

UNITED STATES OF AMERICA  
FOOD AND DRUG ADMINISTRATION

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NEUROLOGICAL DEVICES PANEL  
of the  
MEDICAL DEVICES ADVISORY COMMITTEE

+ + + + +

*Seventeenth Meeting*

+ + + + +

TUESDAY  
JUNE 15, 2004

+ + + + +

The Panel met at 8:00 a.m. at the Holiday Inn Gaithersburg, Walker/Whetstone Rooms, Two Montgomery Village Avenue, Gaithersburg, Maryland, Dr. Kyra J. Becker, Chairperson, presiding.

PANEL MEMBERS PRESENT:

KYRA J. BECKER, M.D., Chairperson, University of Washington School of Medicine, Seattle, WA  
ANDREW K. BALO, Industry Representative, DexCom, Inc. San Diego, California  
JONAS H. ELLENBERG, Ph.D., Voting Member, Westat, Rockville, Maryland  
LAURA J. FOCHTMANN, M.D. Deputized Voting Member, State University of New York, Stony Brook, NY  
ANNAPURNI JAYAM-TROUTH, M.D., Voting Member, Howard University College of Medicine, Washington, DC  
RICHARD P. MALONE, M.D., Deputized Voting Member, MCP Hanneman University, Philadelphia, PA  
IRENE E. ORTIZ, M.D., Deputized Voting Member, University of New Mexico, Albuquerque, NM  
MARY LEE JENSEN, M.D., Director of Interventional Neuroradiology, University of Virginia

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PANEL MEMBERS PRESENT: (continued)

PHILIP S. WANG, M.D., MPH, Dr.PH, Deputized Voting  
Member, Brigham and Women's Hospital, Boston, MA  
CRISSY E. WELLS, R.T., MBA, MHSA, Consumer  
Representative, University of Virginia Health  
Sciences Center, Charlottesville, VA

ALSO PRESENT:

DELIA WITTEN, Ph.D., M.D., Food and Drug  
Administration, Division Director, General  
Restorative and Neurological Devices

SPONSOR PRESENTERS:

RICHARD L. RUDOLPH, M.D., Vice President, Clinical and  
Medical Affairs and Chief Medical Officer,  
Cyberonics  
A. JOHN RUSH, M.D., Principal Investigator, University  
of Dallas Southwestern MC, Dallas, TX  
ALAN TOTAH, Vice President, Regulatory Affairs,  
Cyberonics

FDA PRESENTERS:

CHANG LAO, Ph.D., Statistical Reviewer  
CARLOS PENA, Ph.D., Neuroscientist, VNS Studies,  
Efficacy Reviewer  
MICHAEL SCHLOSSER, M.D., Neurosurgeon, Safety Reviewer

PUBLIC SPEAKERS:

MARNA DAVENTORT, patient in the study  
CHARLES DONOVAN, patient in the study  
COLLEEN KELLY, patient in the study  
LYDIA LEWIS, President, Depression and Bipolar Support  
Alliance  
KARMEN MCGUFFEE, patient in the study  
IRVIN J. MUSZYNSKI, J.D., Director of the Office of  
Health Care Systems & Financing, American  
Psychiatric Association  
LAURI SANDOVAL, patient in the study

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## P R O C E E D I N G S

Time: 8:05 a.m.

MS. SCUDIERO: Good morning. We are ready to begin now. Sorry for a little delay.

I am Jan Scudiero. I am the Executive Secretary of this panel and a reviewer in the Division of General Restorative Neurological Devices.

The usual housekeeping matters: If you haven't signed in at the door, please do so, and pick up agendas and other meeting related information.

Before I turn over the meeting to Dr. Becker, I am required to read three statements into the record. There are two deputization of temporary voting member statements and a conflict of interest statement that were prepared for this meeting.

The first: Pursuant to the authority granted under the Medical Devices Advisory Committee charter dated October 27, 1990, and amended April 20, 1995, I appoint the following person to be a voting member of the Neurological Devices Panel for the duration of this meeting on June 15, 2004: Laura Fochtman, M.D.

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1                   For the record, she is a Special  
2 Government Employee and is a consultant to this panel  
3 or another panel under the Medical Devices Advisory  
4 Committee. She has undergone the customary conflict  
5 of interest review and has reviewed the material to be  
6 considered at this meeting. Signed by Daniel G.  
7 Schultz, M.D., Acting Director, Center for Devices and  
8 Radiological Health, on June 9th of this year.

9                   The other: Pursuant to the authority  
10 granted under the Medical Devices Committee charter  
11 for the Center for Devices and Radiological Health  
12 dated on October 27, 1990 and amended August 18, 1999,  
13 I appoint the following individuals as voting members  
14 for the Neurological Devices Panel for the meeting on  
15 June 15, 2004: Richard P. Malone, M.D., Irene E.  
16 Ortiz, M.D., Richard S. Wang, M.D. MPH, Dr. Public  
17 Health.

18                   For the record, Doctors Malone, Ortiz and  
19 Wang are members of the Psychopharmacologic Drugs  
20 Advisory Committee of the Center for Drug Evaluation  
21 and Research. They are Special Government Employees  
22 who have undergone the customary conflict of interest

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1 review and have reviewed the material to be considered  
2 for this meeting. This is signed by Peter J. Pitts,  
3 until recently the Associate Commissioner for External  
4 Relations, on June 4th of this year.

5 The conflict of interest statement: The  
6 following announcement addresses conflict of interest  
7 issues associated with this meeting and is made part  
8 of the record to preclude even the appearance of an  
9 impropriety.

10 To determine if any conflict existed, the  
11 agency reviewed the submitted agenda for this meeting  
12 and all financial interests reported by the Committee  
13 participants.

14 The conflict of interest statutes prohibit  
15 Special Government Employees from participating in  
16 matters that could affect their or their employers'  
17 financial interest. However, the agency has determined  
18 that the participation of certain members and  
19 consultants, the need for whose services outweighs the  
20 potential conflict of interest involved, is in the  
21 best interest of the government.

22 Therefore, waivers were granted to Doctors

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1 Kyra Jo Becker and Laura Fochtman for their interest  
2 in firms and issues that could potentially be affected  
3 by the panel's recommendation.

4 Dr. Becker's waiver involves an imputed  
5 interest, a contract to her institution for the  
6 sponsor's study in which she has no involvement and is  
7 uncompensated. Dr. Becker's waiver allows her to  
8 participate fully in today's deliberations.

9 Dr. Fochtman waiver involves a contract  
10 to her institution for the sponsor's study in which  
11 she has no involvement and is uncompensated. Dr.  
12 Fochtman waiver allows her to participate fully in  
13 today's deliberations.

14 Copies of these waivers may be obtained  
15 from the agency's Freedom of Information Office, Room  
16 12A-15 of the Parklawn Building.

17 We would like to note for the record that  
18 the agency took into consideration certain matters  
19 regarding Dr. Mary Jensen. She reported an interest  
20 in a firm at issue but not in matters related to  
21 today's agenda. The agency has determined, therefore,  
22 that she may fully participate in all discussions.

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1           In the event that the discussions involve  
2 any other products or firms not already on the agenda  
3 for which an FDA participant has a financial interest,  
4 the participant should excuse himself or herself from  
5 such involvement, and the exclusion will be noted for  
6 the record.

7           With respect to all other participants, we  
8 ask, in the interest of fairness, that all persons  
9 making statements or presentations disclose any  
10 current or previous financial involvement with any  
11 firm whose products they may wish to comment upon.

12           I wish to announce that the August 5th and  
13 6th tentatively scheduled meeting for this Panel was  
14 canceled, because there is no agenda for a meeting.  
15 The remaining tentatively scheduled Panel meeting for  
16 this calendar year is October 28th and 29th.

17           Please remember that this is a tentative  
18 date, and monitor the CDRH Panel website for updated  
19 Panel meeting information.

20           I would now like to turn the meeting over  
21 to our Chairperson, Dr. Kyra Becker.

22           CHAIRPERSON BECKER:    Good morning.    My

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1 name is Kyra Becker, and I am the Chairperson of this  
2 Neurological Devices Panel. I am a neurologist, and I  
3 practice at the University of Washington in Seattle.

4 At this meeting the panel will discuss,  
5 make recommendations and vote on a recommendation to  
6 the Food and Drug Administration on the approvability  
7 of premarket approval application supplement  
8 P970003/S50 for the Cyberonics Vagus Nerve Stimulation  
9 Therapy System.

10 The System is indicated for the adjunctive  
11 long term treatment of chronic or recurrent depression  
12 for patients who are experiencing a major depressive  
13 episode that has not had an adequate response to two  
14 or more antidepressant treatments.

15 We will have an open public hearing and  
16 the sponsor and FDA presentations before lunch. After  
17 lunch, the Panel will deliberate on the approvability  
18 of the PMA. Before the Panel votes, there will be  
19 another open public hearing and a time for the FDA and  
20 sponsor summations.

21 Before we begin this meeting, I would like  
22 to ask for the Panel members, who are generously

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1 giving their time to help the FDA in the matter at  
2 hand, and the other FDA staff seated around this table  
3 to introduce themselves. I think we are going to  
4 start at this end of the table, and I would like you  
5 to state your name, your area of expertise, your  
6 position and your affiliation.

7 DR. ELLENBERG: My name is Jonas  
8 Ellenberg. I am a biostatistician. I am on staff at  
9 Westat, a social services private research firm. I am  
10 a Vice President and Senior Biostatistician.

11 DR. JAYAM-TROUTH: I am Annapurni Jayam-  
12 Trouth. I am the Chair of Neurology at Howard  
13 University, Washington, D.C.

14 DR. FOCHTMANN: I am Laura Fochtmann. I  
15 am a Professor in the Department of Psychiatry at the  
16 State University of New York at Stony Brook.

17 DR. WANG: I am Philip Wang, a  
18 psychiatrist and epidemiologist at Harvard Medical  
19 School.

20 DR. JENSEN: I am Mary Lee Jensen. I am  
21 Director of Interventional Neuroradiology and a  
22 Professor of Radiology and Neurosurgery at the

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1 University of Virginia.

2 DR. ORTIZ: I am Irene Ortiz. I am a  
3 geriatric psychiatrist at the University of New Mexico  
4 and with the Albuquerque BA.

5 DR. MALONE: I am Richard Malone. I am a  
6 psychiatrist and professor of psychiatry at Drexel  
7 University, College of Medicine.

8 MS. WELLS: I'm Chris Wells, and I am the  
9 Consumer Representative on this Panel.

10 MR. BALO: I am Andy Balo, the industry  
11 rep, but I am Vice President of Regulatory Clinical at  
12 DexCom, Inc., in San Diego.

13 DR. WITTEN: Celia Witten. I am Division  
14 Director of the reviewing division for this product at  
15 FDA.

16 CHAIRPERSON BECKER: Thank you. I would  
17 like to note for the record that the voting members  
18 here at the Panel constitute a quorum as required by  
19 21 CFR Part 14.

20 Next Mr. Theodore Stevens, Chief of the  
21 Restorative Devices Branch, will update the Panel on  
22 several matters deliberated on at the last meeting of

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1 the Panel on February 23, 2004. Mr. Stevens.

2 MR. STEVENS: Okay. I don't seem to have  
3 slides going here on the screen.

4 Hi. I am Ted Stevens. I am the Chief of  
5 the Restorative Devices Branch, and I will be giving a  
6 very brief update on the devices that were reviewed by  
7 this Panel previously.

8 At the February meeting there was advice  
9 given to the reviewing branch on the concentric  
10 medical Mercy device that remains under review in the  
11 General Surgical Devices Branch at FDA.

12 We have also recently published a draft  
13 guidance and a Federal Register notice for  
14 availability of vascular and neurovascular  
15 embolization devices. The comment period for that  
16 draft guidance ended on May 25th.

17 Finally, several devices have been cleared  
18 that are reviewed under the Orthopedic Devices Panel,  
19 but because they are devices that are also used by  
20 neurosurgeons and interventional radiologists, I  
21 thought it would be appropriate to mention them here.

22 We have recently cleared several PMMA

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1 cements for use in pathological fractures of the  
2 vertebral body. These 510k's were cleared based on  
3 the reclassification of PMMA bone cements. That  
4 included pathological fractures in general for the  
5 specific indication of vertebral body fractures.  
6 These 510k's included clinical data from the  
7 literature.

8 That concludes the update.

9 CHAIRPERSON BECKER: Thank you, Mr.  
10 Stevens. At this time we will proceed to the open  
11 public hearing portion of the meeting. We ask at this  
12 time that all persons addressing the Panel speak  
13 clearly into the microphone, as the transcriptionist  
14 is dependent on this means of providing an accurate  
15 record of the meeting.

16 Ms. Scudiero will now read a statement  
17 prepared for the open public hearings.

18 MS. SCUDIERO: Both the Food and Drug  
19 Administration and the public believe in a transparent  
20 process for information gathering and decision making.

21 To ensure such transparency at open public hearing  
22 sessions of the Advisory Committee meeting, FDA

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1 believes that it is important to understand the  
2 context of any individual's participation.

3 For this reason, FDA encourages you, the  
4 open public hearing speaker, at the beginning of your  
5 statement to advise the committee of any financial  
6 relationship that you may have with the sponsor, its  
7 product and, if known, its direct competitors.

8 For example, this financial information  
9 may include the sponsor's payment of your travel,  
10 lodging or other expenses in connection with your  
11 attendance at the meeting.

12 Likewise, FDA encourages you at the  
13 beginning of your statement to advise the committee if  
14 you do not have any such financial relationship. If  
15 you choose not to address the issue of financial  
16 relationships at the beginning of the statement, it  
17 will not preclude you from speaking.

18 CHAIRPERSON BECKER: Prior to the meeting,  
19 there were seven requests to speak in the open public  
20 hearing, and each person has ten minutes to address  
21 the panel. They will speak in the order that the FDA  
22 received their requests to present to the panel.

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1 Ms. Colleen Kelly, who is a patient in the  
2 study, will be the first speaker, if you want to come  
3 forward.

4 MS. KELLY: Hi. Is it possible for me to  
5 sit?

6 CHAIRPERSON BECKER: Certainly, yes.

7 MS. KELLY: You can hear me okay? Thank  
8 you. I am Patient 012 from Site 050 of the D-01 study  
9 for Vagus Nerve Stimulation for the treatment of major  
10 depressive disorder. I am here unsolicited to ask you  
11 to approve the VNS in its application to depression.

12 I was not approached by my study site nor  
13 by Cyberonics to speak to this panel. I am here upon  
14 my own accord, inspired by my own experience, and  
15 driven by the necessity that viable alternatives must  
16 be offered to persons suffering from treatment  
17 resistant depression.

18 I have secured and paid for my own travel  
19 here. In fact, it would behoove me financially if  
20 this panel stalled the approval process. I have had  
21 the device for four and a half years and, based on my  
22 parameter settings, replacement surgery is imminent.

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1           As long as I am in the study and as long  
2 as the study lingers, Cyberonics will be responsible  
3 for the cost of replacing my generator battery. So,  
4 actually, I am shooting myself in my financial foot by  
5 encouraging you to approve this device. Upon  
6 approval, I would become completely responsible  
7 medically and financially.

8           That said, my case and testimony may be of  
9 particular interest to this panel. I went into the  
10 study on no medications, remained off medications  
11 throughout the study, and am still on no medications.

12           There is no other explanation for my  
13 response other than the device itself. It is good  
14 science. Turn the device up; I respond. Turn the  
15 device down; I decline.

16           Let me assure you that my stoicism with  
17 medications is not noncompliance. Neither is it an  
18 indicator that I am only mildly affected with the  
19 illness and, therefore, can exist without medications.

20           In short, I had exhausted them as well as every other  
21 treatment currently available to people with illness  
22 at this level, as did so many of my peers in this

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1 study.

2 I realize that most on this Panel and most  
3 in attendance here are experts in their field, be it  
4 neurology, psychology, psychiatry, or mental health  
5 administration; but there is one thing I can offer you  
6 about which you may know nothing. That is first hand  
7 knowledge of what it is like to have severe  
8 recalcitrant depression.

9 To do so, I ask you to imagine the  
10 unimaginable, to think the unthinkable, to experience  
11 second degree emotional burns with third degree  
12 prognosis. All you experience is pain, but with no  
13 cure. In fact, there is no viable treatment.

14 You can attempt to salve it. Only death  
15 solves it. But the medical community does not accept  
16 death as a cure. It asks us to continue to hang on  
17 and to continue to live, yet offers us no viable  
18 treatments. Trust me, it is not that we don't want to  
19 live. It is that we don't want to live like this.

20 Our illness is embedded in our physical  
21 bodies, ourselves. We are prisoners there, and our  
22 sentence is life. Menacing insomnia, isolation, fear,

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1 anxiety, sadness, hopelessness, general malaise,  
2 malingering fatigue, physical exhaustion, apathy, lack  
3 of motivation, concentration and focus, absence of  
4 pleasure, amplification of pain, agitation,  
5 sensitivity to criticism, thoughts that life isn't  
6 worth living -- You are all familiar with this short  
7 sheeted laundry list of symptoms.

8 Now imagine having them all at once.  
9 Imagine passing from one room to another in the house  
10 of pain where some symptoms are more prevalent than  
11 others, sometimes exacerbated by the very medications  
12 that were meant to alleviate them.

13 I will not bore you with the details of  
14 the pharmacopoeia that I have tried and then have  
15 failed, not to mention the acupuncture, homeopathy,  
16 herbal remedies, extreme dietary changes and  
17 supplements, light therapy, counseling, yoga and, of  
18 course, religion. What god would let a child suffer  
19 like this?

20 Then comes the inevitable,  
21 electroconvulsive therapy, ECT, a therapy so beyond  
22 the vernacular that it doesn't even pass an automated

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1 spellcheck. I would stop at the word, too, but as a  
2 person with treatment resistant depression, I could  
3 not stop.

4 I relented to this FDA approved treatment  
5 as a last resort. Average session: Three to five  
6 treatments. I had 33 nearly consecutive treatments.  
7 I lost retrograde 20 years of my life through memory  
8 loss, a dismal blessing. At least I could not  
9 remember the horrific pain that preceded it for years.

10 I asked you to imagine the unimaginable,  
11 to think the unthinkable. I also mentioned that you  
12 are experts in your field. What if, after battling an  
13 abusive lifelong illness, after enduring medication  
14 where side effects trumped minimal benefit, after  
15 relenting to a final last resort -- what if all that  
16 is wiped out? You are etherized on a tabula rasa,  
17 alive, yes, but no more FDA hearings, no more status,  
18 no more career. No more. Someone helps you remember  
19 where the soap is kept and helps you into the shower.

20 I am not here to blast the approval of  
21 ECT. Obviously enough, for better or worse, I am  
22 still here. I am here, however, to say that I am here

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1 today because of the VNS, and I ask you what do you  
2 offer someone after the last resort? What do you  
3 offer someone for whom ECT has failed?

4 I had an experimental study. What will  
5 the next guy get?

6 I would be remiss if I did not mention the  
7 epileptic community who has blazoned the way for  
8 efficacy and safety of the VNS device. For that, I am  
9 grateful.

10 They have shown us the risks and side  
11 effects involved since the FDA approved the device for  
12 them in 1997, and my personal heartfelt thanks go to  
13 those who engaged in experimental implantation even  
14 prior to that date. I offer my gratitude, and I share  
15 their cautious hope.

16 I would also like to thank them for their  
17 honesty and candor, which I found on the Cyberonics  
18 bulletin board. Without their shared experience, I  
19 know for a fact I would not have attained the success  
20 I have had with this device.

21 I followed their histories. I tracked and  
22 evaluated their settings and results, and I searched

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1 and researched my side effects and remedies through  
2 their personal experiences. Their trial and error  
3 resulted in my trial and success.

4 Because of what I learned on the chat  
5 board, I was eager to boost my amplitude to higher  
6 than 1.0 in the first three weeks of the initial  
7 depression study, and keep my settings above what  
8 later became known as efficacy threshold. As a  
9 result, I was one of the first to respond at my study  
10 site, and I continue to reap benefit from the device.

11 I encourage Cyberonics to reopen their  
12 bulletin board. I understand the risks involved and  
13 the abuses that were made to it, but I challenge the  
14 company to research and execute a safe environment  
15 where patients can exchange information regarding this  
16 very new modality of treatment, especially in its  
17 application to depression.

18 It was critical in my success. I know it  
19 would increase the success of others exploring the  
20 device as a possible treatment.

21 I am not going to idealize nor  
22 sentimentalize the device. I know I am one of a third

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1 who have responded to it. I know there are others who  
2 continue to suffer the burden of treatment resistant  
3 depression. I see it in their faces as I sit in the  
4 lobby and wait my turn at the site.

5 I know that pain. I suffered it prior to  
6 the VNS. Still, I have windows of it now and again.  
7 I am passionate, yet realistic, about the device. I  
8 do not romanticize its results for me nor dismiss its  
9 lack of results for others. I am well aware of its  
10 side effects, shortcomings, and its current  
11 experimental status. But I do know one thing. We  
12 need viable treatment options for those with  
13 recalcitrant depression, and VNS has worked for me.

14 In closing, I encourage this Panel to let  
15 the mental health community, both administrators and  
16 recipients, review the data and search the testimonies  
17 to decide if this is an appropriate treatment for  
18 their patients, their loved ones, themselves.

19 This is an option only you can provide by  
20 approving the device for its application to  
21 depression. Give us a choice, a possible key, a  
22 parole to our life sentences of depression. Thank

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1 you.

2 CHAIRPERSON BECKER: Thank you, Ms. Kelly.

3 Our next speaker will be Ms. Lydia Lewis,  
4 who is President of the Depression and Bipolar Support  
5 Alliance.

6 MS. LEWIS: Good morning. I want to thank  
7 the Advisory Panel for this opportunity to talk about  
8 the critical issue of treatment resistant depression.

9 I am Lydia Lewis, and I am here as President of the  
10 Depression and Bipolar Support Alliance, a national  
11 patient-run advocacy organization representing the  
12 more than 25 million people living with depression and  
13 bipolar disorder.

14 I did not receive any financial support  
15 nor do I have any financial arrangement with any  
16 company for my work on behalf of patients with mood  
17 disorders. The Depression and Bipolar Support  
18 Alliance does, however, receive financial support in  
19 the form of program grants, honoraria, consulting fees  
20 or in-kind donations from Cyberonics, Inc. and a  
21 number of pharmaceutical companies. My travel to  
22 Maryland today was not paid for by Cyberonics, and I

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1 am not here to advocate for any particular therapy,  
2 including VNS, but rather for the critical need for  
3 new therapies.

4 While I have suffered from treatment  
5 resistant depression for my entire life and I have  
6 taken more than 20 different medications over the past  
7 36 years, I am not here to tell my story. I am here  
8 to represent the millions of people with mood  
9 disorders who can't get well, people who desperately  
10 need better medications and treatment modalities other  
11 than pharmaceuticals.

12 Just about 4 million people directly  
13 contact DBSA every year. Connecting with millions  
14 touched in some way by Depression and Bipolar Support  
15 Alliance -- by depression and bipolar support make us  
16 particularly qualified to speak on their behalf.

17 As we all know, more than 30,000 people in  
18 the United States take their lives every year, not  
19 because they are weak or because they have a character  
20 flaw. They take their lives because they do not  
21 respond to any of the treatments currently available  
22 for depression or bipolar disorder.

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1           At DBSA we know that new drugs and  
2 nonpharmacologic treatments are desperately needed.  
3 Far too many people are dying or living lives of quiet  
4 desperation, because they can't get sufficient relief  
5 form their symptoms of depression. The more  
6 treatments the FDA makes available, the more lives  
7 that will be saved.

8           Today I want to put a human face on the  
9 tragedy of treatment resistant depression. We can  
10 talk science all we want, but science will never drive  
11 home the devastating consequences our illnesses can  
12 have, if they are not treated.

13           The human face I want to share today is  
14 Barbie's, and I have given you all a picture of  
15 Barbie. It is on the last page of my testimony, and  
16 it is important, if you would, to look at this while I  
17 speak.

18           Barbie has three kids, two girls and a  
19 boy. She works as an oncology nurse. She is very  
20 patient, very smart, very kind, very funny, and very  
21 gentle. She is the nurse of choice, requested by more  
22 doctors when they admit a patient onto her unit.

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1           People report that her care made the  
2 difference in their fight with cancer. Barbie was  
3 finally diagnosed with bipolar disorder after having  
4 been treated for depression for more than 15 years.  
5 She has been hospitalized five times for her  
6 depression.

7           The first two times her insurance covered  
8 some of the costs. The last three times it covered  
9 nothing. She has run through all of her retirement  
10 savings. Her last hospitalization was at a state  
11 facility and, although many of them are quite good,  
12 this one was so horrible and so scarring that she  
13 refuses to ever be hospitalized again.

14           She runs through the insurance money for  
15 her medication within the first two months of every  
16 year. Her parents use much of their retirement  
17 savings to help pay for her meds, and her siblings  
18 contribute as much as they can.

19           She has been prescribed a variety of  
20 medications. Sometimes she shakes. Sometimes she  
21 drools. A time or two she has found herself somewhere  
22 with no idea how she got there, because her mind was

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1 so fuzzy from her medication.

2 She balloons up in weight even though she  
3 eats next to nothing. She has no appetite at all. It  
4 is hard to find a nurse's uniform that fits. She gets  
5 very little sleep, 15 minutes, an hour at a time, no  
6 more. But she also can't concentrate enough to watch  
7 TV, read a book or anything else. So she lies there  
8 worrying, thinking about the patients she is trying to  
9 care for, even though she herself is very, very ill.

10 Once a week she summons up all her courage  
11 and drives, shaking and drooling, to a therapist more  
12 than an hour away. There is none closer. Every month  
13 it takes even more courage to drive two hours away to  
14 see her psychiatrist for 15 to 20 minutes. There is  
15 none closer.

16 They do the best they can to treat her at  
17 reduced fees, but she can still barely pay for their  
18 time, and nothing helps. Quite simply, her life is  
19 hell. She can't sleep. She can't eat. Her phone  
20 rings with creditors. She feels bad and ashamed about  
21 what her family has been forced to go through with  
22 her.

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1 Her medication barely touches her  
2 symptoms, and because of her illness, everything she  
3 does takes tremendous courage. Let me tell you, it is  
4 exhausting to never get better. When no treatment  
5 works or you can't afford something that does, you can  
6 reach a place where there doesn't seem to be any exit.

7 If you haven't been there yourself, count  
8 yourself lucky. I have been there, and it is dark and  
9 full of pain and hopelessness. It is joyless and a  
10 place where nothing matters.

11 You can be young or old, beautiful or  
12 plain, rich or poor, erudite or illiterate. Everyone  
13 who ends up in this place feels the shame. It's hell  
14 on earth.

15 Barbie found herself in this place,  
16 because no matter how hard the doctors tried, nothing  
17 helped; and regardless of her kids, her husband, her  
18 wonderful parents and siblings, and the job she found  
19 so important, the despair of that place was too  
20 overwhelming.

21 Barbie isn't just any patient to me. She  
22 is my co-worker's sister, and I am sorry that we never

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1 met, because I know I really would have liked her.  
2 Barbie took her life three months after this picture  
3 was taken. She was 49 years old.

4 It is a profound honor to speak for Barbie  
5 who can no longer do so, and I hope her death will  
6 have some purpose. No one should have to live with  
7 pain like Barbie's. No one's family should have to  
8 suffer like hers, impotent to help through the long  
9 journey of one failed treatment after another.s

10 The suffering doesn't end when someone's  
11 life ends. Barbie's loved ones still suffer, because  
12 even in this day and age, there was nothing that could  
13 keep her from that dark place.

14 Tragically, aspects of Barbie's story  
15 still ring true for so many. No one's life should be  
16 wasted or ended because efficacious treatment isn't  
17 available. This is why we are all here. This is why  
18 we all must remain here.

19 It is too late for Barbie, but it is not  
20 too late for us to learn from her life and from her  
21 death. Her struggles and loss should inspire all of  
22 us to work tirelessly to bring better treatments to

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1 the millions of Barbies still suffering.

2 That is why I am here today, and why I am  
3 asking the FDA to remember those of us who desperately  
4 need better treatments. It is a race against time,  
5 and I ask you on behalf of the millions of people  
6 suffering with treatment resistant depression to  
7 please do everything you can to help us. Thank you.

8 CHAIRPERSON BECKER: Thank you, Ms. Lewis.

9 The next speaker will be Ms. Laurie Sandoval, who is  
10 also a patient in the Cyberonics study.

11 (A SHORT VIDEO WAS SHOWN.)

12 MS. SANDOVAL: First of all, I have had no  
13 financial involvement with Cyberonics except travel  
14 and hotel accommodations.

15 Someone once said depression is like being  
16 a prisoner of the mind. It could not have been said  
17 better except in that prison I was in solitary  
18 confinement.

19 The video you just saw was me five years  
20 ago. No longer able to keep my depression at bay, I  
21 had just resigned the job of my dreams and lost any  
22 hope of living. At that time I was under the care of

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1 Dr. Lauren Marengel of Baylor Medical College for  
2 treatment resistant depression in which medications,  
3 therapy and, in some cases, electric convulsive  
4 therapy had not worked.

5 Dr. Marengel explained an experimental  
6 study for depression that Baylor was undertaking with  
7 Cyberonics using a vagus nerve stimulator device, and  
8 would I be interested in participating. Sign me up  
9 yesterday, Doc.

10 Living in Nevada and without -- and having  
11 the VNS device five years now, life had been  
12 wonderfully normal, without suicidal depression. That  
13 is until three months ago.

14 I started feeling down, rarely leaving the  
15 house, turning off the phone, and only getting out of  
16 bed to let the dogs out. Normally, when the VNS  
17 device goes off, it causes a tickling sensation in the  
18 throat, but latterly there was no sensation at all,  
19 and I prayed the battery was dead.

20 Calling Dr. Marengel's office, they  
21 couldn't say for sure if the device wasn't working  
22 until the battery was tested. My appointment wasn't

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1 scheduled for another month, and I wondered if i could  
2 hold on that long. I was once again a prisoner of the  
3 mind.

4 In Houston, I told the doctors I felt  
5 desperate, and my only hope was that the depression  
6 was being caused because the VNS battery died.  
7 Scared, I checked myself into Methodist Hospital  
8 psychiatric ward.

9 The good news is two days later, thanks to  
10 the incredible teams at Baylor and Cyberonics, I had  
11 surgery for a new and improved VNS device. This  
12 battery is expected to last eight to ten years.

13 Every day I wake up with a bead of joy in  
14 my heart, or maybe that's the pulse of my new battery.

15 Anyway, I have no doubt that, if it were not for  
16 Cyberonics' innovation and Baylor's tireless  
17 dedication, I would not be here today. Thank you.

18 CHAIRPERSON BECKER: Thank you, Ms.  
19 Sandoval. I want to apologize up front if I  
20 mispronounce the next speaker's name, Mr. Irvin  
21 Muszynski, who is the Director of the Office of Health  
22 Care Systems & Financing of the American Psychiatric

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1 Association.

2 MR. MUSZYNSKI: Your pronunciation is  
3 perfect. Thank you.

4 Good morning, and I, too, would like to  
5 thank you for the opportunity to offer a few remarks  
6 here this morning about your considerations about the  
7 Cyberonics application.

8 As indicated, my name is Irvin Muszynski.  
9 I am the Director of the Office of Health Care Systems  
10 & Financing at the American Psychiatric Association.  
11 In that capacity, my key job responsibilities are  
12 ongoing liaison on behalf of the psychiatric community  
13 and its patients, with third party patients in both  
14 the public and private sector. That includes  
15 employers. It includes Medicare and Medicaid,  
16 insurance companies, both health and disability.

17 In that capacity, I would simply indicate  
18 to you that the question of chronic mental illness  
19 conditions, particular the depressive disorders, is a  
20 recurring issue in questions I get -- or I get  
21 questioned about all the time, and what can the  
22 psychiatric community do, and so on.

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1           In fact, part of my monitoring of the  
2 evolution of the vagus nerve stimulation approach was  
3 stimulated in large part by interactions with  
4 disability insurers who face the burden and the  
5 consequences of recurring or treatment resistant  
6 depression on an ongoing basis.

7           So what I wanted to do here with you today  
8 is just briefly highlight the problem and its  
9 prevalence from our point of view and, secondly, to  
10 talk a little bit about the burdens and costs  
11 associated with major depressive disorder, treatment  
12 resistant depression, however we want to characterize  
13 or define that.

14           That is from the patient, the payer, the  
15 purchaser point of view. I think all three -- Rather  
16 than qualify it every time, let's just suggest that it  
17 is on behalf of all three, albeit they all have  
18 different kinds of interests, and I think you have  
19 heard some compelling stories about the patient point  
20 of view and, I think, what becomes a self-evident need  
21 or an overwhelming need to address the need for new  
22 treatments to begin to better help manage chronic

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1 conditions in a way that people's functioning can be  
2 restored and/or recovery is, in fact, completely  
3 enabled.

4           Respecting disclosure, I have absolutely  
5 no current or previous financial relationship or  
6 interest in Cyberonics. I think probably my travel is  
7 not paid for here, and so on and so forth. I think  
8 probably the only thing that would be maybe  
9 appropriate to indicate in the context of the conflict  
10 of interest is Cyberonics advertises in APA journals  
11 and publications, as does a number of its competitors  
12 that would be on the psychopharmacology side of the  
13 house. But other than that, there is no direct  
14 interest.

15           So briefly, what I want to do is highlight  
16 the problem, and some of this you may well be aware  
17 of. So I don't want to be overly redundant. But as  
18 you know, depression is a diagnosable mental medical  
19 condition.

20           The American Psychiatric Association has  
21 developed the DSM-4TR. The criteria which surround  
22 the nature and diagnosis of depression are well

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1 established, continually refined, and furthered by the  
2 Association and the medical community at large. So  
3 there is nothing new about that.

4 Its prevalence, as you probably may well  
5 be aware, I will rely on National Institute of Mental  
6 Health indications of prevalence which show that seven  
7 to ten percent of the United States population at any  
8 given time suffers from a diagnosable depressive  
9 disorder.

10 As you know, many patients are treated  
11 successfully at first line attempts. Depression is a  
12 eminently treatable disease, but the issue on the  
13 table for us and under consideration here is the  
14 significant proportion of people who fail to reach  
15 acceptable levels of functioning and wellbeing. That  
16 is the population at issue.

17 I will not pretend to tender -- I've  
18 reviewed literature on this subject, and I think I can  
19 say conclusively, there is no one definition of  
20 treatment resistant depression. Maybe it is failure  
21 of one or two psychopharmacological interventions  
22 within a period of six months, and so on.

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1 I think the folks who spoke before me give  
2 you much more operational definitions of what major  
3 depressive disorder or treatment resistant depression  
4 is. But in any case, treatment resistance, from my  
5 point of view, refers to the absence of an acceptable  
6 clinical outcome; that is, sustained remission,  
7 defined in terms of depressive symptoms, severity or  
8 daily function to one or more prior adequate  
9 treatments.

10 So when we subdivide the entire U.S.  
11 population of seven to ten percent that have a  
12 diagnosable depressive disorder, of that group there  
13 are various ranges of who really would be defined, if  
14 you will, as the treatment resistant population, and  
15 the estimates range anywhere from 10 to 50 percent,  
16 depending on the literature review.

17 Let's say the reasonable man standard  
18 would be somewhere in the middle. So 20 to 30 percent  
19 of those with a diagnosable depressive disorder simply  
20 don't respond, do not have sustained remission, and  
21 the human and economic consequences of that, I think,  
22 are kind of self-evident, and I will speak to them a

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1 little bit more here in a moment.

2 Let's look at the consequences then from  
3 the human, the patient, point of view. I won't  
4 elaborate on that. I think you just heard it, but  
5 also from the economic point of view. Here, I want to  
6 again reemphasize, my job, my role as an advocate in  
7 the psychiatric community both for psychiatrists as  
8 medical clinicians who treat this disorder, but also  
9 based on the interaction I do with those who  
10 underwrite health insurance and disability insurance,  
11 and also employers as purchasers who want their  
12 employees back at the job functioning, or those who  
13 are in the public sector, whether on Medicaid and/or  
14 Medicare or dual eligible population, who are  
15 interested in some restoration of ability to resume  
16 some kind of reasonable life in the community.

17 You know, the mortality has a tremendous  
18 range with depression. It can start with suffering  
19 and anguish, but it moves to job absenteeism,  
20 mistakes, loss of job, subsequent financial distress.

21 I think you have heard personal testimonies to this,  
22 and it contributes to familial/marital discord and

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1 community discord in a number of ways.

2           The consequences of this from an economic  
3 point of view or burden point of view are kind of  
4 striking. The average annual cost of folks who are  
5 mildly resistant to treatment is easily double those  
6 for those who are not resistant to treatment, and  
7 those who would be categorized by the health services  
8 research literature who are severely resistant, if you  
9 will, to treatment -- their average annual costs  
10 sometimes are fourfold those who are not resistant to  
11 treatment at all.

12           This is an extraordinary clinical  
13 challenge. It is an extraordinary economic challenge,  
14 since half of the annual costs associated with  
15 treating depression are accounted for by this  
16 population.

17           Not only is health care utilization higher  
18 -- we can measure that by prescription costs. We can  
19 measure it by hospitalization rates. We can measure  
20 it by outpatient visits and so on -- the impact is  
21 significant from a fiscal point of view.

22           Then there are also all sorts of indirect

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1 effects. The type of workdays that are lost by  
2 individuals in the workplaces is on average double  
3 those who are not diagnosed with a depressive  
4 disorder. The preponderance or the prevalence of  
5 individuals on short and long term disability with  
6 major depressive disorders, the cost of which is borne  
7 directly and indirectly by employers and others, is  
8 significantly higher.

9 So in sum, depression not only has a  
10 negative economic burden, but there is no way to  
11 quantify the burden on the patient, their family and  
12 the community at large.

13 As indicated with respect to disability,  
14 you may be familiar that the World Health Organization  
15 now counts depression as the fourth leading cause of  
16 disability worldwide. The trend is severely upward,  
17 and the projections, if all things hold constant, is  
18 that within roughly or so the next ten years it will  
19 become the number two or one cause worldwide of  
20 disability.

21 The United States in that respect is not a  
22 statistical anomaly. The trend is essentially -- It

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1 tracks the world trends.

2 So it is clinical and economic opportunity  
3 loss. It hampers physicians to the extent that first,  
4 second line, third line attempts cannot work, and the  
5 personal tragedy of suicide and loss of life is  
6 untold.

7 I think what these findings underscore is  
8 the need for early identification and effective long  
9 term management of treatment resistant depression.  
10 And given the prevalence and the reality of  
11 nonresponse often to first line treatment, the cost  
12 and burden and the residual symptoms of nonremitting  
13 depression, we think there is a significant need for  
14 new treatments.

15 I am not here to opine on the science.  
16 That is not my job, but I do think, from where I live  
17 in a day to day world and the kinds of folks I deal  
18 with in the public and private sector, whether  
19 insurers or purchasers or human resource individuals,  
20 that the development of new treatments for this subset  
21 of the population diagnosed with a depressive order  
22 would be a significantly welcome development, and I

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1 have no doubts at all in thinking that the  
2 cost/benefit to all of us will be quite positive in  
3 the end. Thank you.

4 CHAIRPERSON BECKER: Thank you, Mr.  
5 Muszynski. Our next speaker will be Charles Donovan,  
6 who is also a patient in the Cyberonics study.

7 MR. DONOVAN: Good morning. First of all,  
8 Cyberonics did pay for my airfare here, in coach, I  
9 might add, and for my lodging. However, I was not  
10 solicited by Cyberonics or the study investigators to  
11 come. I volunteered, and as a matter of fact, to  
12 volunteer I had to go through a third party. The  
13 study investigators would not allow Cyberonics to  
14 contact me. I was not allowed to contact them.

15 What I would like to do, if it is okay, is  
16 read a letter that I sent to the FDA in support of the  
17 application and make a few comments. This is a letter  
18 that I wrote before I had any idea that I would be  
19 here, let alone reading it out loud in a room full of  
20 people. It is dated May 10th, and it is addressed to  
21 the Executive Secretary, Janet Scudiero.

22 "Dear Doctors: I am a patient in the D-02

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1 study, and I am writing to urge you to do everything  
2 possible in your power to unconditionally approve the  
3 vagus nerve stimulator as a treatment for chronic  
4 depression. It not just saved my life, which I really  
5 didn't care about. It changed my life.

6 "In the spring of 1980 I graduated from  
7 Georgetown University -- ironically, less than 30  
8 minutes from where the panel meeting will take place.

9 I also had my first major depressive episode that  
10 spring.

11 "I had accepted a job in the management  
12 training program of what is now J.P. Morgan Chase and  
13 moved to New York City after graduation. I bounced  
14 back during that summer, but the depression was always  
15 there, lurking in the background, and depressive  
16 episodes became more frequent over time.

17 "To keep this letter short, let's fast  
18 forward 15 years. In November of 1995 I eventually  
19 ended up in a lock-up unit of a hospital. I have very  
20 little memory of the details surrounding that  
21 hospitalization. I can only assume that my family  
22 must have had the hell scared out of them, and they

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1 didn't know what to do.

2 "In 1998, I was a 39-year-old man sobbing  
3 uncontrollably, hugging my parents in the doctor's  
4 office after the psychiatrist recommended shock  
5 treatments. I had a series of 15 or so. The ECT  
6 treatments did not work nor did any of the countless  
7 antidepressants I tried.

8 "In late 1999, I was no longer able to  
9 work. I don't know how I was able to continue to work  
10 as long as I did. I put up a long, hard fight, and it  
11 was a big mistake. The physical toll and mental toll  
12 that it took on my body was agonizing, and I am still  
13 recovering physically.

14 "In 2001 I was implanted with a vagus  
15 nerve stimulator. In my final depression rating  
16 interview just prior to implant with Raymond Tate,  
17 Ph.D. of St. Louis University, I simply told him that  
18 I hoped I would die on the operating table. Given the  
19 relative simplicity of the procedure, it was an  
20 irrational thing to hope for, but dying would have  
21 been the ultimate escape.

22 "I have no idea when the device was

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1 activated or how or when it was ramped up. As  
2 recently as a few months go, the study investigators  
3 told me that I may never know. All I can say is that  
4 my life is full of genuine happiness and joy. I don't  
5 have to fake it anymore.

6 "I have lost 30 pounds in the past 18  
7 months. I exercise regularly, swimming, Pilates,  
8 running. I am not ashamed to go to a shopping mall or  
9 other public places for fear of being noticed.

10 "Last Saturday night I attended a small  
11 dinner party that 18 months ago I never would have  
12 gone to. I am also working on several different  
13 projects. This is the most productive I have been in  
14 many years.

15 "The improvement in mood occurred very  
16 gradually over many months, but every morning I wake  
17 up, and I still ask myself the same question: Is it  
18 the depression back? And by the time I get in the  
19 shower, the answer is no.

20 "Because the mood improvement was gradual,  
21 there was no dramatic epiphany. So at this point, I  
22 would have to say that the most remarkable thing is

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1 the staying power of the therapy. It's like the  
2 Energizer battery. It keeps going and going.

3 "With the information learned from the  
4 studies and the benefit of stimulation strategy that  
5 new patients would have that I did not have, many  
6 desperate patients could be helped. Unless you have  
7 personally suffered from chronic depression, you  
8 cannot truly understand it, but it is brutal.

9 "Again, I encourage you to approve this  
10 relatively straightforward procedure for an extremely  
11 gruesome disease. Please give the option of vagus  
12 nerve stimulation therapy to those suffering patients  
13 who are still searching for an answer, just as I had  
14 searched. Some desperate patients stop searching  
15 forever."

16 Last night as I was reading this letter  
17 out loud to kind of time it, terms like chronic  
18 depression and treatment resistant depression are  
19 really slang for an incurable disease or a disease  
20 that is becoming curable. I think that it diminishes  
21 the seriousness of the level of the disease. It  
22 diminishes the need for alternative therapies.

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1 I am guilty of it in this letter. I don't  
2 adequately relay the day to day grind of white  
3 knuckling it. It is exhausting. And again, there is  
4 a casualness about the term chronic depression, but  
5 the casualness is, in effect -- It is chaos. There is  
6 chaos in the family. There is chaos between brothers  
7 and sisters and parents and husbands and wives.

8 I know there was chaos in my family, but I  
9 don't know the half of it, because there were  
10 certainly countless secret meetings amongst my family  
11 members saying, what are we going to do with this guy?

12 It takes a lot of work before you get the  
13 label, treatment resistant depression; and when you  
14 get there, you are stuck.

15 In 2001 I was implanted with the vagus  
16 nerve stimulator, but in November of 2000 I had my  
17 first meeting with the study investigators, and I  
18 remember it was a small office, and the psychiatric  
19 nurse was next to me, and the lead doctor was in the  
20 office.

21 I said to the doctor, "What are the  
22 chances of this thing helping me? You know, what are

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1 the odds?" And he was very measured and cautious in  
2 his response, and he basically said there is an  
3 inkling that there may or may not be something to this  
4 device that could improve mood. And I said to myself,  
5 inkling? I'll take it.

6 But when you think about it, what was I  
7 supposed to say? What were the options? Nothing. So  
8 the litmus test was "inkling," and I think that is  
9 probably true of the 4 million patients that suffer  
10 from chronic depression.

11 You know, there's 20 million people with  
12 depression in the United States, and there are 4  
13 million that have chronic depression. You're talking  
14 the bottom of the barrel, and the therapy that you are  
15 deliberating about today is a therapy for people that  
16 are at the bottom of the barrel.

17 I just want to quickly mention, I  
18 encourage you to improve this relatively  
19 straightforward procedure. During the first three  
20 months after implant, it was clear I had absolutely no  
21 benefit from the device, but it was a very odd time,  
22 because that was when my hoarseness was the worst.

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1                   People would ask me, aren't you mad? And  
2 the answer was no. Somebody was telling me to stop.  
3 How long have I been talking?

4                   CHAIRPERSON BECKER:     A little over 10  
5 minutes.

6                   MR. DONOVAN:   The answer was no. I mean,  
7 I wasn't happy about the hoarseness, but the  
8 hoarseness was completely subordinated to the hopes  
9 that the device would work.

10                  Very quickly in one minute, some desperate  
11 patients stop searching forever. March 14, 2003: I  
12 found the body of my closest friend from seventh  
13 grade, dead. Thankfully, his brother, an M.D., was  
14 with me. His body was laying between the bathroom in  
15 the hallway, and his brother found on his bureau a  
16 bottle of antidepressants, but his search stopped. He  
17 ended his search.

18                  A year before that, another classmate --  
19 we only had 40 -- put a bullet to his head, a  
20 psychologist. And finally, at the same time of the  
21 psychologist's death, the wife of my brother's boss,  
22 the mother of seven children -- I spoke to her

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1 husband, Tony, last week. And unlike Barbie that  
2 Lydia talked about, this family is a very prominent  
3 family in St. Louis, and they had access to absolutely  
4 every possible thing out there. Money was no object,  
5 and they went out on a nationwide search for help for  
6 this beautiful, stunning woman, and they saw the  
7 freight train coming, and there was nothing they could  
8 do about it until one of the seven children found her  
9 hanging in the family home, dead at age 38.

10 So I've gone over. If there's any  
11 questions that you want to ask me as a patient, please  
12 do.

13 CHAIRPERSON BECKER: Thank you. Our next  
14 speaker will be Marna Daventort, who is also a patient  
15 in the study.

16 MS. DAVENTORT: After hearing everyone  
17 else speak, it is really difficult to come up here and  
18 talk about this clinically, because I had really a lot  
19 more prepared, but they have said it all. They are  
20 telling my story. Their lives have been my life.

21 I want you to know that I am a person who  
22 can meet any challenge. I fly airplanes. I have a

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1 Ph.D. I ride beautiful horses, and I ride them fast.

2 I can meet any challenge, but I couldn't beat  
3 depression, not with all the knowledge that I could  
4 gain from studying it, and not with all the energy  
5 that I could put into it.

6 I can go over all the treatments I have  
7 been through, and I have been through it all, every  
8 kind of therapy that you can think of and every drug  
9 that any of you could think of prescribing to me, in  
10 experimental dosages often and in weird combinations  
11 that sometimes even the doctors were afraid to try.  
12 But we had to try anything, because the alternative is  
13 death, and people like me don't want to die.

14 I have a wonderful life now. I have a  
15 wonderful family. I never had drug or alcohol  
16 problems. I never had weight problems. I had no  
17 excuse whatsoever to be depressed, and yet I was  
18 depressed.

19 I think that that is what happens. A lot  
20 of times, we look at people with depression, and we  
21 think that somehow they could just do better. And I  
22 know that you can't just do better.

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1           One reason I am here today, and Cyberonics  
2 paid my plane fare up -- It won't compensate for the  
3 salary I have lost today, but I am here because I  
4 think it is -- The single most important thing that I  
5 can do today is tell you that I was implanted three  
6 year ago.

7           At first there was really no dramatic  
8 result. My family says that they saw results right  
9 away. I didn't, but over the next year, especially  
10 when it became about the 18 month mark, I began to be  
11 the person that my family used to know. My Dad said  
12 he had his daughter back.

13           I think that, with all else I could say,  
14 all I can say to you today is that this worked for me,  
15 and the alternative for me, to put it bluntly, was to  
16 blow my brains out.

17           So I think that it would be unconscionable  
18 for you not to offer this treatment option to people  
19 in my position. It has never been proposed that it  
20 would be a first line of defense. It has never been  
21 proposed to be a replacement for the drug therapy or  
22 for the resolution of psychological problems.

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1 All we are asking for is that you make  
2 this an option to people who have no options  
3 remaining. So I am not going to say everything else I  
4 had to say, other than I do want to point out that in  
5 May, since I have a compromised voice as a result of  
6 the surgery -- it comes and goes -- we did turn the  
7 device off in May to see if I would get some relief  
8 from the hoarseness for my voice; and I became  
9 depressed again.

10 I began to have these feelings of  
11 impending doom, and I just thought to myself, ah, you  
12 know, we can't go there again. So I am turned back  
13 on, and nobody will turn this device off again unless  
14 someone forces me to.

15 You have to give this opportunity to other  
16 people. That's the bottom line, and that's why I am  
17 here today. Thank you.

18 CHAIRPERSON BECKER: Thank you, Ms.  
19 Daventort. The final speaker will be Karmen McGuffee,  
20 who is also a patient in the study.

21 MS. MCGUFFEE: While they are cuing the  
22 video, I would like to state that Cyberonics has

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1 accommodated me, paid for my accommodations and paid  
2 for my flight. However, I did start a new job last  
3 week, and they were not pleased that I would be gone  
4 for a couple of days. So it has not benefitted me  
5 financially at all. The video.

6 (A short video was shown.)

7 MS. MCGUFFEE: That was me a little over  
8 five years ago. For me, it is very hard to define my  
9 first episode with depression. From the time I was  
10 three years old, I was a worrier. I worried about  
11 things that a toddler doesn't need to worry about:  
12 Would my sister die during the night?

13 In kindergarten I drove my teachers crazy.  
14 When my parents wanted to take a short trip, I  
15 insisted that they send books along with me so that I  
16 wouldn't fall behind. When I was nine, I couldn't  
17 sleep. I had nightmares constantly. I would go for  
18 days without sleeping. My mother says I would just  
19 lie in bed and cry and twist the sheets in my hands  
20 until one, two, 3:00 a.m. in the morning.

21 My mother tried everything that year, from  
22 traditional medicine to holistic medicine. We made a

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1 lot of adjustments in the family. It was not easy on  
2 them. All the doctors said there was nothing wrong  
3 with me except my blood sugar.

4 During my teen years, my family and  
5 friends thought that they were dealing with an  
6 overweight hypoglycemic, and those were my two  
7 problems. But then by the time I was 18, I graduated  
8 school with honors from high school. I had a good job  
9 as a computer graphic artist and a quality control  
10 coordinator.

11 I had seen a psychotherapist, and a  
12 psychiatrist had prescribed Prozac. Six months later,  
13 I decided I was cured, and I stopped. Shortly  
14 thereafter, I came home from work quite late one  
15 night, and my mother found me in my room in the fetal  
16 position on the floor, and I had scratched myself on  
17 my legs to the point of bleeding.

18 After a trip to the emergency room, I was  
19 admitted to the psych unit. I stayed there for six  
20 weeks. By the time I left, I was max'ed out on the  
21 dosage of Prozac that was safe for my weight, but I  
22 also had to take a booster, Tofranil.

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1 Over the next few years I took Parnate, an  
2 MAOI, Zoloft, Effexor, Paxil, Xanax, Halcion and  
3 probably a few that I don't remember. There's a lot I  
4 don't remember. Drugs would work for six months, if I  
5 was extremely fortunate, maybe a year, and then they  
6 would have to spin that roulette wheel and come up  
7 with a new combination.

8 I was hospitalized several times. It was  
9 like being in a very dark, downward tunnel. I was  
10 sliding down, and I could not get out. As I  
11 mentioned, the impact on my family and friends was  
12 very high. Friendships were always very strained. I  
13 never had more than one friend at a time, and I always  
14 chased them off. I have difficulty accomplishing the  
15 smallest tasks every day.

16 I required constant reassurance from  
17 everyone around me. My family said they felt as  
18 though they were walking on egg shells. There was no  
19 telling what they would say that would cause me to  
20 just crumple. Sometimes I could not be left by myself  
21 for any amount of time.

22 When I started dating my now husband,

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1 Jason, we addressed my depression, and he told my  
2 parents, well, I've been around Karmen when she is  
3 sick; I know what I am in for. And he admitted later  
4 that he had no idea.

5 Sometimes my husband's only goal in the  
6 morning was how do I get Karmen up? How do I get her  
7 out the door, because if I could pick out my own  
8 clothes, I was doing good.

9 At work I could still function, but my  
10 performance was extremely unpredictable. My  
11 absenteeism was high, and I had a caustic temper. It  
12 caused me to be fired twice.

13 Just prior to VNS implantation, I was  
14 taking five medications daily, seeing a psychiatrist  
15 weekly. I was in weekly group therapy, and ECT was  
16 next on the list. From the drugs, I had a dry mouth  
17 constantly. The MAOI -- I once had a drug interaction  
18 that sent me to the emergency room. I have had memory  
19 loss, and I experienced massive weight gain.

20 Every time I would relapse, it was very  
21 dangerous and very scary. Each pit was worse than the  
22 last, and I always feared they would run out of drugs

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1 to try on me. Every suicidal thought that I ever had  
2 was when the drugs quit working and I was back in that  
3 pit.

4 I continued in anxious moments to scratch  
5 myself to bleeding. I have many scars on my body from  
6 that. In psychotherapy -- I mainly found that very  
7 frustrating. Everyone there had a reason for their  
8 depression, and I had a wonderful family, a healthy  
9 family, a good support system.

10 I used to tell my family, I wish that  
11 something bad had happened to me -- I had been  
12 kidnapped and abused. At least then I would have a  
13 reason to feel so bad.

14 So about two weeks after that video I had  
15 the surgery. I was home that same afternoon, and I  
16 returned to work the same week. My husband and mother  
17 first noticed an improvement within three to six  
18 weeks. At first, they thought they were being overly  
19 optimistic.

20 My mother said she felt like she was not  
21 looking into the eyes of a dead person anymore. She  
22 has told the doctors, I don't care what scale you use

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1 to measure depression; I can tell by looking in  
2 Karmen's eyes. My husband said that the dark funeral  
3 veil over my eyes was lifted, and he could see my  
4 eyes, and they twinkled.

5 Today I feel great. The only regular side  
6 effect I experience is the hoarseness in my voice,  
7 which I don't even notice. Whereas, I was taking five  
8 medications a day for two and a half or three years, I  
9 was taking only Wellbutrin. I was laid off of work  
10 about ten months ago, and they added Lexapro, because  
11 I wasn't dealing with that very well. It was not on  
12 my terms. But prior to my unemployment, I was even  
13 talking to my doctor about coming off of Wellbutrin.

14 I do not believe that VNS therapy has  
15 cured me, but it has helped in ways that words cannot  
16 express. I constantly worry about will the depression  
17 return.

18 I had a baby 17 months ago, and I was told  
19 at my first pregnancy appointment that I was at very  
20 high risk for postpartum depression. I had about 11  
21 days of it, more like the blues, and today I enjoy my  
22 daughter thoroughly. I've gotten to see her first

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1 steps, and I remember them.

2 Thanks to VNS, I have clarity of mind. I  
3 can read books again, whereas I hadn't in years. I  
4 don't sleep away my weekends. I was able to research  
5 gastric bypass surgery, and had that a little over  
6 three years ago. I have lost 226 pounds. I have a  
7 joyful and peaceful life, and my family does, too,  
8 now.

9 In closing, people ask me why would you  
10 cut yourself open and have something foreign put in  
11 your neck and in your chest? My response to them is  
12 always, I had nothing to lose.

13 Please approve this therapy for treatment  
14 resistant depression, because it will give both  
15 patients and their families something that they have  
16 probably lost, and that is hope.

17 CHAIRPERSON BECKER: Thank you, Ms.  
18 McGuffee.

19 At this point I would like to note for the  
20 record that three patients and family members have  
21 written the FDA requesting that the agency approve the  
22 Cyberonics VNS system, and a patient also wrote to the

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1 agency asking that it not approve the VNS system.

2 Is anyone else here who would like to  
3 speak to the Panel now? If so, raise your hand, and  
4 come forward to the microphone. I would just like you  
5 to state your name and affiliation when you come  
6 forward, and whether or not you have any financial  
7 interest in Cyberonics.

8 MS. BARRETT: My name is Mary Barrett.  
9 I've been back there trying to write this in a hurry.

10 I am in the D-02 study. I have no financial interest  
11 in Cyberonics or its competitors, and no one paid for  
12 my trip here today.

13 I originally had not planned on speaking,  
14 but I felt like, because I do have the device and it  
15 is important to me that you consider it for approval,  
16 I just wanted you to hear my story.

17 I have been treated for major depressive  
18 disorder for over 20 years. I have tried almost every  
19 antidepressant drug on the market and combination of  
20 meds. Only one medication helped relieve my  
21 depression for about four years until I developed an  
22 intolerable side effect and was no longer able to take

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1 the drug.

2 Other medications were of no help, and  
3 again caused intolerable side effects. I was  
4 implanted in February of 2001. It wasn't until the  
5 device parameters were turned up to a higher level  
6 that I felt consistently better for the first time  
7 since I was forced to stop taking the medication that  
8 worked.

9 I volunteered for the study, because it  
10 was a last resort. I can only reiterate what previous  
11 speakers have said about the pain of depression. It  
12 permeates every cell of your brain. It affects every  
13 aspect of your life, and it affects the people around  
14 you.

15 This past spring I have had surgery for  
16 breast cancer, radiation treatment, and a major  
17 automobile accident, things that would cause people  
18 without depression to become depressed. I know, had  
19 it not been for the VNS, I would have never been able  
20 to get through these life traumas.

21 The VNS has helped me and others I know  
22 that have the device get their life back, and I only

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1 ask that this device be made available as a choice for  
2 others with this horrific illness. Thank you.

3 CHAIRPERSON BECKER: Thank you. is there  
4 anybody else who would like to address the Panel now?

5 If not, I think we will proceed to the  
6 sponsor's presentation on their vagus nerve  
7 stimulation therapy system.

8 This system is indicated for the  
9 adjunctive, long term treatment of chronic or  
10 recurrent depression for patients who are experiencing  
11 a major depressive episode that has not had an  
12 adequate response to two or more antidepressant  
13 treatments.

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

19 We will begin with the sponsor's  
20 presentations. The first Cyberonics presenter is Mr.  
21 Alan Totah, Vice President of Regulatory Affairs. He  
22 will then introduce the other Cyberonics presenters.

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1 Mr. Totah.

2 MR. TOTAH: Good morning. On behalf of  
3 Cyberonics and people in the United States living with  
4 treatment resistant depression, we thank you for  
5 meeting with us today to review the proposed  
6 depression indication for VNS therapy.

7 My name is Alan Totah, and I am the  
8 Cyberonics Vice President of Regulatory Affairs and  
9 Quality. I will begin today's sponsor presentation  
10 with a brief overview of the agenda, today's available  
11 presenters, VNS therapy system and regulatory history.

12 Dr. John Rush, Professor and Betty Jo Hay  
13 Distinguished Chair, Department of Psychiatry, UT  
14 Southwestern Medical Center, D-01 study investigator  
15 and D-02 principal investigator, will then summarize  
16 depression, treatment resistant depression or TRD, and  
17 the unmet need for an FDA approved effective and  
18 tolerable long term treatment for TRD.

19 Following Dr. Rush, Dr. Richard Rudolph,  
20 Cyberonics Vice President of Clinical and Medical  
21 Affairs, who prior to joining Cyberonics played a key  
22 role over a 16-year period in the development of the

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1 Effexor family of antidepressants at Wyeth, will then  
2 present study design and analysis plan, effectiveness  
3 and safety analysis, and the risks and benefits of VNS  
4 therapy. Dr. Rush will then provide closing remarks.

5 In addition to Dr. Rush, six other outside  
6 experts are with us today, who will be available for  
7 Q&A, representing psychiatry, biostatistics, and  
8 mechanism of action.

9 They are Doctors Harold Sackheim and  
10 Philip Ninan who are psychiatric investigators  
11 representing D-01, D-02, D-04 and D-05 depression  
12 studies; Doctors Phil Lavori and Sonia Davis who are  
13 providing expertise in biostatistics; and Doctors Tom  
14 Henry and Mark George, who are providing mechanism of  
15 action expertise and neuroimaging, and specifically  
16 VNS therapy PET and fMRI imaging.

17 In addition to the outside experts, we  
18 have a number of Cyberonics medical directors and  
19 directors here representing other disciplines to  
20 answer your questions.

21 We are here today to present to you the  
22 data that supports the safety and effectiveness of the

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1 VNS therapy system as an adjunctive, long term  
2 treatment of chronic or recurrent depression for  
3 patients over the age of 18 who are experiencing a  
4 major depressive episode that has not had an adequate  
5 response to two or more adequate antidepressant  
6 treatments, with specific definitions of chronic and  
7 recurrent depression and failed adequate treatment.

8 There are very few devices or drugs that  
9 are indicated specifically as adjunctive, long term  
10 treatments, and there is no FDA approved safe and  
11 effective long term treatment specifically for this  
12 level of chronic or recurrent treatment resistant  
13 depression.

14 The VNS therapy system, the programming  
15 parameters, and the implant technique used in  
16 depression are the same as those approved and used in  
17 epilepsy. The generator is implanted just like a  
18 simple bradycardia pulse generator, and a bipolar lead  
19 is simply tunneled under the skin from the left vagus  
20 nerve where the lead electrodes are wrapped around the  
21 nerve and then down to the generator.

22 I am pointing out to you the generator.

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1 This is the typical implant site. We have a picture  
2 of the lead going up, and you can see this exploded  
3 view of the electrodes which are wrapped around the  
4 left vagus nerve, and we have the other elements or  
5 components of our system illustrated for you.

6 Typically, the device is programmed on for  
7 30 seconds and off for five minutes on a 24/7  
8 schedule. The typical outpatient surgery often lasts  
9 approximately one hour and is a low risk implant  
10 procedure, and surgical complications are minimal.

11 A magnet can be used by the patient to  
12 temporarily control side effects such as voice  
13 alteration during public speaking or singing, if  
14 necessary.

15 From an historical perspective, FDA's  
16 Neurological Devices Panel unanimously recommended  
17 epilepsy approval in June of 1997, and the VNS therapy  
18 system was approved by FDA on July 16, 1997. The  
19 epilepsy safety number shown on this slide are at the  
20 time of the application.

21 Today, over 29,000 epilepsy patients have  
22 been treated with the VNS therapy system, and we have

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1 accumulated a total of 72,000 patient years of  
2 experience.

3 Depression studies were started, because  
4 clinical observations from epilepsy use and findings  
5 from epilepsy, preclinical and human neuroimaging  
6 mechanism of action studies suggested that VNS had a  
7 potential antidepressant effect. Depression studies  
8 began in 1998 following IDE approval of a D-01 pilot  
9 study protocol.

10 Several significant regulatory historical  
11 dates that followed are: In July 1999 when FDA  
12 granted expedited review status; European CE Mark and  
13 Canadian commercial approvals were granted for the  
14 depression indication in March and April of the year  
15 2001, based upon the D-01 results; and in January of  
16 2002 the D-02 acute 12-week study results were  
17 unblinded and analyzed.

18 The primary endpoint did not reach  
19 statistical significance. However, the results did  
20 show a positive trend in favor of VNS, and a key  
21 secondary endpoint was statistically significant.

22 After consideration of the acute results,

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1 the proposed indication for use and the existing D-02  
2 and D-04 protocols, a revised D-02 long term and D-02  
3 versus D-04 standard of care prospective analysis plan  
4 was submitted to the FDA in September of 2002. The  
5 FDA notified Cyberonics that no manufacturing site  
6 inspection would be required, due to Cyberonics good  
7 compliance history.

8 The PMA Supplement was submitted and  
9 accepted for filing by the FDA on October 27, 2003.  
10 Since then Cyberonics has completely responded to  
11 FDA's deficiency letter regarding this PMA  
12 application.

13 That brings us to today's Panel meeting  
14 that is occurring just two weeks shy of the seventh  
15 anniversary of the original epilepsy panel in June of  
16 1997. During today's meeting Cyberonics is prepared  
17 to address FDA's Panel questions and any questions the  
18 Panel members may have.

19 These are the studies that comprise the  
20 six-year depression program. Dr. Rudolph will present  
21 details in his presentation. There was one important  
22 revision during the program that you will hear about

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1 today.

2 For clarity, let me describe the reason  
3 for the revision and what was changed. When the acute  
4 study endpoint did not reach statistical significance  
5 despite a favorable trend, and significance on  
6 secondary endpoints, we decided to provide a more  
7 definitive evaluation of long term effectiveness by  
8 adding an active control for the D-02 outcomes.

9 The sole change indicated on this slide by  
10 a double checkmark added a one-year comparison of D-02  
11 patients treated with adjunctive VNS plus standard of  
12 care treatment with D-04 patients treated only with  
13 standard of care treatment.

14 The existing D-04 protocol, which had been  
15 previously intended as a comparison with D-02, was  
16 then formally added into the statistical plan as a  
17 long term active control. This revised plan provided  
18 the FDA with comprehensive one-year clinical data and  
19 analysis on 460 patients with treatment resistant  
20 depression.

21 Cyberonics and its team of outside  
22 clinical, statistical and regulatory experts deemed

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1 the revised analysis plan the most appropriate for the  
2 determination of safety and effectiveness for the  
3 proposed indication for use, after careful  
4 consideration of the urgent unmet need for a long term  
5 treatment for TRD, which you certainly heard about  
6 from our patients today.

7 They consist of the following: First, the  
8 nonsignificant yet encouraging results from the acute,  
9 sham control phase of D-02; second, the increasing  
10 response rates seen over time in D-01 patients;  
11 thirdly, the adjunctive, meaning VNS would be added  
12 onto currently available standard of care treatments,  
13 long term proposed indication; fourth, the majority of  
14 PMA device and neurological device approval precedents  
15 did not include randomized controlled trials  
16 consistent with 21 CFR 860.7 of the regulations;  
17 fifth, D-04 study which started in the year 2000 and  
18 was originally designed to be compared with D-02  
19 patients provides a valid, prospective, active  
20 standard of care control consistent with the proposed  
21 indication; and finally, the infeasibility and limited  
22 value of alternative long term study designs in

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1 treatment resistant depression patients relative to D-  
2 02 versus D-04 comparative analysis.

3 In conclusion, allow me to once again  
4 thank you for your time today, and mention that we are  
5 all here primarily because of the significant unmet  
6 need for an FDA approved informed use, safe and  
7 effective long term treatment for treatment resistant  
8 depression.

9 FDA initially recognized this need in 1999  
10 when expedited review status was granted. Four and a  
11 half years later, FDA reconfirmed the continuing unmet  
12 need in their December 2003 PMAS filing letter.  
13 Please see the noted quote on the slide.

14 I now invite Dr. Rush to help us better  
15 understand treatment resistant depression and the  
16 significant unmet need for an effective long term  
17 treatment for TRD. Thank you.

18 DR. RUSH: Thank you very much, and good  
19 morning. I am John Rush. I am a full time employee  
20 of UT Southwestern, Dallas. I have provided  
21 consultation to Cyberonics and received fees for that  
22 consultation.

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1 I am going to very briefly review for you  
2 probably much of what the Panel is quite familiar  
3 with, and certainly what you heard this morning  
4 already from the several patients. That is the  
5 importance of treatment resistant depression, its  
6 impact from a public health significance and from a  
7 personal significance impact, and provide you some  
8 sense of the kinds of patients that we are talking  
9 about that entered into the VNS studies.

10 So to recap what I think is quite familiar  
11 to most of you, a very common syndrome affecting 16  
12 percent of the individuals in the U.S. in their  
13 lifetime. This is not TRD. This is major depressive  
14 disorder. Two-thirds are female, 9.5 million treated  
15 annually and, as mentioned previously, substantially  
16 disabling, second most disabling condition in the  
17 U.S., fourth worldwide currently, the most disabling  
18 condition for women in the United States presently.

19 It is associated with a marked increase in  
20 mortality due to suicide. Thirty thousand suicides  
21 per year have been mentioned. Eighty percent of those  
22 are attributable to depression, and increased

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1 mortality as well due to worsening of the outcome of a  
2 number of general medical conditions; for example,  
3 cardiovascular disease, but others as well clearly  
4 investigated and studied.

5 It is well known that depressed patients,  
6 for obvious reasons, are high utilizers of not just  
7 mental health services but general health services.

8 Very briefly, these slides are, I am sure,  
9 presenting you with what you know. So I'll just go  
10 very quickly over them. We 30 years ago had the  
11 stigma of depression. We didn't even recognize it  
12 much as an illness. They were seen as troubled  
13 individuals. Obviously, that is not the case. These  
14 are individuals suffering from a syndrome defined by a  
15 variety of biological abnormalities.

16 Thirty years ago we thought of these  
17 depressions as situational adjustment reactions,  
18 basically brief, time limited, and of modest impact on  
19 individuals' lives. When I was at the University of  
20 Pennsylvania, I was taught to treat these individuals  
21 with medication for four to six months to facilitate  
22 psychotherapy, and the need for long term medication

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1 was not recognized and was not part of training.

2 We now know that 60 percent of people in  
3 the first depressive episode will go on to have either  
4 a recurrent, subsequent episodes, or chronic course.

5 The next level of stigma is that we have  
6 now accepted it as an illness, but I think in many  
7 people's minds it is a very benign illness. In fact,  
8 it shortens life span due to the causes I previously  
9 mentioned, suicide, increased mortality from general  
10 medical conditions. It is massively disabling. I  
11 reviewed the data with you.

12 The third level of stigma: So now we  
13 recognize an illness. We are beginning to recognize  
14 just how profoundly severe and disabling this illness  
15 is, and costly on a human suffering basis as well as  
16 an economic basis. But the third myth that we deal  
17 with is, well, the treatments we have are really  
18 pretty good.

19 The fact of the matter is the treatments  
20 we have are good, but they are not good enough, and  
21 some of that is described here. So our current  
22 medications are effective. Fifty percent of

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1 symptomatic volunteers, individuals who have  
2 uncomplicated non-treatment resistant depression --  
3 those are the individuals that typically enter  
4 randomized efficacy trials for regulatory purposes, by  
5 the way -- do respond to the first medication, and  
6 within that group of responders the substantial  
7 majority achieve a remission, virtual absence of  
8 symptoms. But that only gives us 35 to 40 percent of  
9 the uncomplicated, nonchronic, non-treatment resistant  
10 patients achieving remission, the goal of treatment  
11 with the first drug.

12           What about the second or the third drug?  
13 We had some discussion about that earlier. This is  
14 being evaluated, but at the moment the estimates are  
15 that somewhere between 15 and 20 percent of patients  
16 will not achieve remission with two or even three  
17 medications.

18           The other element in treatment is  
19 sustaining that benefit, if achieved, and I will  
20 describe that and discuss that in just a minute.

21           I will show you some of the data that  
22 indicates that, even in non-treatment resistant

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1 depressed patients, a substantial proportion having  
2 achieved a benefit in acute treatment and continuation  
3 phase -- so three months plus four more months, seven  
4 months -- do in fact suffer a return of the episode.

5 Treatment resistant depression: The field  
6 has begun to coalesce around an accepted definition.  
7 This is obviously on a continuum. There have been  
8 various staging systems to define treatment resistant  
9 depression, but studies have been launched that accept  
10 this definition as certainly a reasonable one. I  
11 think a consensus of experts would agree.

12 It is the lack of an adequate clinical  
13 response after at least two well delivered treatments.

14 Looking at symptomatic volunteers from the efficacy  
15 trials that we have abundantly, as I mentioned, 50  
16 percent respond. About 35 to 40 remit, no symptoms  
17 after the first trial.

18 It is also known that, if you go to the  
19 second treatment -- these are largely open trials, but  
20 there are quite a number of them -- about 20 to 25  
21 percent of the original sample respond to the second  
22 treatment, having not responded to the first. So that

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1 gives us roughly 75 percent of the original sample.

2 That leaves us with about 20 to 25 percent  
3 of individuals who will not achieve the goal of  
4 response, which is short of remission, after two  
5 treatments.

6 So what do we know about TRD? It has  
7 actually become a focus of research over the last  
8 several years. It is quite clear that treatment  
9 resistant depression is clearly associated with worse  
10 function, worse prognosis, higher health care costs,  
11 health care utilization, increased risk of  
12 complications, including general medical problems and  
13 substance abuse, as we have already heard on an  
14 individual basis and has been shown in studies, high  
15 risk of family burden, high risk of suicide, and as  
16 you know, 8 to 15 percent of previously hospitalized  
17 depressed patients do go on to commit suicide, and the  
18 worsened mortality we talked about in terms of general  
19 medical conditions.

20 Importantly, treatment resistant  
21 depression has a very low response and very high  
22 relapse rate, and I will show you a little bit of data

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1 to justify that statement in a minute.

2 I really don't have to spend very much  
3 time on this issue, because you have heard the  
4 clinical picture of treatment resistant depression  
5 from the patients. But these individuals are exactly  
6 as described, tearful, suicidal, hopeless, desperate,  
7 hanging on by their knuckles, their fingernails,  
8 frequent users of hospitalization, emergency room,  
9 seeing psychiatrists frequently, often failing to be  
10 fully employed or even being unemployed, and a  
11 remarkable percentage on ongoing full time disability.

12 I would point out that in the Texas Public  
13 Health System, one-third to 40 percent of the  
14 individuals served by the Texas public sector have  
15 depression. They outnumber the individuals that are  
16 still substantial in number who have schizophrenia.  
17 This is a very serious condition.

18 These individuals depend heavily, as you  
19 heard, on families and others, and it really is a  
20 different kind of depression. This is not the kind of  
21 depression that enters typical efficacy trials, and I  
22 will show you a little more data.

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1           These people have long standing disabling  
2 illness, rarely achieve sustained remission even  
3 spontaneously, have very modest responses to  
4 medication, but they are grateful to have even that.  
5 They are much more akin to congestive heart failure,  
6 chronic renal or lung disease, the kinds of chronic  
7 disabling general medical conditions, by the way, for  
8 which patients do not take their lives. Eighty  
9 percent of suicides are due to depression. This  
10 condition is so bad that people kill themselves  
11 because of it.

12           What about utilization? Just very  
13 briefly, one slide. This is a study we recently  
14 completed. This is the number of different  
15 medications, changes that the individuals went  
16 through, and this is an estimate of, in this case,  
17 cost but, obviously, then frequency of utilization of  
18 inpatient/outpatient, pharmaceutical and total health  
19 care utilization costs.

20           The point is the greater the degree of  
21 treatment resistance, the greater the use of all of  
22 these services, in, out and pharmaceutical.

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1                   Clinical management of TRD at the moment:  
2           Basically, we do not have an FDA approved treatment.  
3           Multiple medication is very common, as you heard.  
4           Which treatments, however, are best or what  
5           combinations are best is really not known. Is there a  
6           preferred series of treatment steps? What treatment  
7           to give first, second, third, and when to go to  
8           combinations -- that is really not known.

9                   In fact, I am the principal investigator  
10          on an NINH sponsored trial called the Sequence  
11          Treatment Alternative To Relieve Depression Trial. We  
12          have just completed enrollment with over 4,000  
13          patients, and it is a nested, multiple randomized  
14          controlled trial effort to see what to do, what is  
15          best, if the patient does not respond to the first  
16          treatment.

17                   So they are randomized to four different  
18          switches or three different augments in the second  
19          stage, and the third stage there is again  
20          randomizations to different switching and augmenting  
21          treatments.

22                   So we hope to have, really for the first

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1 time, randomized controlled evidence for what to do  
2 after the first treatment doesn't work, and certainly  
3 after the second treatment doesn't work.

4 At the moment -- and I would point out  
5 that this trial was launched in October of 1999. It  
6 is going to cost \$35 million, and I think it  
7 represents the importance of TRD now in terms of the  
8 public health agenda. This has come on the radar  
9 screen.

10 In 1990, if you talked about this  
11 condition, people would deny it existed. But every  
12 clinician knew about it, because those are the  
13 patients we are treating.

14 ECT is our best treatment right now for  
15 treatment resistant depression. It does work very  
16 nicely acutely, but it does not -- it can't be used in  
17 a sustained, long term maintenance basis for easily  
18 for most patients, because of some cognitive side  
19 effects. And when you stop the treatment, as I will  
20 show you, the outcomes with ECT are not good, the  
21 treatment being discontinued.

22 The management of TRD involves side

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1 effects and adherence difficulties due to multiple  
2 medications, and it is known that the greater level of  
3 resistance is associated with lower response and  
4 higher relapse rates.

5 The reality of treatment of TRD today is  
6 keeping the patient alive, and basically you heard  
7 that from the patients. Let me give you one example.

8 There is a case of a young man, 29-year-old graduate  
9 student, been in graduate school since age 21. He  
10 could not take the full course load. He was taking  
11 two courses, seeing a psychiatrist two to three times  
12 a week. He had been depressed for 10 years, in an  
13 episode for 10 years.

14 He had been on multiple medications. He  
15 had finally settled on a combination of Risperidone  
16 and Prozac 80 milligrams. That was the best that he  
17 could do. He was having panic attacks, but he was  
18 able to stay outside the hospital. He was preoccupied  
19 regularly with suicide and suicidal ideation,  
20 basically living by himself in the dorm room, totally  
21 dependent on his family, clearly ashamed of his life  
22 and what he had not become, given his peers with whom

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1 he had graduated from college, and this was one of the  
2 first patients that we actually entered into the VNS  
3 study.

4 That is very typical, as we have heard  
5 from the other patients, of treatment resistant  
6 depression.

7 What about long term outcome with what we  
8 have now? Well, here is the results with medication.  
9 pay attention to this column. This is from John  
10 Greden's recent publication. He looked at long term  
11 recurrence rates, comparing placebo and medication.

12 Indeed, the medication does provide a  
13 benefit, but look at the recurrence rate, and this is  
14 non-treatment resistant depression. The recurrence  
15 rate over a year is up to, in some studies, 50  
16 percent, obviously depends on the population.

17 All of these individuals had responded  
18 acutely and stayed well for four more months of  
19 continuation treatment. So in non-TRD long term  
20 outcome is not as we hope.

21 This is another slide of the same  
22 question, a different population. This is a

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1 population that we recently treated in the Texas  
2 Medication Algorithm Project in the public sector.  
3 They were treated for a year under algorithm based  
4 conditions. So we used an algorithmic sequence with  
5 augmented resources.

6 The algorithm based treatment did very  
7 well as compared to treatment as usual. So this is  
8 the best outcome, and this is a measure of depressive  
9 symptoms analogous to the Hamilton, and what you see  
10 is the sustained response rates. That is, response at  
11 nine and 12 months out, 14 percent sustained  
12 remission, five percent -- and it doesn't matter,  
13 really, if it is observed case or LOCF. These are  
14 very, very remarkably low figures, much lower than you  
15 expect from, of course, RCTs with non-TRD patients.

16 A couple more slides on long term outcome,  
17 and then I will turn over the podium to Dr. Rudolph.  
18 This is work from Dr. Sackheim's group. These  
19 individuals that we are showing you here had a  
20 successful acute phase response to ECT, our most  
21 effective treatment for treatment resistant depression  
22 at the moment.

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1           He then randomized patients to placebo,  
2           nortriptyline plus placebo, or the combination of  
3           Lithium and nortriptyline, followed the patients over  
4           subsequent six months. As you can see, the relapse  
5           rates in patients who had done quite well with ECT and  
6           were given the best treatment, still 40 percent were  
7           relapsed within six months, and this is under research  
8           conditions.

9           Eighty-four percent of those individuals  
10          relapsed with placebo. Not all these people were  
11          treatment resistant. Of course, many were, because  
12          they received ECT. If you look at the effect of  
13          treatment resistance at baseline on the long term  
14          outcome following successful ECT, you see this here.

15          Again, work from Dr. Sackheim's group,  
16          patients had done well with ECT, and they were  
17          designated at the beginning, blind to this outcome,  
18          whether or not they had been medication resistant --  
19          this is one or more medication failures in the current  
20          episode -- or had not been so exposed.

21          You notice, in the people that had  
22          medication resistance, two-thirds of these individuals

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1 actually relapsed over the subsequent year, after  
2 successful treatment with ECT. And this is still an  
3 ongoing treatment. This is not in placebo. So these  
4 individuals have a very difficult long term course.

5 Finally, just to provide you with a sense  
6 of who the patients are that you are going to hear  
7 about. Let me just talk a little bit from a clinical  
8 perspective.

9 What this does is this is a comparison of  
10 individuals represented in the community ECT sample  
11 developed by Dr. Sackheim from multiple New York  
12 metropolitan area hospitals. These are just  
13 individuals that are in the community, are receiving  
14 ECT.

15 We then compare them to the individuals,  
16 all of them that enter the D-02 and D-04 studies.  
17 This is the number of adequately delivered treatments  
18 which were scorable by the antidepressant treatment  
19 history form, Dr. Sackheim's scale.

20 The first thing that you see is that level  
21 of treatment resistance in the VNS patients, noted in  
22 red, is far higher. Almost half, in fact, are not

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1 even included within patients who receive ECT in the  
2 community. Put the other way, half the patients  
3 receiving ECT in the community do not have the level  
4 of resistance that we are talking about with patients  
5 in the D-02 trial.

6 That makes some sense. Fifty percent --  
7 Over 50 percent of these patients in the trial had  
8 already had ECT in their lifetime, and over a third in  
9 the current episode.

10 The number of hospitalizations in the VNS  
11 group nearly twice that for the ECT community group.  
12 So we are dealing in these studies with a very, very,  
13 very difficult, hard to treat, at the end of the line  
14 almost, depressed patient population.

15 I can tell you, I have done trials for 30  
16 years. I have never ever come close to putting this  
17 level of difficult patient, difficult disease in any  
18 trial. These patients would not even come ever close  
19 to getting into a pharmaceutical trial, because the  
20 pharmaceutical trials typically exclude people that  
21 have failed on more than one treatment in the current  
22 episode.

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1           The other comment is about what is the  
2 meaning of these numbers. I just want to help  
3 convert. This is a research definition that is  
4 extremely conservative. That is, Dr. Sackheim's scale  
5 only rates drugs that have been demonstrated to be  
6 effective in randomized controlled trials.

7           Many things that we do clinically with the  
8 treatment resistant depressed patient have not been  
9 subjected to randomized controlled trials. An example  
10 is a typical anti-psychotic augmentation has been  
11 subjected to one trial that has been published, and it  
12 was widely used practice.

13           We think it is effective. That would not  
14 count in Dr. Sackheim's ratings. To give you a sense,  
15 if in his scale there are two to three ATHF failed  
16 trials, what is the actual number of clinical trials  
17 these patients failed on? Twelve, twelve clinical  
18 trials, and I am not talking about all the  
19 combinations used, 12 medicines.

20           When you get to four to five, the number  
21 of clinical trials is 16. When it is six or greater,  
22 the number of clinical trials is 20. These are

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1 extremely resistant patients who are really at the end  
2 of the line.

3 So let me just briefly summarize. I am  
4 sure you are convinced that TRD is highly disabling.  
5 It affects a large number of people, 20 percent of  
6 people with major depression. It is a clear unmet  
7 need.

8 These patients have a high suicide risk.  
9 They have very low response rates, high relapse and  
10 recurrence rates with our current treatment, high  
11 utilization of health care services. They are really  
12 analogous to any of the very severe psychiatric or  
13 chronic general medicine conditions.

14 We have no FDA approved treatment that is  
15 effective, safe in the long run for TRD. ECT is  
16 excellent, but difficult for the reasons I have  
17 outlined previously. Multiple medications are used in  
18 combinations and in sequences for which there is  
19 virtually no evidence. Side effects and adherence,  
20 especially with multiple medications, is a huge  
21 problem, and we clearly need a treatment for these  
22 desperate but important and substantial in number

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1 depressed patients. Thank you.

2 Let me turn the podium over to Dr. Richard  
3 Rudolph, Vice President, who will go through the D-01  
4 to 6 studies.

5 DR. RUDOLPH: Thank you, Dr. Rush. I want  
6 to start by thanking the Panel Chair, Panel secretary,  
7 Panel members and the FDA for this opportunity to  
8 provide an overview of the clinical data supporting  
9 safety and effectiveness for VNS for the indication  
10 that you are considering today, treatment resistant  
11 depression.

12 This is an outline of the presentation  
13 that I am going to give this morning. I am going to  
14 provide some general background, and then spend some  
15 time going over design and analysis considerations to  
16 help you better understand the effectiveness data that  
17 I will then present. Then finally, I will move on to  
18 safety data and a short set of conclusions.

19 Well, why did Cyberonics become  
20 interested, in the first place, in developing the VNS  
21 therapy for depression? There were a number of  
22 initial considerations that led us to believe VNS

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1 therapy might be useful for this indication.

2 Those consisted of anecdotal reports of  
3 mood improvement in patients in our epilepsy trials  
4 where the improvement in mood seemed to be out of  
5 proportion to the improvement in the seizure counts  
6 that the patients were experiencing.

7 Also, knowledge that the use of anti-  
8 convulsants have been used in the past and currently  
9 are used as mood stabilizers and augmenting agents in  
10 the treatment of depression, and the observation that  
11 electroconvulsive therapy has both antidepressant and  
12 anti-convulsant actions.

13 Subsequently there were some additional  
14 considerations that provided a biological rationale  
15 for the use of VNS for this indication. These  
16 included: A more formal analysis of mood changes in  
17 the epilepsy studies, which confirmed the anecdotal  
18 reports; a variety of neuroimaging data, some of which  
19 I will show you shortly; effects on neurotransmitters  
20 which showed that VNS does have effects on  
21 norepinephrine and serotonin, the normal transmitters  
22 most closely implicated in the action of

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1 antidepressant drugs; and most recently, activity in  
2 an animal antidepressant model called the 4-SWIM test  
3 in which VNS had similar effects to desipramine, a  
4 standard antidepressant drug, and clearly  
5 distinguishable from placebo.

6 As I indicated, we have done a variety of  
7 neuroimaging studies, and our findings from the  
8 neuroimaging studies have shown us that VNS affects a  
9 widespread array of autonomic, reticular, and limbic  
10 structures within the brain.

11 The immediate effects of VNS on the  
12 central nervous system implicate brain areas known to  
13 be primary and secondary vagal projections. So just  
14 what you would assume that happens.

15 Longer term effects of VNS on the central  
16 nervous system implicate limbic and paralimbic brain  
17 circuits associated with depression and mood  
18 regulation. An example of that is shown on this  
19 slide. These are PET images three months after the  
20 initiation of vagus nerve stimulation.

21 What one finds is effects, modulation in  
22 areas such as the orbitofrontal cortex, L. insula, and

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1 the Mid-Cingulate Gyrus. These are areas that are  
2 implicated in the regulation of mood.

3 Our six-year development program for VNS  
4 for the TRD indication consists of the studies on this  
5 slide. The most important studies, the ones I will be  
6 spending the most time on in my presentation, are the  
7 ones above the yellow bar.

8 Those are the D-01 study which was an  
9 open-label feasibility study, the D-02 study which had  
10 two parts, an acute phase which was a double blind  
11 randomized control of sham stimulation and active VNS  
12 therapy, and the second phase, a long term phase in  
13 which the sham treated patients crossed over into  
14 active treatment. So all patients continued out to  
15 one year and beyond in an open label fashion.

16 Then the D-04 study, which is a  
17 prospective observational, which is a prospective  
18 observational study of treatment resistant depression  
19 patients treated with standard of care therapies,  
20 which we used as a control for the long term D-02  
21 outcomes.

22 Other studies that were in our submission

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1 that I won't be speaking too much about were the C-03  
2 study which is actually still enrolling -- it is a  
3 European open label study; the D-05 study which was  
4 per se not a study but a video tape assessment used to  
5 ascertain the inter-rate of reliability of those that  
6 were performing the ratings for the D-02 study; and  
7 then the D-06 study, which is a study, a pilot study  
8 in a very different population. This is an open label  
9 feasibility study in rapid cycling bipolar disorder.

10 Next I would like to go through some  
11 design and analysis considerations to help facilitate  
12 your understanding of the effectiveness data that I  
13 will be presenting subsequently.

14 There are several lines of evidence to  
15 support the effectiveness of adjunctive VNS therapy  
16 for TRD indication. The most important evidence comes  
17 from a comparison of the 12-month outcomes in the D-02  
18 patients, and again these are patients in the long  
19 term that are receiving adjunctive VNS therapy, in  
20 comparison with the 12-month outcomes from patients in  
21 a separate study, D-04, which were enrolled as similar  
22 patients to receive only standard of care therapy.

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1           Other evidence comes from a comparison of  
2 the D-02 acute treatment outcomes that compared VNS  
3 with sham control, and then longer term outcomes, both  
4 from the D-02 patients and from the D-01 patients in  
5 the feasibility study, particularly with a focus on  
6 the durability of their response.

7           This slide gives a schematic of the D-02  
8 study design. Patients in the study were qualified  
9 during an initial 45-day period, and those that met  
10 protocol entry criteria were then implanted and  
11 randomized.

12           Following that, there was a two-week  
13 period during which stimulation was not turned on for  
14 any patients. It was a period for recovery from the  
15 surgery. At that point, the group that was randomized  
16 to the active VNS therapy group had their stimulators  
17 turned on, and for two weeks underwent a period of  
18 stimulation adjustment.

19           Whatever parameters were obtained and  
20 optimized at that period were continued for an  
21 additional eight weeks of therapy.

22           Meanwhile, the sham stimulation group

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1 underwent all the same procedures, but never had the  
2 output current turned on for their stimulators. So  
3 they served as the control.

4           Following the end of that period, the  
5 patients in the sham treatment group had the  
6 opportunity to cross over to active therapy and  
7 underwent the same procedures, and then both groups of  
8 patients continued into a long term open label phase.

9           During the acute phase, medications had to  
10 be fixed. So whatever medications the patients came  
11 into the study on had to remain the same. During the  
12 long term study phase, medications could be added or  
13 increased at the discretion of the investigators.

14           Here we have some more details on the  
15 study design. I have already covered the top part of  
16 the slide. There were 235 patients that were  
17 implanted in the study at 21 different study sites.  
18 The main inclusion criteria to be enrolled in the  
19 study were that you could be a male or female between  
20 the ages of 18 and 80 years of age. You had to have a  
21 current diagnosis of being in a major depressive  
22 episode with a background history of having chronic or

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1 recurrent depression.

2 Most importantly perhaps, you had to have  
3 failed at least two adequate treatment trials in the  
4 current major depressive episode as measured by  
5 standardized scale that Dr. Rush referred to before,  
6 the antidepressant treatment history form; and  
7 patients had to have a minimum score of 20 on their  
8 baseline Hamilton reading.

9 Here are some similar details for the D-04  
10 study design. D-04 was a 24-month prospective  
11 observational study in which patients received  
12 standard of care treatment but no VNS. So if you  
13 think about it for a moment, essentially what we have  
14 in the D-02 study is a group of patients receiving VNS  
15 long term plus various medications at the discretion  
16 of the physicians taking care of the patients, and in  
17 the D-04 study we have a similar group of patients,  
18 but they are receiving medications only, no vagus  
19 nerve stimulation.

20 The D-04 study enrolled 127 patients at 13  
21 total study sites, 12 of which were overlapping sites  
22 with the D-02 study. The main inclusion for the D-04

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1 study were identical to the inclusion criteria for the  
2 D-02 study.

3 So why do we think this nonrandomized D-04  
4 serves as an appropriate control for the D-02, a long  
5 term study? Well, for several reasons. First of all,  
6 it was a prospectively designed study for comparison  
7 with D-02 outcomes. It just wasn't randomized with D-  
8 02.

9 It does represent a clinically relevant  
10 control in that it is an active treatment control that  
11 corresponds to the proposed indication for VNS, which  
12 is adjunctive long term VNS therapy.

13 The study was done primarily at  
14 overlapping sites, as I have already indicated, and it  
15 did use the same principal enrollment criteria.  
16 Moreover, the study was conducted over a similar time  
17 period, which is important, because it helped ensure  
18 that patients would have access to the same types of  
19 treatments in terms of their standard of care therapy.

20 Finally, the D-04 represents a large  
21 sample size which, of course, facilitates statistical  
22 comparisons.

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1           Now for the benefit Panel members that may  
2 not be that familiar with research methodology in  
3 depression trials, I have included some slides to  
4 provide some additional background. The first slide  
5 tells you how we measure effectiveness outcomes in  
6 depression studies.

7           In depression studies, effectiveness is  
8 measured by standardized validated rating scales.  
9 These may be either multi-dimensional scales -- that  
10 is, scales that cover different aspects of the  
11 depressive syndrome, and examples of this would be the  
12 Hamilton rating scale for depression, the inventory of  
13 depressive symptomatology self-report, and the  
14 Montgomery Asberg Depression Rating Scale -- or the  
15 rating scales may be a Licher type scale like the  
16 Clinical Global Impression Scale.

17           The scales may be either clinician or  
18 patient rated. For the multi-dimensional scales, the  
19 way the scales are analyzed is to total all the  
20 individual items, obtain a total score, and then  
21 analyze the total score. Higher scores on these  
22 scales indicate a patient who is more severely

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