy (ECT). Ms. Kelly reported that she has had the device for 4 ½ years. She still experiences brief periods of depression and recognizes the devices shortcomings, but she feels there is no other possible treatment for her condition.

Lydia Lewis, President, Depression and Bipolar Support Alliance, said that she was speaking to the panel to highlight the critical need for new therapies, not necessarily to support the approval of VNS. She noted that more than 30,000 people take their lives each year because they do not respond to the current treatments for depression and bipolar disorder. Ms. Lewis showed a photograph of Barbie, her co-worker's sister who eventually committed suicide, and discussed Barbie's extensive efforts to combat depression. She asked the panel to do all they could to help people with TRD.

Lauri I. Sandoval, a patient in the Cyberonics study, showed a video of herself 5 years ago, before having the VNS implantation, being assessed for chronic depression. She had just resigned her job and been diagnosed with TRD. Ms. Sandoval decided to participate in the VNS device study; eventually, she said, life became "wonderful." Three months ago she felt no throat sensation from the device and hoped the battery was dead. She underwent implantation of the "new and improved" VNS device, which will not need batteries for 8 to 10 years.

Irvin J. Muszynski, J.D., Director, Office of Health Care Systems and Financing at the American Psychiatric Association, spoke about TRD from the point of view of employers and third party payers. He went over the prevalence of diagnosable depressive disorders, including an estimate that 20-30% of those diagnosed with depression do not respond to treatment. From an economic point of view, Mr. Muszynski said that the cost of treatment for those who are even “mildly resistant” is easily double that of patients who do respond; those who are severely resistant to treatment incur costs four times greater than those who do respond. He added that the World Health Organization reports that depression is the fourth leading cause of disability worldwide and may become the second or first cause in the next decade. Mr. Muszynski told the panel that improved early identification and long-term management techniques are needed, as well as new treatments.

Charles Donovan, a patient in the Cyberonics D-02 study, read the letter he recently sent to the FDA in support of the device and urged the panel to unconditionally approve VNS as treatment for chronic depression. In the letter he described his history of depression and treatment. He noted that he had undergone about 15 ECT treatments and by 1999 his condition forced him to stop working. In 2001, he had the VNS device implanted. Mr. Donovan reported that at first his mood only gradually improved, but now he pursues an active and productive life. He said he is especially impressed with the sustained nature of the treatment. Mr. Donovan noted that by the time he met with the study investigators he had run out of treatment options. He said the side effect of hoarseness is bothersome but tolerable.

Marna Daventort, a patient in the Cyberonics study, explained her road to finally getting treatment for her TRD. She noted that despite her accomplishments, including acquiring a Ph.D., depression was something she could not master. After trying all of the options, none of which worked for very long, Dr. Daventort had the VNS device implanted three years ago. After about 12 to 18 months she began to see results. She said that she understands it is not a replacement for drug therapy and other therapies, but she asked the panel to make it an option for those patients who have no where else to turn.

Karmen McGuffee, a patient in the Cyberonics study, showed a video of herself in an assessment interview five years ago, before she had the VNS device implanted. Ms. McGuffee said that she had experienced depressive symptoms since childhood, and had been prescribed numerous drugs and other therapies and combinations. These would work for 6 to 12 months, and then the depression would return. She was in and out of hospitals for the depression, as well. Her family noticed an improvement in her condition 3 to 6 weeks after VNS implantation, as if “a dark funeral veil” had lifted. Ms. McGuffee said that she does not believe VNS has cured her, but she knows that it has helped in ways “that words cannot express.” She urged the panel to approve VNS for TRD.

Dr. Becker noted that three patients and family members wrote the FDA requesting that the agency approve the device, and one patient wrote asking that the device not be approved. She asked if anyone in the audience wanted to speak during the open public hearing. **Mary Barrett, a patient in the D0-2 Cyberonics study**, then asked that the panel approve the VNS device. She reported that she had been prescribed many

drugs, only one of which provided her with relief but she stopped taking it because of side effects. Ms. Barrett received the VNS implant in 2001; she said that the parameters had to be increased but afterwards she better for the first time since having to discontinue the medication with side effects. She added that she volunteered for the study as a last resort.

SPONSOR PRESENTATION

Alan Totah, Vice President for Regulatory Affairs and Quality at Cyberonics, introduced the sponsor's presenters and the outside experts. Mr. Totah presented the indications for use of the VNS device and the operation of the device. He noted that there is no FDA-approved treatment for this level of chronic or recurrent depression. The VNS system for TRD works exactly like the VNS system for epilepsy, unanimously approved by the FDA in 1997; more than 29,000 epilepsy patients are using the device. The device is typically programmed on for 30 seconds and off for 5 minutes, 24 hours a day and 7 days a week. Surgical complications are minimal. The patient can temporarily turn off the device if hoarseness is problem during singing or public speaking.

Mr. Totah discussed the regulatory history of the device. Studies to use the device began in 1998 after some epilepsy patients using the VNS device reported mood elevation. FDA granted expedited review status in July 1999; in January of 2002 the D-02 acute 12-week study was unblinded and the results were analyzed. The primary endpoint for this study did not reach statistical significance; however, the results did show a positive trend in favor of VNS for TRD and a key secondary endpoint was

statistically significant. In September 2002, Cyberonics submitted a revised D-02 long-term and D-02 versus D-04 analysis to FDA. The PMA supplement was submitted October 2003; since then, Cyberonics has responded to FDA's deficiency letter regarding the PMA.

Mr. Totah explained the changes Cyberonics made when the acute study endpoint did not reach statistical significance. They added an active control for the D0-2 outcomes to analyze long-term effectiveness and a one-year comparison of D0-2 patients treated with adjunctive VNS with D0-4 patients treated only with standard-of-care. This provided the FDA with 12-month data on 460 patients with TRD.

A. John Rush, M.D., Principal Investigator for the D-02 study and Professor of Psychiatry at the University of Texas Southwestern Medical Center explained the personal and public health impact of TRD and treatment of TRD using the VNS device. Sixteen percent of Americans will experience major depressive disorder (MDD) in their lifetime; it is the second most disabling condition in the United States. Dr. Rush defined TRD as the lack of an adequate clinical response after two well-delivered treatments and discussed its symptoms; more than 20% of depressed patients suffer from TRD given this definition. TRD is a chronic, disabling disease similar in scope to chronic heart failure, except that TRD patients have a high suicide risk. ECT is currently the best response clinicians have to TRD, but it cannot be used long-term due to adverse effects.

Dr. Rush reported data on relapse rates in depressive patients (non-TRD), and noted that the rates are as high as 57% when patients are on medications; even after ECT and drug therapy the relapse rates for TRD patients in H. A. Sackeim's study (*JAMA* 2001;285:1299-1307) reached as high as 60%. Dr. Rush added that these are the most

difficult to treat patients he has ever included in a trial—they would never have been accepted into any pharmaceutical trial. These are extremely resistant patients “at the end of the line.” There is currently no FDA-approved treatment for TRD.

Richard L. Rudolph, M.D., Vice President for Clinical and Medical Affairs and Chief Medical Officer at Cyberonics, began his overview of the clinical safety and effectiveness data from the VNS studies by discussing the sponsor’s rationale for investigating the use of VNS therapy in TRD patients. These include the mood stabilizing effects of anticonvulsants, neuroimaging data, studies confirming the anecdotal reports of mood enhancement in VNS epilepsy patients, effects of VNS on neurotransmitters, and work on an animal antidepressant model.

He presented information on four of the seven VNS studies: D-01, an open label feasibility study; D-02 acute, a double-blind, randomized, sham treatment-controlled study; D-02 long-term, an open label study; and D-04, a prospective, observational study of TRD patients treated with standard-of-care therapies for comparison with D-02. The other three studies did not apply to the treatment indications under review or are ongoing. He noted that the comparison of the 12-month outcomes for the D-02 patients receiving adjunctive VNS therapy with the D-04 patients receiving standard-of-care therapy provide the strongest evidence for the effectiveness of the adjunctive VNS therapy.

Dr. Rudolph noted that the main inclusion criteria were identical for both the D-02 and D-04 studies, and the patient populations in both were comparable. He explained the reasons why the non-randomized D-04 study was an appropriate control for the D-02 long-term study, including that it was a prospectively designed study for comparison with D-02; it represents a clinically relevant active treatment control corresponding to the

indication for VNS; there were overlapping investigation sites during a similar time period; and the D-04 study includes a large sample size which facilitates statistical comparisons. Dr. Rudolph also explained that outcomes in depression studies are measured using standardized and validated rating scales; in multidimensional scales, such as the Inventory of Depressive Symptomatology—Self Report (IDS-SR) and the Hamilton Rating Scale for Depression (HRSD); the higher the total score the more severely depressed is the patient. The main baseline scores for patients in their studies fall in the severe range.

Dr. Rudolph compared the outcomes of the D-02 and D-04 studies, noting that there was a high level of statistical significance on the primary outcome analysis over 12 months: specifically, the D-04 patients improved very little in their IDS-SR scores while the D-02 patients receiving adjunctive VNS improved to a greater degree in absolute measurement and their IDS-SR scores were lower, as well. The statistical significance is maintained when alternative analysis methodologies are used. The results of the primary analysis were also confirmed when looking at a variety of secondary analyses over 12 months. The response criteria rate using the IDS-SR scale for patients in the D-02 group was 22% versus 12% for the D-04 group; the response criteria rate using the HRSD scale for patients in the D-02 group was 30% versus 13% for the D-04 group.

Dr. Rudolph also went over how the investigators made sure that the VNS treatment was responsible for the differences between the D-02 and D-04 groups, and not such factors as baseline patient differences, medications, ECT, and placebo effect. Of the 56 patients who, at 3 months, fell into the extraordinary, highly meaningful, or meaningful clinical benefit categories, 71% maintained at least a meaningful clinical

benefit through 12 months with adjunctive VNS therapy. Of the 118 patients who, at 3 months, did not fall into the extraordinary, highly meaningful, or meaningful clinical benefit categories, 47% first obtained meaningful to extraordinary benefit after more than 3 months of adjunctive VNS therapy. Dr. Rudolph said that this was “the most persuasive data as to VNS’s long-term effectiveness.”

Dr. Rudolph’s discussed the epilepsy safety results as compared with the depression safety results. The depression studies safety overview showed that the adverse events were primarily stimulation-related and minor. Voice alteration (hoarseness) was the most common adverse event, affecting 68% of patients. The suicide attempts and suicide rates for study participants were comparable with the published literature looking at active treatment groups and placebo groups.

Dr. Rush offered closing remarks to the sponsor’s presentation by looking at the data and information presented from the point of view of a clinician. He reminded panel members that more than half of the individuals being treated had received ECT resulting in no sustained benefit. Dr. Rush explained how the study recruited patients. They went to those physicians who did complex medication management for depressed patients and asked for two each of their “very worst, most difficult depressed patients.” He said the clinical results of the study are meaningful because 1) the benefit for many in this otherwise untreatable population gets better with time; 2) placebos typically work early in treatment and their results eventually wear off, but this device seems to have the opposite effect; 3) while the induction of hypomania is an adverse event, it was more common in bipolar disorder patients; and 4) patients have seen improvement in results after battery replacement, which shows a significant effect. He finished the presentation by noting

that, given the statistics on suicide and TRD, four individuals have committed suicide over the previous 2 ½ hours, and if VNS can help one out five of TRD patients it should be approved.

FDA PRESENTATION

Carlos L. Peña, Ph.D., FDA lead reviewer, described for the panel the indications for VNS and the components of the device. He presented the regulatory history, noting that the FDA approved the device in 1997 for epilepsy. In 1998 the sponsor embarked on a pilot study for TRD indications (D-01). The pilot D-01 study results led to the pivotal D-02 study in 2000; however, unblinding the pivotal D-02 study in January 2002, data failed to demonstrate a difference in improvement between those with active stimulation and sham stimulation for the primary efficacy endpoint. The sponsor suggested that the full effect of VNS might take longer, and proposed the non-significant risk control study called D-04 as a comparison to the pivotal D-02 long-term clinical data. The FDA advised the sponsor of serious concerns about the validity of this comparison, due to a lack of a randomized data set. The sponsor submitted their PMA in October 2003.

Dr. Peña reviewed the pilot D-01 study, the pivotal D-02 study, and the observational control D-04 study. He noted that the pilot D-01 primary efficacy endpoint was the proportion of patients that responded to therapy (50% or more decrease in their HRSD] score after 12 weeks). Twenty-one of 59 patients implanted underwent concomitant changes in their treatment, and total of 77 serious adverse effects appeared in 38 patients. At the acute phase exit, 18 of 59 patients were defined as responders.

In the pivotal D-02 study, patients were required to maintain stable medication regimen during the acute phase but were allowed concomitant medications and ECT treatment during the long-term phase. During the pivotal D-02 acute phase, 9 patients had changes in their concomitant treatment (no ECT treatment reported) while 169 of the 205 evaluable patients in the long-term phase had changes in their concomitant treatment; 14 patients also received ECT during the long-term phase. The primary efficacy endpoint of the acute randomized, controlled phase failed to show a significant difference between the treatment and sham control groups (15% versus 10%).

In the control D-04 study, Dr. Peña noted that it was conducted under local IRB jurisdiction and expressed concern over the D0-2/D-04 enrollment outcomes and time of overlap, noting that the majority of control D-04 subjects enrolled after the pivotal D-02 study closed. According to the sponsor, he added, sites were more focused on the pivotal D-02 treatment study rather than the observational, control D-04 study. After the pivotal D-02 study closed, subjects that had expressed an interest in the pivotal D-02 study were subjects that typically enrolled in the control D-04 study. The demographic characteristics between the two study participants were for the most part comparable; however, there were significant differences in ECT history between the two study populations. He also expressed concern about the “permissive use of concomitant treatments during the long-term study” and how that might impact the determination of effectiveness of the VNS device

Michael Schlosser, M.D., FDA clinical reviewer, began by reviewing the stimulation parameters used in the study. The study protocol limited current output to 0.25–3.5 mA, with adjustments in 0.25 mA steps until a maximum tolerable level was

reached. The programming phase of the study's acute phase lasted two weeks, during which programmers could adjust a participant's current level. The sponsor sent a letter to the pivotal D-02 study investigators in April 2002 outlining a new stimulation protocol used for nonresponders.

Dr. Schlosser first covered the safety data for the pilot D-01 study, in which every subject reported at least one adverse event. Greater than 50% of the patients reported serious adverse events, including 12 suicide attempts, 34 cases of worsening depression, and one death during a surgery for rectal prolapse.

In the pivotal D-02 acute phase, nearly every patient reported an adverse event; severe adverse events were reported among 61 subjects in the treatment control group (including one suicide) and 73 in the sham group. In the long-term phase of the pivotal D-02 study, there were seven suicide attempts. Dr. Schlosser remarked that the sponsor believes that the 62 episodes of depression among 31 subjects in the long-term phase to be due to a lack of efficacy of the device than a true serious adverse effect. Safety data was not collected for the observational, control D-04 study.

The European D-03 study, an open label, non-randomized, single-arm study, is still underway. The 47 subjects receiving implantation of the VNS device reported 14 serious adverse events, including two suicides. Dr. Schlosser also briefly presented the Sponsor-Investigator D-06 study, an open label, non-randomized, study with a single treatment arm that looked at VNS therapy for patients with rapid cycling bipolar disorder. One suicide and two suicide attempts were reported in the seven implanted patients.

Dr. Schlosser noted that the FDA is concerned about the number of suicide attempts among the participants in these studies. He reminded panel members that the

safety analysis of a device is done as a risk-benefit equation; therefore, the safety in the epilepsy population does not equate safety in the TRD population.

Dr. Peña then summarized the efficacy and safety issues. He noted that the absence of systematically collected safety data in the observational control D-04 study to compare with the investigational study is a concern when determining the safety of the VNS device. FDA also had the following efficacy concerns: that the long-term pivotal D-02 study/control D-04 study comparative analysis was not from a randomized data set but rather from a comparison of outcomes from an investigational device study and observational control study; that a persistent placebo effect for patients with the VNS device was observed in the acute phase and that patient expectation may have been greater in the pivotal D-02 study than the observational, control D-04 study; and that permissive use of concomitant treatments during study including the fact that concomitant medications and ECT use were not standardized in either the D-02 long-term study or the D-04 observational study.

Chang S. Lao, Ph.D., Division of Biostatistics, presented a comparison between the D-02 and D-04 statistical data. He evaluated the primary and secondary effectiveness endpoints; the study sites; propensity score analysis; repeated measures linear regression; concordance analysis (IDS-SR versus HRSD scores); and provided statistical conclusions about the comparison between the two studies. He noted that the 3-month double blind study reported significant values using the IDS-SR. In the 12-month non-randomized unblinded study comparing the pivotal D-02 study and the observational, control D-04 study, the sponsor successfully used propensity scores to adjust for an imbalance in measured covariates; however, the propensity scores cannot balance unmeasured

covariates. Dr. Lao noted that the sponsor carried forward data about treatment alteration, but the effect of this on the study's analysis is unclear. The results of the concordance study are unclear, as well, and there is some doubt as to whether IDS-SR scores can be used to predict scores on the HRSD assessment.

Dr. Peña closed by directing the panel's attention to the five discussion questions that ask about issues of valid scientific evidence to assure that the device is safe and efficacious.

PANEL DISCUSSION

Dr. Becker asked the panel if they had any questions for the FDA presenters. Dr. Ellenberg asked Dr. Lao about the information he presented on the difference between the pivotal D-02 study and the observational, control D-04 study at one year, looking at improvement in IDS-SR scores and site difference issues. Dr. Lao said that he believed that using only the overlapping sites would be a more accurate way to complete the analysis, rather than using all 22 sites. He also discussed why it was important to look at the sites by treatment, as there may be an interaction between the treatment and the individual site. Dr. Wang asked about the IDS-SR as a more relevant measure of depression. Dr. Peña responded, saying that the FDA has concerns about lack of improvement between the treatment and control groups using other psychometric assessment tools used by the sponsor, which raises questions about the strength of IDS-SR outcomes.

Dr. Becker opened the floor for panel members to ask questions of the sponsor. She began by asking why the sponsor chose 12 weeks for the acute study and why they

didn't extend the trial. Dr. Rudolph said that 12 weeks is standard for a drug trial, and that by the time they unblinded the acute phase results the patients were beyond the acute phase and it could not be continued as a double-blind randomized trial. Dr. Ellenberg asked why the sponsor does not see the need to do a new randomized study, given the issues around bias, enrollment timing, and study group comparisons. Dr. Rudolph responded that every other study plan we envisioned had significant limitations; Dr. Rush walked the panel through a number of the other study possibilities the sponsor considered, noting that because long-term safety of the device is now better understood, they could conduct a randomized trial, but interactions with medication changes will still be an issue. He added that he feels very confident about the results, given that the 12-month outcomes are largely sustained and the number of patients benefiting from VNS has increased. Dr. Sackeim addressed Dr. Ellenberg's question about the impact of patient expectations on outcomes. He said that a previous study of ECT patients—a comparable population— found no association between patient expectations and outcomes. He also addressed Dr. Ellenberg's question about bias introduced at various study sites, noting that the tapes were also rated by third parties who had no information about where the patient was in the treatment course.

PANEL DELIBERATIONS

Dr. Ellenberg was scheduled to make a formal statement but declined because he agrees fully with the FDA statistical and clinical reviews. Dr. Wang opened the panel's deliberations with a statement. He gave an overview of the VNS device, its indications, components, and the sponsor's results. The D-02 study did not meet its efficacy

endpoints, and Dr. Wang noted that the sponsor suspected that the device's full effect could require more than 10 weeks. This result prompted the D-02/D-04 12-month comparison study. He noted the propensity score analysis done on the primary endpoint analysis to reduce potential bias; Dr. Wang added that there are still confounding possibilities due to "poorly measured" and unmeasured variables. He continued to describe other concerns about the study design and possible compromised efficacy results raised during the FDA's presentation. He noted that there were issues that made it difficult to assess safety results in the studies, primarily because safety data were not systematically collected in the D-04 study, providing no comparison group for the D-02 long-term study. Dr. Wang expressed concerns about training for the VNS device, specifically about who should implant the device; who should program the device; how will they be trained; and what guidance is available on titrating the current? He closed by raising questions about the implications of device approval, such as whether there would be pressure to forgo effective but stigmatized treatments such as ECT.

GENERAL PANEL DISCUSSION

Dr. Becker called on the panel members to offer any comments or raise any questions about the device to both the FDA and the sponsor. Dr. Jayam-Trouth asked the sponsors why there was a drop off in the number of responders after two years. The sponsor said that there were four or five individuals who were explanted for lack of efficacy, and as many as 10 patients who could not or did not return in the time period, some because they were feeling well. About 90% still had the device implanted at two years. Dr. Jayam-Trouth, Dr. Becker, and the sponsors also discussed the protocols for adjusting the levels of stimulation for participants in the treatment arm and the sham arm.

Dr. Fochtmann asked the sponsors about the difference in the stimulus parameter settings between the responders and the nonresponders; the sponsor answered that the parameters were the same for nonresponders and responders in both the acute and the long-term studies. She also asked whether there was comparable efficacy in patients with a chronic episode lasting more than two years versus those with multiple recurring episodes. The sponsor said that the two groups showed comparable rates of response, but a statistical test was not done, only an exploratory analysis. She and the sponsors also discussed the concomitant use of antipsychotic medications.

Dr. Wang brought up the concerns the FDA expressed about residual confounding in the D-02/D-04 propensity score adjustments and the fact that the comparative study was not randomized. The sponsor said that they proceeded this way because of the sample sizes were large, the measured covariates were equally distributed, and they felt they could assume that unmeasured covariates would be equally distributed, as well. The sponsor addressed a possible panel misunderstanding that there was no covariate adjustment in the secondary analysis when, in fact, there was covariate adjustment.

Dr. Jensen asked a number of questions about safety, including why the infection rates for the depression study patients appears to be higher than for the epilepsy patients. The sponsor noted that only one patient required explanation due to infection and the rest were treated with antibiotics; in fact, the infection rate for the depression subjects was lower. Dr. Jensen also asked about Cyberonics' position about what is to be done with the implant in nonresponsive patients; this is of special concern because most of the patients are relatively young and will likely undergo a brain MRI in their lives. The sponsor noted that if the device is left in, the patient retains risks when receiving whole-body and

cervical spine diagnostic MRIs and diathermy, but they can still undergo a head MRI.

The sponsor also said that they had not seen any long-term problems relating to corrosion of the device's components in the epilepsy patients. Dr. Jensen requested more information on which clinicians are allowed to perform the implantation and how they will be trained. The sponsor noted that they offer proctoring and suggested that surgeons should be experienced working within the carotid sheath, adding that about 64% of surgeons performing the procedure are neurosurgeons. Dr. Jensen said that she supported the creation of a TRD registry.

Dr. Ortiz questioned the sponsor about the patient comorbidity in the study. The sponsor noted that there were some specific exclusions in the D-02 protocol, including patients with psychotic depression, substance abuse, schizoaffective disorder, and mixed or rapid cycling bipolar disorders. They did not diagnose or exclude personality disorders.

Dr. Malone made general comments about the design of the studies. He said that the same criteria for drug trials should be used to judge the VNS depression study data, and that the study should have been done as a double-blind randomized study, as appears in much of the literature on psychiatric treatment. The sponsor noted that the literature generally refers to common depression, not necessarily TRD. The sponsor agreed that randomized control trials should be done, but only when they can be accomplished in a safe and ethical manner, and when the outcome of the disorder is not "uniformly terminal." Now that they have established long-term safety of VNS, the sponsor believes that they could do such a study.

Ms. Wells asked whether the sponsor had any intermediate effectiveness outcomes for the ongoing D-03 study. The sponsor said that the response rates are similar to the D-01 study. Mr. Balo asked Dr. Lao whether the information provided earlier in the panel discussion about the propensity score analysis and the covariate analysis answered his concerns. Dr. Lao said that he still had some questions. Mr. Balo asked Dr. Peña why there was never any discussion about safety data in the D0-4 study. Dr. Peña responded that the D-04 study was conducted under local IRB jurisdiction so it required no FDA approval. He also noted to the panel that FDA had expressed serious concerns on several occasions about the D02/D-04 comparison.

Dr. Fochtman had additional safety questions for the sponsor. She wondered if patients should be screened for sleep apnea and should receive ongoing assessments for this disorder. The sponsor said that the label already includes a warning for obstructive sleep apnea, but there is no screening. Dr. Fochtman expressed concern that nonadherent patients would not carry the magnet component of the VNS device, for cases in which they needed to turn off the stimulation. The sponsor noted that the magnet is mostly a convenience to stop minor side effects temporarily; they supply patients with multiple magnets for convenience.

FDA QUESTIONS

- 1. A chief limitation of the long-term D02, D04 comparative analysis is that the data are not derived from a randomized subject data set, but rather a comparison of outcomes from an investigational device study and observational control study. A propensity adjustment strategy was used to reduce potential bias (i.e., patient characteristics, disease characteristics) in the comparative analysis. This type of strategy is not able to address the problems of potential bias due to other unmeasured patient variables (e.g., past thyroid dysfunction, neurotic pre-morbid personality, familial predisposition for affective disorder, multiple loss events, or socio-cultural level). Please discuss the impact of a comparative analysis of non-randomized subject data, comparison of outcomes from an investigational study and observational study, and unmeasured patient variables upon efficacy outcomes in the PMA.**

Though most panel members thought that the sponsor did a good overall job with the comparison study data, they also noted that there were limitations in the comparison. Panel members noted this was a unique population that desperately needs alternative treatments and generally agreed that the device appeared to show some promise for TRD.

- 2. The sponsor believes D-02 long-term outcomes are not due to a placebo effect. Data provided in the PMA includes a 20% (21/106) placebo effect rate in sham-treatment control subjects at acute phase exit (12 weeks) as defined by a HAM-D score less than 18. Patient expectation of participating in an investigational study for a new therapy (D-02 study) may have also been greater than the expectation of participating in an observational control study. Please discuss the placebo effect and impact upon clinical outcomes presented in the PMA.**

The panel noted that the non randomized study design made it difficult to understand or measure the placebo effect, but there was general consensus that there was evidence of a placebo effect on the clinical outcomes. Panel members expressed concern that the value of the blinding in the short-term study was limited. They also suggested that only a true randomized control trial would answer questions about placebo effect.

- 3. Concomitant medications and ECT use were not standardized in either the D-02 long-term study or the D-04 observational control study. Please discuss the impact of concomitant medications and ECT use on interpretation of the efficacy of VNS therapy for treatment resistant depression.**

The panel believed that because the study was not randomized and the concomitant medications were not standardized, the effect of the concomitant medications and ECT treatments on the efficacy outcomes of the VNS device was difficult to appreciate. Some panel members suggested that more information about the types of ECT used, as well as the specific types of concomitant medications, would also be helpful.

- 4. 21 CFR 860.7(d)(1) states that there is a reasonable assurance that the device is safe when it can be determined that the probable benefits to health from use of the device for its intended uses, when accompanied by adequate instructions for use and warnings against unsafe use, outweigh any probable risks. Do the clinical data in P970003/S050 provide reasonable assurance that the device is safe?**

Panel members agreed that the device appears generally safe but, based on efficacy questions, the safety-benefit ratio cannot be determined. Panel members

recognized the limited treatment alternatives this patient population faces, as well as the large numbers of nonresponder patients with the implanted device and the impact this may have on their lives.

5. **21 CFR 860.7(e)(1) states that there is a reasonable assurance that a device is effective when it can be determined, based on 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 produce clinically significant results. Considering your responses to questions 1, 2, and 3, do the clinical data in P970003/S050 provide reasonable assurance that the device is effective?**

The chairperson noted less consensus on this question than on the previous four questions. Some panel members believed that the device is effective; others want more rigorous testing; while others recognize the benefit in the TRD populations despite limitations from the study design.

OPEN PUBLIC HEARING

No comments were made.

FDA AND SPONSOR SUMMATIONS

The FDA did not offer a summation.

Cyberonics representatives noted that the panel agreed that the device is safe.

They stressed that the study population is one in which the chance of a placebo response is quite small. The VNS device separates itself from other TRD treatments in the long-term benefits it provides to a population among whom remission rates are quite high. The sponsors added that they are realizing the possibility that 70% of patients will retain benefits from VNS treatment for 2 years. They reiterated that most of these patients have undergone 20 to 40 years of treatment; as a result, standard-of-care treatment can often be dangerous and unacceptable.

The sponsor suggested that, even though the D-04 was not randomized, the study should be thought of as more than just a “haphazard control study”. It had elements that offer a high degree of comparability and confidence to determine efficacy. It was prospective with overlapping sites and maintained the same principal enrollment criteria and was conducted over the same time frame as the D-02 study. They asserted that even randomized control trails do not guarantee equally distributed baseline covariates. The sponsor asked the panel to consider whether the lack of a randomized study is enough to delay approval of the device.

The sponsor also believed that they needed to explain the full context of the regulation mentioned in the fifth discussion question. They noted that 55% of all approved medical device PMAs were supported by non randomized clinical trails and 7% included no controls. The sponsor reminded the panel that TRD is a “highly lethal” condition and in the time it takes to conduct a randomized trial they will loose 1,000 potential patients a month to suicide. They asked that the panel look at the patho pneumatic evidence of efficacy for the device, as well as the trial evidence of safety, and approve the device.

VOTE

Executive Secretary Scudiero read the panel voting options. The panel voted five to two that the PMA P970003/S50 for the Cyberonics VNS system was approvable with the following conditions:

1. Patients should have failed four or more trials of traditional treatment modalities for TRD (medications and ECT) before using the VNS device.

2. Surgeons should undergo appropriate training and be experienced working within the carotid sheath before implanting the VNS device.
3. Primary care providers should receive training on how to electronically program the device.
4. Additional patient labeling should include information about device complications and removal of the device, and patients should receive an identification card.
5. The sponsor should help establish a patient registry to collect clinical data to identify adverse effects, stimulation levels, and information about prognostic factors.
6. The physician labeling should be revised as per the following: that the study was a 12-month open label follow-up trial; in the section on the variable effect of treatment, change the wording from “highly statistically significant effect” to “significant effect” and delete the P value; in point 6, change “VNS therapy should be considered” to “VNS therapy may be considered”; in point 12, delete blood flow imaging claims; and in point 6, delete “intolerant”.

POLL

When asked to explain the rationale behind their votes, those panel members voting against conditional approval believed that the data failed to show a sufficient level of efficacy, and that a new randomized study was necessary to establish a reasonable assurance of safety and efficacy. Those voting to approve the PMA with conditions noted that the device demonstrated safety, and that some level of efficacy was shown, albeit with less-than-ideal data, for a particularly difficult group of patients to treat.

ADJOURNMENT

Dr. Becker adjourned the meeting at 5:42 p.m.

I certify that I attended this meeting
of the Neurological Devices
Advisory Panel Meeting on June 15,
2004, and that these minutes
accurately reflect what transpired.

Janet L. Scudiero, M.S.
Executive Secretary

I approve the minutes of this meeting
as recorded in this summary.

Kyra J. Becker, M.D.
Chairperson