

1 asking a very simplistic question. If the sponsor  
2 wants to take the table. I was wondering how you  
3 chose the 12-week time frame for the acute study,  
4 which seemed not to be effective, but in the long term  
5 it was. Why did you initially choose that acute time  
6 frame? And when you saw that the study was negative,  
7 why didn't you continue in a randomized sham  
8 controlled fashion?

9 DR. RUDOLPH: The 12-week period is pretty  
10 standard for a drug trial. So we were following the  
11 pattern that's been used for drug trials. They're  
12 typically nowadays eight to twelve weeks. So that's  
13 the explanation for why it was set up that way  
14 initially.

15 I think the second part of your question  
16 was why didn't you just extend that longer. Well, by  
17 the time of course we un-blinded the results for that  
18 acute phase, the patients were all beyond the acute  
19 phase, so there wasn't an opportunity to continue it  
20 as a double-blind randomized trial.

21 CHAIRPERSON BECKER: There wasn't the  
22 opportunity just to continue stimulating one group and

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1 not stimulating the other group?

2 DR. RUDOLPH: Well, by the time that we  
3 saw the results, the sham treatment patients had  
4 already crossed over into the continuation long-term  
5 VNS stimulation.

6 CHAIRPERSON BECKER: Okay. Further  
7 questions for the sponsor?

8 DR. ELLENBERG: Yes, if I may. In  
9 reviewing the material and in hearing the superb  
10 presentations today by the sponsor, it seems to me  
11 that the analyses that have been presented in detail  
12 make every attempt to cover the issue of potential  
13 bias in making comparisons between one group of  
14 patients who have the essentially standard of care  
15 plus the VNS versus another group of patients who had  
16 basically equivalent standard of care. But patients  
17 that based on the FDA testimony just finished might  
18 not overlap totally in time, patients that might not  
19 be coming from the same centers, and most importantly  
20 patients that were not randomized to the two treatment  
21 arms.

22 At the end of the day, I wonder if you

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1 could respond to a reasonably direct question, whether  
2 the analyses that you have presented today make the  
3 presentation and our job in terms of making a  
4 recommendation to FDA based on a non-randomized  
5 comparison an okay decision. Can you try and help me  
6 to understand why there is not a need to do a new  
7 randomized study to make this comparison based on the  
8 initial findings, which looked extremely promising,  
9 especially after all the analyses that you presented  
10 today. Can you just help at least me, if not the rest  
11 of the panel, in arguing the case?

12 DR. RUDOLPH: Certainly.

13 DR. ELLENBERG: Thank you.

14 DR. RUDOLPH: One of the very first things  
15 we did when we saw the results and understood the  
16 results from the acute study was consider the  
17 possibility of doing another study. Ultimately we  
18 decided that the use of the D04 group as a control  
19 would give -- could potentially give high confidence  
20 in a determination of effectiveness. But we were also  
21 influenced by the fact that every other study design  
22 that we envisioned and discussed, both internally and

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1 with external consultants such as Dr. Rush, had  
2 significant limitations. And Dr. Rush can walk you  
3 through some of our concerns about doing another  
4 study.

5 DR. RUSH: Could I have the slide up,  
6 please? Let me try to take you through the thinking  
7 in the pattern, because the timing is very relevant  
8 here. Obviously it would be wonderful to have a  
9 randomized control trial. We began the entire  
10 evaluation of VNS in depression at a time when there,  
11 in fact, were no short or long-term randomized control  
12 trials in TRD short of acute trials with ECT that a  
13 few investigators had conducted. In fact, the natural  
14 course of TRD had not been mapped out by anyone, under  
15 routine treatment conditions for a 12-month period.  
16 And of course there was no long-term safety. In fact,  
17 in the initial study there as no short-term safety of  
18 Vagus nerve stimulation in depressed patients at all.

19 So the plan, which you saw as the D02  
20 trial, was to conduct based on the epilepsy model.  
21 Part of the reason for the 10 weeks was the epilepsy  
22 model. It was an acute trial, 10 weeks long,

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1 following two weeks recovery after implantation, and  
2 it would compare sham versus VNS with very tight  
3 controls. So no medication changes within that three-  
4 month period. If you found a positive difference  
5 between the two groups, you could uniquely and  
6 absolutely attribute cause to VNS, and that would be  
7 the best evidence for efficacy. Even if it were  
8 modest in the short run, you could say it was the VNS.

9 And then the plan actually agreed to with  
10 the FDA was that there would be a long-term  
11 uncontrolled follow-up of a significant number of  
12 people who had had VNS to see whether or not there was  
13 a sustained benefit which would be extremely unusual  
14 in treatment-resistant depressed patients, as I showed  
15 you from the data this morning. So that was the plan.

16 And the reason for it was simple, it's direct, has  
17 minimal patient exposure, long-term safety could be  
18 established. It's the most efficient path to  
19 approval, and it just made a lot of sense. And we had  
20 already done the D01 open trial to indicate that in  
21 fact there was a reasonable chance of a reasonably  
22 good benefit in the 10-week time period.

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1           So as you know, the results, the primary  
2 outcome failed the positive finding on the secondary  
3 outcome. Then the question obviously is raised, gee,  
4 was the sample size too small? Well, I guess if it  
5 had been made larger we might have achieved a  
6 difference in the primary outcome. And what about a  
7 longer duration, a subject you already raised.

8           So as Dr. Rudolph said, at the end of that  
9 trial period, we couldn't then go back. The trial had  
10 already shut down. So, next slide. We then  
11 considered a variety of next-step options. One is to  
12 just simply conduct a longer term acute trial. Let's  
13 go out nine to twelve months. You have now maximized  
14 the duration, and if you don't change the medications,  
15 you can attribute with absolute certainty cause to  
16 VNS. It's a terrific design except it's not feasible,  
17 it's not ethical, and it's not safe. And you couldn't  
18 have any patients sign up for it. Because these are  
19 treatment-resistant depressed patients. The number of  
20 medication changes that occur over even a six-month  
21 period just to keep the patients intact, safe, and  
22 alive, is significant. So we would have lost all the

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1 patients probably by even four to five months, or at  
2 least a large proportion. So that then, the long term  
3 here mitigates -- prevents us, really, from  
4 attributing absolute 100 percent certainty cause to  
5 VNS, because medicines will change. And I'll come  
6 back to that in a second.

7 One of the difficulties is if VNS works in  
8 one group, and the other group does not receive real  
9 VNS, there's a differential management with  
10 medications. One group will have medicines changed at  
11 a different rate or time or so on. We'll come back to  
12 that.

13 Another possibility that we thought of is  
14 simply go after electroconvulsive therapy versus VNS  
15 acute, in an acute trial modality perhaps. A couple,  
16 two, three, four weeks -- I'm sorry, four weeks to,  
17 say, eight to twelve weeks. The problem is ECT is a  
18 terrific acute treatment, but can't be given over the  
19 long run in most patients. And VNS is not an acute  
20 treatment and has to be given over a long run. So it  
21 just wouldn't make any sense. And secondly, even as I  
22 showed you and Dr. Rudolph showed you, the patients

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1 entering the VNS trial, 40 to 50 percent had already  
2 had ECT and had failed. Thirty-some percent, 38  
3 percent in the current episode. So we'd have to  
4 change the patient population.

5 Another possibility we discussed at  
6 length, and really brought this around, was the idea  
7 of taking the patients who had received VNS who had  
8 benefited from the D01 trial or the D02 trial and  
9 simply randomizing them to a discontinuation. Just  
10 turn off the device. Two difficulties with that. One  
11 is, of course, there's risking of un-blinding. But  
12 more important than that, we would probably need an  
13 even larger sample pool than could be generated. The  
14 problem is we went to patients. We asked them, we  
15 surveyed the patients directly. I spoke to a number  
16 of patients, other investigators did. To a person,  
17 and you heard it also from a patient today, the  
18 patient said with this emotion you are not going to  
19 turn this device off. I do not want this device to  
20 turn off. So we would have to go after people with  
21 really minimal benefit who might have been more  
22 willing to have the device turned off, but that's not

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1 the population that would be appropriate for  
2 discontinuation trial. Next slide, please.

3 DR. ELLENBERG: If you don't mind, can I  
4 interrupt?

5 DR. RUSH: Sure. Yes, sir. Please go  
6 back.

7 DR. ELLENBERG: In the first bullet.

8 DR. RUSH: Yes.

9 DR. ELLENBERG: If I remember correctly,  
10 there were a significant number of meds changes in  
11 D02.

12 DR. RUSH: That's correct.

13 DR. ELLENBERG: So --

14 DR. RUSH: And a significant number in  
15 D04, which I think --

16 DR. ELLENBERG: Understood.

17 DR. RUSH: Take D04 as evidence that you  
18 couldn't do this with medications not changing.

19 DR. ELLENBERG: Well, that's what I want  
20 to follow up on.

21 DR. RUSH: Okay.

22 DR. ELLENBERG: So, the protocol as I

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1 recall, once the acute phase was finished allowed but  
2 discouraged medication changes in D02. And with that  
3 allowance you got, I think it was 60 percent  
4 medication changes. So in real life, that probably is  
5 going to be the way VNS will be given, with the  
6 allowance for medication changes.

7 So why then -- I understand your point  
8 based on the assumption that the cleanest way to do  
9 this is with no medication changes. But why couldn't  
10 a randomized trial be done where medication changes  
11 were discouraged but allowed, since effectively for  
12 the long-term results in D02 that's what happened? So  
13 why couldn't that trial be redone with the medication  
14 change discouraged but allowed?

15 DR. RUSH: Oh, I think at this moment it  
16 could. I think that the data that we now have in  
17 terms of long-term safety, which we didn't have at the  
18 end of the D02 acute. We still didn't have long-term  
19 safety data. We had a good feeling from epilepsy, and  
20 some modest sample size from the D01, but we really  
21 didn't know and couldn't tell the patients what the  
22 longer term safety risks were. So we, for example,

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1 have noticed the induction of mania, or hypomania.

2 DR. RUDOLPH: I think Dr. Ellenberg,  
3 you've essentially described the D02/D04 paradigm,  
4 except as a randomized study.

5 DR. RUSH: Exactly.

6 DR. RUDOLPH: I think that's what you're  
7 suggesting.

8 DR. RUSH: Let me just go through two  
9 more, because actually the last one deals just with  
10 what you're asking.

11 We thought of another possibility, which  
12 is we would prescribe -- we would control the  
13 medications in a reasonable standard of care. So we'd  
14 have less deviation across doctors. So we wouldn't  
15 have too much exotic, potentially dangerous  
16 pharmacotherapy. And both -- then one group would get  
17 algorithm only, and the other group would get  
18 algorithm plus VNS. That's terrific, except when you  
19 look at the level of resistance in these patients.  
20 Nobody knows how to write an algorithm for any of  
21 them, because they're at level 6 and the algorithms --  
22 that is that half are beyond ECT. So we have no

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1 evidence with which to write the algorithms.

2           And secondly, because of the huge number  
3 of treatments that have been tried. I mean, some of  
4 these patients -- remember, if it's two to three ATHF  
5 treatments, it's exposures to 12 different treatments,  
6 not counting combinations that were used. And then  
7 when you go to four to five, and remember the average  
8 here is four, you're looking at 16 clinical  
9 treatments, not counting all the potential  
10 combinations that you layer on one drug after the  
11 other after the other.

12           So in order to do that experiment, which  
13 would be very interesting, the only suitable  
14 population is one that's much less resistant, one  
15 that's maybe had one or two steps. Then we could take  
16 three more steps in an algorithm developed by  
17 consensus. That could be done. That's not the  
18 population that's going to be the primary target for  
19 this treatment. And so the relevance of the research  
20 is limited due to generalizability issues.

21           And then the last point is the point that  
22 you were just raising in the question. Could we do

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1 such a trial, that is randomize what we've done now?  
2 Yes. Now that we know long-term safety, I think it's  
3 possible to do such a trial. You will still have  
4 interaction with medication changes that are likely to  
5 differ between the two groups, if there's an effect of  
6 VNS, of course. And the other risk which is always  
7 true with this level of depression is both groups will  
8 still be exposed to exotic, unstudied combinations.  
9 And finally, at the time that this was done -- we  
10 could do it now -- we had no idea of effect sizes. We  
11 wouldn't know how large to make the sample to figure  
12 out whether we have a difference.

13 So, last slide please.

14 DR. RUDOLPH: Can I -- before you go on  
15 just comment on that?

16 DR. RUSH: Yes.

17 DR. RUDOLPH: So while that's feasible,  
18 our assessment was there wasn't much gain to do that  
19 over the strategy we followed. Because you would  
20 still be faced with trying to establish the  
21 comparability of medications, as you still had that  
22 major issue. Yes, the randomization would give you a

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1 greater level of certainty with regard to baseline  
2 covariates. You'd still have, even in a randomized  
3 control -- we've heard a lot of talk about unmeasured  
4 covariates. Even in randomized control, that's still  
5 potential problem. So you're still left with that.

6 And frankly, with VNS therapy, you always  
7 have an issue of blinding. Blinding is never perfect  
8 with VNS because a good number of patients do perceive  
9 when they're getting stimulation. So yes, maybe  
10 there's a slight gain to that particular paradigm, but  
11 it's only a slight gain I would say.

12 DR. RUSH: Let me just -- I know we're  
13 getting near lunch period, so let me just finish if I  
14 could, this slide and the very last one. So, this is  
15 in brief of course what we have. And put the next one  
16 up for me to see. No, no, the other one. Back,  
17 please. Okay.

18 So what we have done is exactly everything  
19 short of the randomization, comparing -- trying to  
20 find out what is the long-term outcome of TRD at this  
21 level given standard care. Remember when we started  
22 this was never defined. This was not known. So we

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1 had no idea whether these patients are getting better,  
2 getting worse. Obviously D04 shows really not much  
3 benefit. So that's the first study that's available  
4 to comment on this. That's D04, not yet published.

5 D02, then as you know, simply was extended  
6 with doctor's choice. Again, the first study of long-  
7 term adjunctive VNS establishes safety. So now, we  
8 now have the effect size and safety and expected  
9 outcome. So clearly at this moment we could do such a  
10 randomization, but up until this point we could not do  
11 that.

12 And as you know, the results, we've  
13 reviewed them, so I'm not going to detail that other  
14 than to indicate that most of the responders at three  
15 months were still there at a year, and some of the  
16 non-responders at baseline -- I'm sorry, at three  
17 months, actually responded by a year.

18 The one comment is this design actually  
19 provides a better control of longer term VNS than was  
20 originally agreed to with the FDA. Because it has a  
21 comparison. Not randomized, but a comparable group,  
22 if you will, by which to gauge the most salient

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1 portion of this treatment, which is the longer term  
2 outcome. And then if I have just the final slide.

3 So you are asking, in a sense, how do we  
4 deal with a non-randomized evidence base, and is it  
5 really safe and okay to support this treatment. So,  
6 this is sort of the way I put things together. The  
7 question is is VNS the cause of better outcomes in 02  
8 versus 04. How certain are we. And Dr. Rudolph went  
9 through a number of explanations, and illuminated a  
10 placebo not likely in TRD, not a sustained effect,  
11 typically occurs early. Medication changes, yes there  
12 were more in 04 than 02. That would be consistent  
13 with more efficacy in 02 due to other causes. The EC  
14 differences were equivalent in terms of percentage use  
15 and unrelated largely to outcome.

16 Sample differences, we went through that  
17 at baseline. Unmeasured sample differences. Here we  
18 could look at anxiety. Anxiety subscales. We  
19 anticipate, based on the Hamilton, the anxiety  
20 subscale highly correlates with the total on the  
21 Hamilton, the two totals are the same and we'll  
22 probably have that number for you this afternoon.

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1           The other issue is access to personality  
2 disorders. Personality disorders are very common in  
3 TRD. And in fact, many patients with TRD, once the  
4 TRD is fixed, actually have a resolution of these  
5 personality disorders. The incidence is on the order  
6 of 75 to 85 percent. And in fact, they have not been  
7 found to affect outcomes except for borderline  
8 personality disorder in Dr. Sackheim's ECT trial, and  
9 Tracy Shea back in 1990 reported the NIMH  
10 collaborative psychotherapy trial. Personality  
11 disorders did not affect symptomatic outcome. It did  
12 affect social functioning, but that was it.

13           The final thing is maybe there are  
14 differences that we don't know that we didn't measure.

15       So I call them unknown sample differences. Now if  
16 they're present, they would have to explain the 12-  
17 month outcomes -- that's possible -- the fact that  
18 they're sustained largely -- that's very unusual in  
19 this group -- and the fact that we have an increasing  
20 number of beneficiaries in the VNS group over time.  
21 Whatever that thing is, we would have to create it out  
22 of whole cloth. So I feel, personally and

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1 scientifically, very persuaded by this level of data,  
2 which I must say is a bit short of the one-year,  
3 randomized control trial that we can now do based on  
4 all the evidence that we have. And the question  
5 becomes how necessary is it to establish with that  
6 level of certainty for this population in the context  
7 of this device for epilepsy already widely used.

8 DR. ELLENBERG: I think the last bullet is  
9 the key bullet on this. On that slide. I have a  
10 naïve question and then I'll stand down. In terms of  
11 the masking of the IDS-SR or the HAM-D, looking on the  
12 Web, it seems that while that is a self-report, both  
13 of them are self-reports by the patient, there is  
14 someone that's working with them to complete the  
15 questionnaire. Someone asking the questions. Is that  
16 not correct?

17 DR. RUSH: No, sir. If you're asking  
18 about the IDS-SR?

19 DR. ELLENBERG: Yes.

20 DR. RUSH: No. Typically that's given to  
21 the patient and they're asked to fill it out in the  
22 waiting room.

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1 DR. ELLENBERG: So they're doing that all  
2 alone. Alright, then that's the primary outcome.

3 DR. RUSH: Some of these patients are very  
4 depressed. And so we may have to explain some of the  
5 words. But that happens at just pretty much the  
6 baseline. Most of the patients are able to fill this  
7 out throughout on their own. They may ask a query,  
8 but generally IDS-SR is totally a self-report. This  
9 population needed a little bit of help.

10 The Hamilton is -- the interviewer you  
11 saw, Dr. Husain, doing that on one of the tapes. You  
12 know, that's a clinician interview.

13 DR. ELLENBERG: They were prompting, and  
14 helping them.

15 DR. RUSH: Exactly. And that was  
16 independently rated.

17 DR. ELLENBERG: Then going to just the  
18 IDS, the subjects, both the delayed onset and the  
19 immediate onset subjects in D02 were being measured by  
20 the IDS with let's assume it's full self-report.  
21 Those patients all knew that they were turned on.

22 DR. RUSH: Well, you're asking the degree

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1 of blindness with regard to the subjects.

2 DR. ELLENBERG: Correct.

3 DR. RUSH: And we purposely did not ask  
4 the patients whether they thought they were receiving  
5 active treatment or not.

6 DR. ELLENBERG: In the long-term, after  
7 the three-month period?

8 DR. RUSH: Well, you heard --

9 DR. ELLENBERG: Did the patients know that  
10 they were going on?

11 DR. RUSH: Not necessarily. Not  
12 necessarily.

13 DR. RUDOLPH: After three months.

14 DR. RUSH: Not after the acute they  
15 didn't. They knew there was three months and three  
16 months, no? I'm sorry. Let me --

17 DR. ELLENBERG: My impression was --

18 DR. RUDOLPH: After three months  
19 considered the study to be un-blinded.

20 DR. ELLENBERG: Yes. Okay. So the  
21 outcomes we're looking at, in addition to the repeated  
22 measures, which included the three-month period, but

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1 most of the data was coming from a point in time where  
2 all patients knew that they were on treatment in the  
3 D02. In the D04, all of the patients knew that they  
4 were not on VNS.

5 DR. RUSH: Yes. Correct.

6 DR. ELLENBERG: Could you assess for us  
7 what impact that might have had in terms of one group  
8 knowing that they weren't on treatment and the other  
9 group knowing that they were?

10 DR. RUSH: It is true the D04 patients  
11 knew they were not getting VNS, and the majority  
12 actually weren't offered VNS. So some, as pointed out  
13 by the report, were eligible for both and might have  
14 had a discussion with both. Most of them when there  
15 was a choice were offering D02. So the knowledge that  
16 they didn't get VNS may not even be in the heads of  
17 people getting D04, but they know that was just  
18 routine care.

19 They are having their medications changed.

20 They're under still expert care. And so the  
21 medication changes, they would have an anticipation, I  
22 would think, as any patient would, of making a change

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1 that might work out for the better, but they're often  
2 very discouraged because many other medication changes  
3 have not worked. If the fact that the patients  
4 receiving VNS, they say this is terrific, I can feel  
5 it, I know, I'm un-blinded, hooray, I'm in the right  
6 ballpark because I have nothing else left, you would  
7 have to say that that is a -- if that's the placebo  
8 response rather than the VNS, right, because I'm aware  
9 of it. It would have to last for another nine months  
10 and it would have to be characterized by a sustained  
11 benefit. Okay? We don't know of any placebo that  
12 does that.

13 DR. ELLENBERG: I'm not sure I understand  
14 why it's a placebo effect. If the group for nine  
15 months of the year in which they're followed knew that  
16 they were on the VNS.

17 DR. RUSH: Right. You're asking couldn't  
18 that have been cause for the difference between the  
19 groups.

20 DR. ELLENBERG: Have caused their response  
21 -- yes.

22 DR. RUSH: Right. And I'm saying it would

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1 either be the active VNS itself, or you'd have to say  
2 it's non-specific effects. And I'm saying I don't  
3 think it's non-specific because of the magnitude and  
4 the growth over time. So I'd have to attribute it to  
5 the active VNS itself.

6 DR. RUDOLPH: Additionally, you have  
7 clinician ratings being done at the same time, and the  
8 clinician ratings were videotaped and sent out to a  
9 third party blinded rater which established the  
10 legitimacy, if you will, of the clinician ratings.

11 DR. ELLENBERG: That was done both with  
12 the 04?

13 DR. RUDOLPH: That was done for D02.

14 DR. ELLENBERG: D02.

15 DR. RUSH: Just one other comment on the  
16 IDS and I'll get out of here. That would avoid more  
17 questions. The IDS is a self-report. And while it is  
18 highly related and has been published in a number of  
19 articles, the psychometric properties, it's highly  
20 related to the Hamilton and to the clinician-rated  
21 IDS. It was accepted as an outcome measure off-the-  
22 shelf, ready-made, at least the IDSC was, the

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1 clinician rating at an NIMH conference held a couple  
2 of years ago, with the IDS-SR. If a self-report were  
3 acceptable to the FDA, that would be an acceptable  
4 metric.

5 One comment, though, that we know,  
6 especially in chronic, longstanding depression, self-  
7 report tends to be a little more sluggish to change  
8 than clinician ratings. And you heard from the  
9 patients, a couple this morning. My family members  
10 saw me change before I knew I was getting better.  
11 That is very common, especially when you're looking at  
12 multifunction impairment over a long time. We know  
13 we're better when we can do things we love to do. And  
14 we can't do those right away. The symptom changes by  
15 the clinician rating will happen a little quicker. So  
16 let me get out of here.

17 DR. SACKHEIM: Hi, I'm Harold Sackheim, a  
18 professor of psychiatry and radiology at Columbia.  
19 Just two comments. I believe that part of what you  
20 may be getting at, Dr. Ellenberg, is the idea that  
21 patient expectancies can have an impact on outcomes.  
22 In this population, I know of only -- or a population

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1 that's relatively similar -- only one attempt to look  
2 at the relationships between expectancies and outcome.

3 And that's what we've done over the years in terms of  
4 asking ECT patients whether they expect to get better,  
5 whether they expect to have cognitive effects, and so  
6 on. In that population, there is no association  
7 between patients' beliefs about whether the treatment  
8 is going to work for them or not and the final scores.

9 And I think that would be pretty much  
10 comparable here given the history of these patients in  
11 terms of repeated failures with other treatments. In  
12 fact, the correlations tend to be negative. Those  
13 patients who are most pessimistic tend to do better  
14 with the treatment. So that's one point.

15 Then the second point regarding the  
16 validity or the bias that could've entered into the  
17 ratings by the raters at the individual sites. It was  
18 at Columbia that we did the blinded ratings of these  
19 tapes. And it was time blind as well. So the people  
20 that were rating the tapes didn't know when in the  
21 course of treatment -- could I have the slide please -  
22 - they were rating. And these are the ICCs for the

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1 ratings by site. And as you can see, the ICCs are not  
2 bad at all, particularly since there's variability in  
3 the ends at each site.

4 Overall in this study, the reliability of  
5 the Hamilton ratings -- we're talking about an  
6 assessment of 400 different interviews -- was on the  
7 order of 0.93 was the overall ICC. Can I have the  
8 next slide, please?

9 To give you a sense of how the tight the  
10 ratings are, but even more importantly, the absence of  
11 a bias in the ratings. You see that the intercept for  
12 this regression is essentially zero. That the blinded  
13 rater did not see these patients as either more or  
14 less well on average than did the ratings at the site.

15 And that there's a very tight association. These are  
16 the individual points for each of the interviews that  
17 were rated.

18 DR. ELLENBERG: So this is the clinical  
19 taped evaluation?

20 DR. SACKHEIM: On the Y axis.

21 DR. ELLENBERG: Versus the HAM-D or the  
22 IDS?

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1 DR. SACKHEIM: No, this is the HAM-D where  
2 it's a blinded rater at Columbia rating it versus the  
3 original rating at the site. And these are each of  
4 the individual ratings, where the rater was time  
5 blind, not knowing when in the course of treatment,  
6 whether this was baseline, or after a year, or what  
7 have you.

8 And then just to echo the remarks of Dr.  
9 Rush. What at least to me is very unusual, having  
10 spent many, many years working with treatment-  
11 resistant patients, is the fact that not only is there  
12 a group of patients who showed benefit late, but the  
13 people who benefited on average by my estimate, we're  
14 talking about 70 percent of them, holding it for at  
15 least a year or two years. Now, when we contrast that  
16 with the relapse rates that we see with other  
17 treatments, particularly in treatment-resistant  
18 patients. And so can I have this slide, please.

19 These are the percent of patients in an  
20 analysis that we've completed of D01 and D02 who were  
21 responders at three months, who would continue to be  
22 classified as responders at one year. And you can see

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1 that it's 72 percent in D01 and 63 percent in D02. If  
2 we look at the --

3 DR. RUDOLPH: And let me just interrupt.  
4 The reason why these percentages are a little  
5 different than I showed this morning is because it's a  
6 different set of criteria.

7 DR. SACKHEIM: This is, in fact, a more  
8 conservative set of criteria. We're not allowing in  
9 the 25 to 49 percent, but looking at people who were  
10 50 percent and above at three months. And we allowed  
11 them wiggle room down to 40 percent. So how many of  
12 those who were at least 50 percent and above had at  
13 least 40 percent improvement at one year. And you can  
14 see those figures there. And obviously we do have the  
15 data now on the longer term. And it's very, very  
16 promising.

17 CHAIRPERSON BECKER: I think with that  
18 we'll hold any further questions or comments till  
19 after lunch. So if everybody could return in an hour,  
20 let's say at 1:45, we'll pick up with the  
21 deliberations.

22 (Whereupon, the foregoing matter went off

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1 the record at 12:48 p.m. and went back on the record  
2 at 1:48 p.m.)

3 CHAIRPERSON BECKER: It's now 1:50 and I'd  
4 like to call the meeting back to order.

5 And I'd like to remind the public again  
6 that while the meeting is open for public observation,  
7 public attendees may not participate except at the  
8 specific request of the panel.

9 We'll now begin the panel deliberations.  
10 Two voting members of this panel will open this part  
11 of the meeting with their remarks.

12 Dr. Philip Wang will give his remarks.  
13 Dr. Wang will give his remarks on the clinical  
14 information.

15 And Dr. Ellenberg was going to address the  
16 statistical analysis but I understand he's in  
17 agreement with the FDA analysis and will not be making  
18 any specific comments.

19 After this, the panel will have a general  
20 discussion at which the panel will focus their  
21 deliberations on the FDA questions.

22 There will then be a second public opening

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1 hearing and FDA and sponsor summations.

2 Then the panel will conclude the  
3 deliberations and vote on the recommendation  
4 concerning this PMA.

5 I want to remind the panel that they can  
6 ask the sponsor or the FDA questions at any time.

7 So at this point, I'd like to ask Dr. Wang  
8 to take the microphone and open this part of the  
9 panel's deliberations.

10 MEMBER WANG: That's perfect, thanks.  
11 Great. I'm going to be brief because everything I  
12 have to say you've already heard.

13 Again, just to recap, this is a pre-  
14 marketing supplement application for a new indication  
15 for VNS.

16 It was approved in '97, again for -- as an  
17 adjunctive therapy to reduce the frequency of seizures  
18 in patients who are refractory to anti-epileptics.

19 Now it's being considered for approval for  
20 a new indication as an adjunct long-term treatment for  
21 chronic or recurrent major depression that hasn't  
22 adequately responded to two or more treatments.

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1           Again, it's similar to the previously  
2 approved device. It has an implantable pulse  
3 generator, a lead to the left vagus, an external  
4 programming wand, programming software and a  
5 compatible computer to run the software.

6           The VNS clinical studies include these two  
7 which are perhaps the most relevant to our discussions  
8 today.

9           There's the D-02 Pivotal Study which had  
10 two phases, a 12-week acute phase in which 235  
11 patients with chronic or recurrent treatment-resistant  
12 major depressive episodes were implanted and then  
13 randomized to either receive the stimulation or sham-  
14 control treatment.

15           This was then followed for both arms by a  
16 12-month long-term phase in which all patients were  
17 then given VNS.

18           Also of relevance, perhaps most relevant  
19 to our discussion today is this D-04 Observational  
20 Study in which 138 patients with chronic or recurrent  
21 treatment-resistant major depressive episodes were  
22 given usual care and then followed for a year.

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1 Other studies we've heard about, the D-01  
2 Pilot Study that originally got things going, a D-03  
3 European Post-Marketing Study, D-05 Videotape Study in  
4 which there was an examination of the inter-rater  
5 reliability of depression assessments in the D-02  
6 study, and the D-06 Pilot Study of not necessarily  
7 depressive episodes but rapid-cycling bipolar  
8 disorder.

9 In terms of the D-02 acute phase results,  
10 this now is again the first 10-week portion of the D-  
11 02 study. The difference on the primary end point, as  
12 defined by a 50 percent reduction in HAM-D scores,  
13 again was -- there was a tendency but that wasn't  
14 statistically significant to favor VNS.

15 The sponsor has brought up that their full  
16 VNS effect may take longer than the ten weeks in the  
17 acute phase portion of the trial, especially  
18 considering that the first two weeks of that ten-week  
19 period was for adjustment of the VNS device.

20 So this was the rationale for the D-02/D-  
21 04 12-month comparison, which we heard about, in which  
22 outcomes during the long-term phase, in which everyone

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1 in D-02 was receiving VNS was compared to the 12-month  
2 outcomes in the D-04 study.

3 On this primary endpoint analysis, which  
4 again it was the change in monthly IDS-SR scores from  
5 a repeated measures linear regression model, on this  
6 primary endpoint it was statistically significant in  
7 favor of the VNS therapy.

8 There were also secondary endpoints in  
9 this D-02/D-04 comparison and there was also  
10 statistically significant differences in favor of  
11 VNS. This included an analysis of responders, as  
12 defined by 50 percent reduction in IDS scores,  
13 complete remission as defined by having less than a 14  
14 on the IDS. That's actually not greater, it should be  
15 less than.

16 Also in terms of an analysis of responders  
17 as measured through 50 percent reduction in HAM-D  
18 scores and also an analysis of complete remission as  
19 defined by -- that's less than nine on the HAM-D.

20 Issues, however, were raised in the FDA  
21 review in terms of this D-02/D-04 comparison.  
22 Principal among these are the patient and disease

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1 characteristics may have differed between subjects who  
2 were in the D-02 and the D-04 study due to the fact  
3 that it was not a randomized trial.

4 There was a propensity score adjustment  
5 analysis that was done in terms of the primary  
6 endpoint analysis to reduce potential bias. However,  
7 as was brought up in the FDA review, there's still  
8 confounding possible in this primary endpoint analysis  
9 due to the possibility of unmeasured variables. And I  
10 added there also poorly measured variables.

11 Also brought up was the fact that the  
12 simple comparisons are proportions as was done in the  
13 secondary analyses. Secondary endpoint analyses were  
14 completely unadjusted. There were no potential  
15 confounders controlled for.

16 The other issues brought up by the FDA  
17 include placebo effects, which may have been greater  
18 in D-02 than in D-04 due to the higher expectations.  
19 D-02 was known to be an intervention study while D-04  
20 was billed and known to be only a control  
21 observational study.

22 There were also allowed changes in

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1 concomitant therapies including antidepressant drugs  
2 and ECT, which may have potentially altered the  
3 apparent efficacy of VNS.

4 And there was an analysis presented in  
5 which patients were censored if they added or  
6 increased treatments. And this reduced the observed  
7 effects of VNS not only in terms of the statistical  
8 significance but as you can see also, in terms of the  
9 observed effect size.

10 In terms of safety issues of VNS, there  
11 are issues that make it difficult to assess the safety  
12 of VNS for depression. The primary reason for this is  
13 that the safety data were not systematically collected  
14 in D-04. So there's no comparison group for the D-02  
15 long-term phase data.

16 Another difficult when just looking at the  
17 acute phase data of D-02 is that as was brought up,  
18 the treated end-sham groups both received a lead that  
19 was attached -- they received the implantation and a  
20 lead was attached to their vagus nerve so the adverse  
21 event rates do reflect that.

22 Just looking at the incidence of adverse

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1 events in D-02 is also difficult to interpret due to  
2 the fact that there are non-negligible background  
3 rates of many of the adverse events examined. And I  
4 just put down there reproduced the cardiovascular  
5 events as were seen in the D-02 study by phase.

6 There were three deaths in D-02. One was  
7 a sudden death and considered to be possibly related.

8 It was the only one of the three that was considered  
9 to be possibly related to VNS but unfortunately no  
10 autopsy was done so it's hard to conclude much about  
11 that.

12 As was raised, the safety data from  
13 epilepsy studies may be informative here. What I've  
14 reproduced here is just the treatment emergent adverse  
15 events in a trial that was done of VNS in epilepsy  
16 patients, E-05. And what's shown here is the adverse  
17 events that occurred in greater than ten percent of  
18 subjects and were statistically significantly  
19 different between the baseline and the treatment  
20 phases of the study.

21 I think what's potentially reassuring here  
22 is that 99 percent of the side effects were rated as

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1 mild or moderate.

2 In terms of the long-term safety of VNS,  
3 there is some data. And that, again, comes from this  
4 E-05 trial of VNS in epilepsy patients in which after  
5 five years, 31 of 51 patients were still -- still had  
6 their VNS therapy system implanted and were presumably  
7 receiving stimulation.

8 And as you can see here, these are --  
9 here's the profile of adverse events that were found.

10 And, again, providing some reassurance is the fact  
11 that this profile of long-term side effects is  
12 generally similar to the adverse events that were  
13 reported during the E-05 trial.

14 I raise here, just sort of in closing, a  
15 few things. One relates -- there are some issues  
16 related to training that are worth considering. One  
17 is who should implant this device? Two is who should  
18 be programming this device? Should it be  
19 psychiatrists? Neurologists? Any physician?

20 Should there be mandatory training courses  
21 for these -- whoever is going to be doing the  
22 implanting and programming? And also what kind of

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1 guidance can be given on titrating the output current?

2 And based on what data?

3 And finally there would be some  
4 implications of an approved device, which I've put up  
5 here. As was mentioned, there are currently very few  
6 options for treatment-resistant depression. Some  
7 options currently used in typical practice have very  
8 little evidence to support their efficacy or safety.

9 But on the other hand, would there  
10 potentially be unrealistic expectations. I remind  
11 everyone that in absolute terms, the apparent effect  
12 sizes seen for VNS were relatively small. Would there  
13 also be pressure to forego effective but stigmatized  
14 modalities such as ECT? So these are all some issues  
15 to ponder.

16 CHAIRPERSON BECKER: Thank you, Dr. Wang.

17 Does anybody have any questions for Dr. Wang?

18 (No response.)

19 CHAIRPERSON BECKER: I guess if not then  
20 we'll move on to the general discussion portion of the  
21 panel's deliberations. At this time, the panel may  
22 ask the sponsor or the FDA any questions that they

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1 might have.

2           And I think in order to kind of start with  
3 a fairness to everybody in the panel, we'll just go  
4 around the panel and solicit questions and comments.  
5 And we'll start with Dr. Ellenberg at the end.

6           MEMBER ELLENBERG:     I don't have any  
7 additional questions. Thank you.

8           MEMBER JAYAM-TROUTH: Hi. I had a couple  
9 of questions. One is I'm looking at the D-01 study  
10 and, you know, there were 25 out of 55 responders at  
11 one year and 18 of 42 responders at two years. My  
12 question is were the stimulation parameters  
13 equivalent, you know, to the D-02 study?

14           And was it a drop out of these patients,  
15 55 patients to 42 patients? You know, why did the  
16 patients drop out if VNS was that effective?

17           MR. TARVER:     I'm Brent Tarver. I'm a  
18 Senior Director in Clinical and Regulatory -- in  
19 Medical Affairs at Cyberonics.

20           About the stimulation settings, the  
21 settings were similar in D-01 and D-02. Out over the  
22 long term, the D-01 settings tended to be maybe a

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1 quarter of a milliamp higher but which would be very  
2 similar.

3 And the second part of the question?

4 MEMBER JAYAM-TROUTH: Why was there such a  
5 drop out from 55 to 42 in the responders? In, I mean,  
6 the groups, 25 to 55, they were responders. And then  
7 by two years, there were only 42 people still having  
8 VNS.

9 MR. TARVER: Right.

10 MEMBER JAYAM-TROUTH: You know, who  
11 dropped out?

12 MR. TARVER: Okay. The drop is in -- what  
13 you're looking at is the rating scores. There were a  
14 number of patients, about ten, that did not have the  
15 rating at two years but were still receiving  
16 stimulation in the study. So they're only included in  
17 the last observation carried forward analysis.

18 MEMBER JAYAM-TROUTH: So it wasn't a real  
19 actual drop?

20 MR. TARVER: Well, to some extent it was,  
21 and Dr. Rush, who was -- there were only four  
22 investigators in D-01. Dr. Rush can comment at least

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1 on the experience at his site.

2 DR. RUSH: Actually, I can do it for the  
3 whole study. I'm sorry, I should have brought the  
4 paper that had to be submitted.

5 As I recall, there were, I think, four or  
6 five people that had either had it turned off or were  
7 explanted. And that was because of lack of efficacy,  
8 not due to side effects, starting with the original  
9 59.

10 There were probably, as mentioned, eight  
11 or ten patients we just couldn't get back in that  
12 particular time period. One of the interesting things  
13 is those individuals, the young man I presented this  
14 morning, the graduate student, is out in California.  
15 He doesn't like to deal with doctors any more because  
16 he's undepressed. So some of those individuals are  
17 not coming back because they're well. So that  
18 accounts for the large shift in -- the drop in the  
19 number.

20 But the vast majority, I think it would be  
21 fair to say 90 percent still had the device implanted,  
22 maybe two had it turned off.

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1 MEMBER JAYAM-TROUTH: I see.

2 DR. RUSH: So it's a pretty high retention  
3 at two years.

4 MEMBER JAYAM-TROUTH: You know, along the  
5 same lines, you know, Dr. Rush, along the same lines  
6 my question is if I was a responder, you know, I would  
7 want to keep my, you know, device on --

8 DR. RUSH: Yes.

9 MEMBER JAYAM-TROUTH: -- you know, and  
10 therefore I should see a bias in greater numbers, you  
11 know, out of 42, I should have seen more numbers, you  
12 know, who were still continuing to be responders, not  
13 a drop from 25 to 18, you know?

14 DR. RUSH: Yes, but in fact what actually  
15 happens is it's not biased in that favor because we  
16 can talk to the patients on the phone. So some  
17 individuals, of course, are coming back hoping that we  
18 can readjust the parameters or their doctor just  
19 changed the medication and now with the parameters  
20 changes, maybe help them.

21 So there is a tendency to come back  
22 actually if you're a little more ill than if not.

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1 It's not just one way or the other.

2 MEMBER JAYAM-TROUTH: Is there a greater  
3 drop between the first year and the second year? I  
4 know this is a one-year study. And there was a steady  
5 improvement, you know, with the VNS. But was there a  
6 difference between the first year and the second year?

7 DR. RUDOLPH: Dr. Sackheim was one of the  
8 other four investigators in that first study.

9 DR. SACKHEIM: I think what would help  
10 would be to show you the data on the number of  
11 patients that sustained improvement from three months  
12 to one year and from three months to two years. So  
13 can we have that slide?

14 You'll see this separately for D-01 and  
15 for D-02. I'll just comment on it while we try to  
16 find the slide. This is uncharted territory because  
17 what percent of patients should maintain a response to  
18 say that a treatment has a persistent on-going  
19 benefit? Nobody has ever put a benchmark on that.  
20 Can we show this?

21 And what you see here is the D-01 where we  
22 actually are breaking down the patients into whether

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1 they had a 50 to 60 percent improvement, 60 to 80  
2 percent, or 80 to 100 percent, or simply the total  
3 group in D-01.

4 And in this slide, we are looking at the  
5 percent that are showing sustained benefit over time.

6 And we're doing it -- we should have had the markings  
7 on the bottom. But to the left, we're looking at the  
8 group that were responders at three months, and  
9 maintained it for one year.

10 You'll notice that D-04 is listed there as  
11 well. Of the patients who had a -- who were  
12 responders at three months in D-04, none were  
13 responders at one year. That was a small number of  
14 patients.

15 There was only seven patients that --  
16 because D-04 actually obviously had poorer results.  
17 But none maintained it while we have a 70 percent rate  
18 of maintaining it in D-01 basically. And we're around  
19 63 percent in D-02.

20 Now the next set of bars presents --

21 DR. WITTEN: Excuse me, can I just ask --  
22 is this information that's in our file?

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1 DR. RUDOLPH: Yes, I was going to say at  
2 the end of the comments for disclosure, it's not in  
3 your file. These are not even the sponsor --

4 DR. WITTEN: Okay, and we haven't --

5 DR. RUDOLPH: -- these are not even the  
6 sponsors' analyses.

7 DR. WITTEN: -- received these yet, okay.

8 DR. RUDOLPH: These are analyses that were  
9 done by Dr. Sackheim.

10 DR. SACKHEIM: The next set of analyses  
11 looks at patients who were responders at three months,  
12 had at least a 50 percent reduction in their Hamilton  
13 scores in this case, and then we're looking out at two  
14 years. Were they still responders?

15 And here, again, we're defining response  
16 as at least a 40 percent improvement so that we  
17 wouldn't punish the people who went from let's say 52  
18 percent to 48 percent.

19 And again what you see is that we're,  
20 certainly with D-01 and D-02, in D-02 where over 70  
21 percent of the people who were responders at three  
22 months held it at two years. And this to me was quite

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1 remarkable, unexpected really.

2 Then finally we have data on a very  
3 interesting group of people, the people who were not  
4 responders at three months but who at one year became  
5 responders, the late emerge. And those I would have  
6 thought would have been a very difficult group because  
7 they didn't benefit initially but benefitted later on.

8 Did they hold it? And so we then go from  
9 the end of the first year to the end of the second  
10 year. And what you can see is we're certainly above  
11 50 percent for both the D-01 and the D-02 there as  
12 well.

13 So these, I thought, were very compelling  
14 data that the most treatment-resistant group of  
15 patients I think anyone has really ever studied, where  
16 we expect them if they benefit at all to lose it very  
17 rapidly, we're not seeing that rapid loss. Actually  
18 over a two-year period of time, we're seeing it  
19 sustained.

20 DR. RUDOLPH: So again, just to make it  
21 clear, these are Dr. Sackheim's own analyses of our  
22 data set. The sponsor hasn't seen them and they

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1 certainly have not been submitted to the Agency.

2 MEMBER JAYAM-TROUTH: Can I ask one more  
3 question?

4 CHAIRPERSON BECKER: Sure.

5 MEMBER JAYAM-TROUTH: The -- I understand  
6 that you kind of stimulated the -- in the D-02 group,  
7 not the sham, but the ones who had the stimulation on  
8 over a two-week period. Now did these patients come  
9 in every single day and you kept increasing their  
10 milliamps? The parameters?

11 You know, how did you do that? I mean was  
12 it rapid stimulation that you did? And then you held  
13 it at one spot? Or you continued to change the  
14 parameters during the acute phase and during the long-  
15 term phase?

16 DR. RUDOLPH: During the acute phase for  
17 those patients who were assigned or randomized to the  
18 active treatment group, their adjustments were all  
19 done in the first two weeks after the device was  
20 turned on.

21 MEMBER JAYAM-TROUTH: Every single day  
22 they would come and you would increase it?

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1 DR. RUDOLPH: The protocol gave wide  
2 latitude to the investigators. I think -- and some of  
3 the investigators can correct me if I'm wrong. I  
4 think, in general, however, the patients were only  
5 seen at weekly intervals because that is what one is  
6 used to doing when they're conducting a clinical  
7 trial.

8 So although they had latitude to see the  
9 patients more frequently, I don't think practically  
10 that actually happened.

11 Then during the long-term extension phase,  
12 anybody that had entered that phase could have  
13 stimulation parameters adjusted at the investigators'  
14 discretion.

15 MEMBER JAYAM-TROUTH: Into the long-term  
16 phase?

17 DR. RUDOLPH: All throughout the long-term  
18 phase --

19 MEMBER JAYAM-TROUTH: A throughout --

20 DR. RUDOLPH: -- all throughout it.

21 MEMBER JAYAM-TROUTH: -- so there were  
22 variations in what parameters they had?

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1 DR. RUDOLPH: That's correct.

2 MEMBER JAYAM-TROUTH: Was there a  
3 difference in the non-responders and the responders?

4 DR. RUDOLPH: No, there was not.

5 MEMBER JAYAM-TROUTH: So they also had  
6 stretched to the limit of tolerability --

7 DR. RUDOLPH: Yes.

8 MEMBER JAYAM-TROUTH: -- and they didn't  
9 respond.

10 DR. RUDOLPH: In fact, as you know, as you  
11 are probably aware, what happens in trial where an  
12 investigator is given sort of free range, if you will,  
13 to make adjustments, the non-responders are often  
14 those that are receiving the higher doses because  
15 they're not getting better and they're constantly  
16 pushed up in dose.

17 But there was no distinction between the  
18 responders and the non-responders in terms of their  
19 settings.

20 DR. RUSH: I just wanted to make it clear  
21 that in both the D-01 and D-02, there was only a two-  
22 week period during which the parameters could be

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1 adjusted. And after that, they were fixed for the  
2 entire duration of the trial.

3 MEMBER JAYAM-TROUTH: Okay.

4 DR. RUSH: So it's a very truncated  
5 opportunity to make the adjustments. And in that  
6 context, with weekly visits, while we could send the  
7 patient away for a few hours and come back to see if  
8 we can adjust further up in terms of current, it's a  
9 truncated time period for adaptation and a truncated  
10 opportunity.

11 So we may have, in a sense, injured  
12 ourselves in terms of what might really have been more  
13 effective.

14 MEMBER JAYAM-TROUTH: So for the whole  
15 year, they didn't change after that?

16 DR. RUSH: No, no, no. I'm talking about  
17 just the acute trial.

18 MEMBER JAYAM-TROUTH: Acute phase.

19 DR. RUSH: Just the acute phase, yes.  
20 Then after the acute phase, then adjustments can be  
21 made.

22 MEMBER JAYAM-TROUTH: Then adjustments --

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1 and for the sham people, they were also adjusted over  
2 two weeks? And then they --

3 DR. RUDOLPH: Once the sham people crossed  
4 over --

5 MEMBER JAYAM-TROUTH: Yes.

6 DR. RUDOLPH: -- into an acute phase, if  
7 you will, following the acute study, they went through  
8 the same procedures as the original VNS group did.

9 MEMBER JAYAM-TROUTH: Okay.

10 DR. RUDOLPH: And then --

11 MEMBER JAYAM-TROUTH: And then they could  
12 be adjusted?

13 DR. RUDOLPH: Well, they could be adjusted  
14 over two weeks first. And then they had to have  
15 another ten -- another eight weeks at a fixed dose  
16 range increment. And then beyond that, then they were  
17 also available or they were allowed to have unlimited  
18 changes at the investigators' discretion.

19 MEMBER JAYAM-TROUTH: Okay.

20 CHAIRPERSON BECKER: And actually before  
21 Dr. Fochtman asks her questions or makes comments, I  
22 just want to follow up on this particular issue.

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1 Do you have data on how many adjustments  
2 were made in each patient? And I guess in particular,  
3 I'm interested in how the different number of  
4 adjustments would correspond to the different changes  
5 in their medications as well. Is that data available?

6 DR. RUDOLPH: I don't believe so. No, no  
7 it's not.

8 CHAIRPERSON BECKER: And on Slide 56 of  
9 the sponsor's presentation, it gives the time course  
10 of response in D-02 and D-04. And it looks like the  
11 biggest benefit is actually very acute on that non-  
12 adjusted graph. And I was wondering if you could  
13 comment on that.

14 Since the efficacy is really at the long  
15 term, why is it that the benefit in this analysis  
16 appears to actually happen straight away?

17 DR. RUDOLPH: It's true that a good deal  
18 of the benefit occurs early as is the typical pattern  
19 in drug trials over a shorter period of time. And  
20 just as a reference point, could we have E-151? So  
21 that's typical of trials in general.

22 It's also true in this case, and I'll show

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1 that in a minute. It's also true that the separation  
2 between the D-02 and D-04 groups continued to grow  
3 after that initial phase. Slide on please.

4 So this is actually taken from a real drug  
5 trial. We washed it of the identifiers as to what  
6 drug it was. But this is a very typical pattern that  
7 you see in an antidepressant drug trial. So most of  
8 the drop does occur early.

9 And then where you really start to get  
10 statistically significant separation is usually at the  
11 later part when the placebo group will start to  
12 flatten out and the drug continues to improve.

13 I think what's -- as we've been -- as  
14 we're probably sounding like a broken record but what  
15 we've tried to underscore throughout the whole morning  
16 is -- what's probably really important here is the  
17 sustained nature of the response, which is what you  
18 don't -- wouldn't expect in this group without an  
19 effective treatment.

20 CHAIRPERSON BECKER: Well, I guess that  
21 one could make the argument that they're getting some  
22 kind of augmentation on the placebo response because

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1 they're coming in for frequent readjustments of their  
2 stimulation.

3 Having said that, we'll ask Dr. Fochtmann  
4 if she has any questions.

5 MEMBER FOCHTMANN: I have a number of  
6 questions.

7 First of all, to follow up on the  
8 questions about the stimulus settings, you said that  
9 there was no difference between the responders and  
10 non-responders in the stimulus settings. Was that  
11 just for the acute trial? Or was that also analyzed  
12 for the open phase, open label phase of the followup  
13 trial?

14 DR. RUDOLPH: Let me check with the  
15 clinical team. Doctor? You want to come up?

16 DR. BRANNAN: Hi, I'm Steve Brannan. I'm  
17 one of the Medical Directors at Cyberonics. The --  
18 let's see, both for the acute and for the long term,  
19 the parameter settings did not differ between the  
20 responders and the non-responders.

21 When you have, just at the highest  
22 settings, there was a slight preponderance of people

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1 who were non-responders who had some of the higher  
2 settings.

3 And again, without having your kind of  
4 trial set up to be looking at a fixed dose, then that  
5 ends up the people who are necessarily doing very  
6 well. And so they're increased on their parameters.

7 So you actually see that better in the  
8 long term than you do in the acute phase where their  
9 parameters, again, were set after the first two weeks  
10 and so no adjustment could be made after those first  
11 two weeks of stimulation.

12 MEMBER FOCHTMANN: Was there any dose  
13 response relationship to the observation of adverse  
14 effects?

15 DR. BRANNAN: The only adverse event I am  
16 aware of would be the voice alteration that you have.

17 MEMBER FOCHTMANN: Okay.

18 The next question I had related to the  
19 proposed indication and there were two aspects of it  
20 that I wanted to inquire about.

21 You specifically defined chronic or  
22 recurrent depression as a current major depressive

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1 episode that is of at least two years in duration or a  
2 current major depressive episode in a patient with a  
3 history of multiple prior episodes of depression.

4           While those could be overlapping groups of  
5 individuals, they do seem to be also in some instances  
6 very discreet groups of individuals. And I wondered  
7 whether you had analyzed the data to determine whether  
8 you had comparable efficacy in individuals who just  
9 had a chronic episode lasting more than two years  
10 versus individuals who had shorter lasting episodes  
11 but who had had multiple recurring episodes?

12           DR. RUDOLPH: Yes, well, we did. I  
13 presented a slide this morning where we did it in the  
14 form of an exploratory analysis. And on the slide, if  
15 we can pull it up from my presentation, it focused on  
16 the chronic group only.

17           And in the chronic group, which was -- and  
18 I'm talking about the D-02/D-04 comparison, in the  
19 chronic group, which was again two-thirds -- next  
20 slide -- no, not that one. The next slide. Yes,  
21 there we go.

22           In the chronic group, which was two-thirds

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1 of the patient population for D-02 and D-04, and these  
2 again were patients defined as having an episode  
3 lasting at least two years of duration, and see the  
4 overall response rate in D-02 is 29 percent, 10  
5 percent for D-04, and if you'll recall, and this is  
6 from the Hamilton, if you'll recall for the entire  
7 sample set, it was 30 versus 13 percent.

8 So by extension, you can figure that the  
9 recurrent patients had approximately the same rates.

10 MEMBER FOCHTMANN: Okay.

11 DR. RUDOLPH: So the bottom line is --

12 MEMBER FOCHTMANN: But did you analyze it  
13 specifically for the recurrent --

14 DR. RUDOLPH: No, we didn't.

15 MEMBER FOCHTMANN: Okay.

16 DR. RUDOLPH: But, you know, I think you  
17 can probably make that -- you can surmise that by  
18 subtracting out those patients. It's not going to  
19 differ that much. And so I think we can conclude that  
20 the overall rates of response, and particularly the  
21 difference between D-02 and D-04, are similar whether  
22 we're looking just at the recurrent patients or the

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1 chronic patients.

2 MEMBER FOCHTMANN: Okay. I was curious in  
3 terms of -- from a statistical standpoint whether you  
4 had been able to demonstrate efficacy in both of those  
5 subgroups of patients that you were including in the  
6 indication statement.

7 DR. RUDOLPH: We did not do a statistical  
8 test on this because it was an exploratory analysis.

9 MEMBER FOCHTMANN: Okay.

10 The second question that I had about the  
11 other definition in the indication statement was  
12 related to the definition of failed adequate treatment  
13 which mentioned a failure to respond to  
14 electroconvulsive therapy or an established  
15 antidepressant drug administered at an adequate dose  
16 for an adequate duration.

17 And my question there was whether  
18 electroconvulsive therapy adequacy was assessed either  
19 in terms of stimulus titration methodologies or in  
20 terms of electrode placement or in terms of numbers of  
21 treatments or any of the usual ways of assessing ECT  
22 adequacy.

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1 DR. RUDOLPH: I'll ask Dr. Sackheim to  
2 answer that because the standard scale that we used  
3 for assessing adequacy was the antidepressant  
4 treatment history form.

5 DR. SACKHEIM: Right. On the -- I'm  
6 Harold Sackheim. On the antidepressant treatment  
7 history form, ECT is one of the treatments that is  
8 assessed in terms of whether or not the patient has  
9 had an adequate trial.

10 There is a slight bias on that form. One  
11 can have a higher rating for bilateral than for  
12 unilateral. We don't believe that we can determine  
13 usually retrospectively whether a stimulus test  
14 titration was used or what the dosage settings were or  
15 the adequate seizures.

16 We try and get that information when it's  
17 possible but it is based primarily on the number of  
18 treatments with the threshold number of treatments to  
19 be considered adequate and they differ for unilateral  
20 and bilateral.

21 MEMBER FOCHTMANN: Okay. Was -- I guess  
22 the follow up to that question would be is there a

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1 reason that the indication did not include failure to  
2 respond to an adequate trial of electroconvulsive  
3 therapy since adequacy was mentioned in terms of the  
4 antidepressant treatments.

5 DR. RUDOLPH: The reason the proposed  
6 indication was written as it was is because we were  
7 trying to parallel as close as possible the inclusion  
8 and exclusion criteria in the D-02 protocol.

9 MEMBER FOCHTMANN: Okay. The next  
10 question that I had was related to the other  
11 treatments that were used.

12 You censored the data based on a change in  
13 antidepressant treatment and yet as has been pointed  
14 out, the individuals in these trials are on multiple  
15 medications in addition to the antidepressants.

16 And one of the reasons for not changing  
17 the medications was presumably that any of these  
18 medications that they were on would have some  
19 potential to be of help in managing their depressive  
20 disorder.

21 And so even though these weren't specific  
22 antidepressants per se, I wondered whether you had

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1 looked at the effects of changes in other medications  
2 that people might be on be they antipsychotic  
3 medications, benzodiazepines, stimulant medications.

4 Some of the characteristics that at least  
5 appeared to perhaps be different in the frequency of  
6 use between the D-02 and the D-04 subgroups.

7 DR. RUDOLPH: I think and I'll ask for  
8 some confirmation. I think that the censoring  
9 actually encompassed more than just traditional  
10 antidepressants. It was -- we encompassed -- tried to  
11 encompass a whole group of medications that would be  
12 used to treat mood disorders.

13 DR. BRANNAN: It is certainly true that  
14 most of these patients were on concomitant  
15 medications. It is also true that when we looked at  
16 this, and we looked at it very carefully in a number  
17 of ways that the data do not show that they had an  
18 effect on outcome.

19 Can I have the slide with Responders/Non-  
20 Responders? Slide up please. Thank you. This one.

21 All right. When looking at this, and I  
22 think something like this was already shown when Dr.

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1 Rudolph initially had his presentation, one would  
2 think if you were having additional medications, you  
3 know, just did that benefit who was getting well?

4 And the answer, and I'll show you two  
5 ways, this is the first. It is clearly not. When you  
6 just concentrate on the two columns on the left and in  
7 the middle, the responders actually had fewer changes  
8 in the ARR than did the non-responders.

9 And again, similar to the parameter  
10 settings that we were just talking about, part of this  
11 is when people are not doing well over the course of  
12 year, then they're going to have more changes than  
13 those people who are actually doing better.

14 Can I see the next slide please? Another  
15 way of looking at that is to look at the patients who  
16 had ARR scores who increased or showed no increase in  
17 their ARR score.

18 And what you see clearly is is the people  
19 with no increase in their ARR score actually had a 51  
20 percent response. So quite a bit better than the  
21 group as a whole. And so those with increases you  
22 actually see did less well overall.

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1 But in addition to this, there are other  
2 parameters that are kind of hard to quantify. How do  
3 you know exactly? Do we have the slide of the  
4 medications that they were using during the one-year?

5 MEMBER FOCHTMANN: When you classified  
6 antidepressant medication changes, are you including  
7 only antidepressants per se?

8 DR. BRANNAN: No. I think that --

9 MEMBER FOCHTMANN: Are you including  
10 benzodiazepines, antipsychotics, stimulant  
11 medications, any of the medications that they were on  
12 that would be a psychotropic medication are included  
13 in the censoring?

14 DR. RUDOLPH: I apologize. And I think  
15 that was the core of your original question.

16 MEMBER FOCHTMANN: Right.

17 DR. RUDOLPH: And we are encompassing in  
18 there more medications than just standard  
19 antidepressant. It does include atypical  
20 antipsychotics, stimulants, benzodiazepines. They're  
21 all captured through the use of the ATHF form.

22 DR. SACKHEIM: Just to clarify what some

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1 of the difficulty may be, a benzodiazepine could  
2 never, as a treatment alone, be considered adequate in  
3 the treatment of depression.

4 MEMBER FOCHTMANN: Right.

5 DR. SACKHEIM: And so it would not, ATHF  
6 criteria for what constitutes adequacy are quite  
7 different than the information it captures on all the  
8 psychotropics. So we would capture the atypicals and  
9 all the others that were mentioned. But there is a  
10 real distinction between what can reach the level of  
11 adequacy.

12 CHAIRPERSON BECKER: Okay. We're going to  
13 continue to go around that table. Dr. Wang, do you  
14 have any questions?

15 DR. BRANNAN: We actually did have a slide  
16 on the atypical antipsychotics --

17 CHAIRPERSON BECKER: Okay.

18 DR. BRANNAN: -- if that would be helpful.  
19 E-164.

20 As I'm sure some of the panel members are  
21 aware, atypical antipsychotics in combination with  
22 other antidepressants are thought potentially to be

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1 something that might be very useful for patients who  
2 are not responding so as augmenting agents.

3 Slide on please. We do see, and I had a  
4 slide looking at all sorts of medications but this  
5 will kind of show you for the antipsychotics. There  
6 is a difference in the percentage of patients in D-02  
7 who had atypical antipsychotics, 47 percent in D-02  
8 and 32 percent in D-04.

9 What you see in the D-02 patients, so  
10 those 47 percent, they had a response rate of 26  
11 percent as opposed to 30 percent as measured by the  
12 Hamilton Depression Rating Scale.

13 So there was no benefit from the -- in  
14 fact a slight decrease for patients in D-02 who were  
15 on an atypical antipsychotic.

16 Of the 32 percent of the patients in D-04,  
17 18 percent had a response, which actually is slightly  
18 better than the 13 percent that they had. So the  
19 response is somewhat higher than the overall response.

20 So in terms of does this create a little  
21 bit of a confound, the answer is yes. But it makes  
22 the difference between the groups appear more robust

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1 in that this actually gives more advantage to D-04 and  
2 less advantage to D-02. So it should hide the  
3 difference.

4 DR. RUDOLPH: And the antipsychotics, I  
5 might add, were the only category of medication where  
6 there was really a substantial difference in usage  
7 between the D-02 and D-04 patients.

8 CHAIRPERSON BECKER: Dr. Wang?

9 MEMBER WANG: Yes, I'd like to go back to  
10 the FDA's major concern about residual confounding,  
11 you know, in the D-02/D-04 comparison that used  
12 propensity score adjustment.

13 Dr. Rudolph, you mentioned that you didn't  
14 think that the distribution of unmeasured variables  
15 might be equally distributed because of the large size  
16 of D-02 and D-04? How is that possible since that  
17 principle only really applies if you are randomizing?

18 DR. RUDOLPH: Randomization certainly  
19 gives you that assurance but also we made that  
20 evaluation because the sample sizes were so large here  
21 and the measured covariates were so equally  
22 distributed that I think it's a reasonable assumption,

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1 not -- obviously not proven, but a reasonable  
2 assumption that for unmeasured covariates, it would  
3 probably be equally distributed as well.

4 Obviously there is an assumption there but  
5 we -- Dr. Davis has some information that I think  
6 bears on this question that you'll find interesting.

7 DR. DAVIS: Hi. I'm Sonia Davis, Director  
8 of Biostatistics at Clean Tiles.

9 First, as Dr. Rudolph had described  
10 before, we evaluated through the propensity score the  
11 differences for the covariates that we had measured at  
12 baseline.

13 Slide up please. And this is a list of  
14 all the 17. This happens to be the input that each of  
15 the 17 had on the propensity score but of all of these  
16 17, only four of them were significantly different  
17 between the groups at baseline. Two of them were  
18 quite related to each other, ECT and lifetime, or in  
19 the current episode. So we used these parameters to  
20 incorporate the propensity score.

21 Next slide please. As Dr. Rudolph already  
22 presented, when we used the propensity score to adjust

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1 for our primary efficacy model, on the top row, you  
2 can see, in the top right box, did not have a  
3 significant impact on the changes over time in the IDS  
4 scores. So this tells us that there were very minimal  
5 differences between the groups even when we combined  
6 them all together.

7 Even down -- looking at the very bottom  
8 row of this table, if we did not adjust for propensity  
9 scores at all, we still get a very strongly  
10 significant linear study effecting the primary  
11 parameter.

12 Now you might say well the propensity  
13 score maybe didn't catch all these parameters that  
14 were different at baseline. So is you could look at  
15 the next slide -- slide up -- we did an additional  
16 exploratory analysis that actually put each of these  
17 covariates -- there was a strong influence into the  
18 logistic regression and also for the propensity score  
19 and also were different at baseline to see are these  
20 covariates having an effect on our primary analysis  
21 with our linear study effect.

22 And in the first column we can see that

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1 after putting each of these predictors that were the  
2 strongest ones in there, we see there is essentially  
3 no differences to our linear study effect. We always  
4 had very consistent and very strong answer results.

5 So this led us certainly to conclude that  
6 everything that we measured, although we saw very  
7 small differences, had no impact in the difference  
8 between D-02 and D-04.

9 Switching now to what about the covariate  
10 that possibly had not been measured. Slide up please.

11 In order to have a strong impact into the response  
12 rates that we saw over time, the unmeasured covariates  
13 would have to be correlated with response.

14 They would have to be in balance between  
15 the studies, otherwise we wouldn't have an impact.

16 They would have to be recurring in a  
17 reasonable number of patients in order to have an  
18 impact on response. If they were very small number of  
19 patients, it wouldn't have a meaningful impact on the  
20 overall group.

21 And they would need to be uncorrelated  
22 with all the other covariates that we have adjusted

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1 for.

2 And we feel that these four things are  
3 quite hard that we would reasonably expect that it's  
4 very, very unlikely there would be some unmeasured  
5 covariates that we did not measure.

6 And I'd like to turn it over to Dr.  
7 Brannan now if I could to talk about possible --

8 DR. BRANNAN: Sure. Just as an example,  
9 one of the unmeasured covariates talked about by the  
10 FDA had to do with thyroid disease. We did not  
11 measure that specifically but we did have an estimate  
12 for it. Slide up please. And that was thyroid  
13 medication use.

14 Now again, this is not going to tell us  
15 exactly whether people had thyroid or not because a  
16 fair number of these patients may be having this as  
17 thyroid augmentation which is one of the strategies  
18 one has for treatment-resistant depression. So again  
19 there is some appropriate caveats.

20 But what it is reassuring is when you look  
21 at the difference in thyroid medications either  
22 lifetime or in the current episode, you see it's just

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1 almost equally distributed between the two groups.

2 Kind of bearing up again those four  
3 measures are pretty hard to find something that's  
4 going to be -- have that imbalance between the groups,  
5 have a strong correlation with outcome, and even  
6 treatment doesn't have that strong a correlation with  
7 outcome in depression. And also not even be  
8 correlated at all with any of the covariates that are  
9 already there and measured.

10 DR. RUDOLPH: This might be an opportune  
11 time to correct something that you either heard from  
12 the FDA this morning or you saw in their review and  
13 that was the statement that there is no covariate  
14 adjustment in the secondary analysis. That was not  
15 true. There was covariate adjustment in the secondary  
16 analyses.

17 And let me just ask Dr. Davis to comment  
18 on that because I think it's a very important point.  
19 It's come up a couple times.

20 DR. DAVIS: Yes, this is Sonia Davis.  
21 It's true. All of our analyses for D-02 versus D-04  
22 adjusted for the propensity score, for the baseline

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1 value whether it be Hamilton or the IDS, depending on  
2 what measures we were looking at for the outcome, and  
3 also for the pooled site.

4 So all analyses, not matter what we did,  
5 adjusted for those parameters.

6 MEMBER WANG: Did you model in the  
7 categorical analyses?

8 DR. DAVIS: That is correct. The  
9 categorical analyses were modeled with logistic  
10 regression. And I would have to point out that we did  
11 follow that up with an exact logistic regression due  
12 to relatively small sample sizes of our events.

13 If you looked at that exact logistic  
14 regression, because of the sample sizes, we could only  
15 adjust for one covariant. We adjusted for the  
16 propensity score in every case, our exact logistic  
17 regression adjusting for the propensity score gave  
18 very similar results to the logistic regression that  
19 adjusted for all the covariates.

20 And also our results were quite similar  
21 with the Fisher's Exact Test that Dr. Lao performed  
22 during his review.

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1           MEMBER WANG:  Actually, Dr. Davis, if you  
2 could -- probably I'm going to be asking this to you.

3           I mean this issue of unmeasured confounders is, you  
4 know, we're probably not going to come to any sort of  
5 clear resolution because it would probably be sort of  
6 speculating.

7           But in terms of estimating whether there  
8 is residual confounding, one thing to wonder about is  
9 also how you categorized -- how you dealt with your  
10 propensity score.  And I see you used -- you left it  
11 as quintals.

12           To sort of begin estimating whether there  
13 is residual confounding, did you try more categories?

14           You know, even through it in as a continuous  
15 variable?  And if so, did it change the results?  
16 Because I might --

17           DR. DAVIS:  Yes, we did.  And it did not.

18           Slide T-50, T-50 please.  Slide up.  The middle row  
19 here shows the results of the primary model if we  
20 treated the propensity score as a continuous measure  
21 rather than the five levels.

22           The five levels that we used were what we

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1 already specified in our analysis plan but this row is  
2 an exploratory analysis, supportive analysis to  
3 confirm that results are not different.

4 MEMBER WANG: My last set of questions  
5 have to do with this concomitant treatment issue. In  
6 the D-02 analysis, I mean in the -- when people who  
7 had either adjustments to their medication or ECT  
8 added or dropped, the apparent benefit, you know, it  
9 not only became less significant but the actual effect  
10 size went down which -- there's a couple ways to  
11 interpret that.

12 You know, one potential way to interpret  
13 that is some of the apparent efficacy of, you know,  
14 VNS, may actually be attributable to the superior  
15 efficacy of the rescue treatment.

16 I'm wondering if you have some either data  
17 or some way to sort of reassure us that that is not  
18 happening.

19 DR. RUDOLPH: While Dr. Brannan is coming  
20 back up, I will remind you that the censoring analyses  
21 were done as sensitivity analyses. They're very -- we  
22 had available to us a number of methodologies. The

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1 methodology I presented this morning was actually the  
2 most conservative of the methodologies that we could  
3 envision.

4 And even with that methodology, as I  
5 presented this morning, although statistical  
6 significance wasn't achieved, it came awfully close at  
7 .052. The confidence -- the 95 percent confidence  
8 interval for that range from -.37 to zero. So it  
9 never crossed zero.

10 And one should bear in mind that it did  
11 truncate the VNS effect to about seven months. So the  
12 patients in that censored D-02 group did not have even  
13 the full benefit of VNS assuming that there is an  
14 accruing benefit over time.

15 DR. BRANNAN: Let me just ask again -- the  
16 point of your question again was?

17 MEMBER WANG: It's not really the  
18 significance issue.

19 DR. BRANNAN: Okay.

20 MEMBER WANG: It's the effect size.

21 DR. BRANNAN: Okay.

22 MEMBER WANG: You know when you censor --

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1 DR. BRANNAN: Yes.

2 MEMBER WANG: -- the effect size reduces  
3 suggesting that, you know, maybe the rescue  
4 treatments, you know, ECT, maybe that's what has this  
5 appeared efficacy. Anyway, just sort of -- you  
6 partially answered it. Actually Dr. Rudolph partially  
7 answered the potential reasons why but --

8 DR. BRANNAN: Okay, as he mentioned, this  
9 was part of a number of sensitivity analyses. We  
10 actually looked at several things. Can I have the  
11 slide up a second?

12 So there's actually a lot of different  
13 ways to kind of do the censoring. The original is on  
14 the top. If you actually censor both, which is not  
15 necessarily very helpful to answer the question,  
16 there's still a huge difference.

17 One of the things that was attempted was  
18 not to censor D-04 until after the first three months.

19 As you will recall, in the first three months, people  
20 were not supposed to have medications added in D-02.  
21 So that was done. And that actually does reduce what  
22 you saw from the original one some but it's still

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1 fairly large.

2 Then an attempt was done just to do a  
3 censoring without anything -- without carrying forward  
4 anything but treating everything as missing value.  
5 And that again had such a large value.

6 So you are correct. When we actually go  
7 to the extent of going and censoring at the first ARR  
8 change and then carrying that forward, LOCF fashion,  
9 which again truncates both the benefit in terms of  
10 whatever interaction or VNS effect that you're getting  
11 as well as shortening effectively how long they are in  
12 the trial, so on average, they're about seven months  
13 instead of twelve months, at that point then you do  
14 see this decrease.

15 And I think it's a good point that since  
16 this is a sensitivity analysis, what are the P values  
17 really talking about. But you still see actually a  
18 fairly substantial -- you do cut it down by about  
19 half. But it's still fairly different.

20 DR. WITTEN: Can I just request of the  
21 sponsor that you -- when you present these slides,  
22 just clarify which analyses were in the submission and

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1 which weren't -- for each -- just in general.

2 DR. RUDOLPH: Oh, I'm sorry.

3 DR. WITTEN: For each slide.

4 DR. RUDOLPH: Okay, for this one, slide  
5 back on, for this one, the original and then the  
6 bottom were done in the original submission. And then  
7 I believe only the second from the top was also  
8 submitted during some of the questions back and forth.

9 Yes?

10 DR. DAVIS: Hi, this is Sonia Davis, I  
11 just want to add a summary about this to bring home  
12 this point. The analysis that we did with the LOCF  
13 censoring, which is the last bottom line here that was  
14 submitted, is an exceedingly conservative post hoc  
15 analysis that we did.

16 We expected it full well to be very  
17 conservative. We didn't present some of the others to  
18 the FDA because they are quite non-conservative. So  
19 the idea was for us to say under this very unusual  
20 situation where almost 50 percent of the time that  
21 people were on D-02 was taken away from the analysis.

22 Is there a difference between that and a

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1 full 12-months of the D-04 analysis? And we said yes,  
2 we still see a signal even in the most exceedingly  
3 conservative situation.

4 CHAIRPERSON BECKER: Dr. Jensen?

5 DR. JENSEN: My questions primarily have  
6 to do with safety. So if you have a safety person,  
7 want to stick him up?

8 First I noticed in the study that the  
9 wound infection rate was eight percent for the VNS  
10 group and two percent for the sham control. And  
11 you've mentioned only a 1.4 percent infection rate in  
12 your epilepsy study that required explantation. So  
13 were these patients, did they require explantation?  
14 Or were they treated only with antibiotics and they  
15 recovered from that?

16 And if not, if they required explantation,  
17 then why do you see such a substantial difference in  
18 infection rates?

19 DR. WINGARD: My name is Peggy Wingard.  
20 I'm one of the Medical Directors at Cyberonics.

21 In answer to your question about the  
22 difference in the rates of the infection, eight

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1 percent versus two percent -- is that the information  
2 that you are referring to?

3 DR. JENSEN: Well, that's in the  
4 depression study but you compared that to the  
5 infection rate in your epilepsy group, which I believe  
6 was 1.4 percent required explantation due to  
7 infection.

8 So it's not clear to me whether this eight  
9 and two percent required just explantation -- required  
10 explantation? Or if they were treated with  
11 antibiotics?

12 DR. WINGARD: I see. Okay. In answer to  
13 your question, there was only one patient that  
14 required explantation due to infection. And the rest  
15 of them were treated with antibiotics.

16 DR. JENSEN: And that is in the depression  
17 group?

18 DR. WINGARD: Yes, ma'am.

19 DR. JENSEN: Which means it is equivalent  
20 to what you saw in the epilepsy group? Is that true?

21 In your -- because you were comparing the safety data  
22 between those patients that have had the device for

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1 epilepsy. And I just want to make sure that between  
2 the two groups, you're not seeing a difference in --

3 DR. RUDOLPH: Well, it actually results in  
4 a lower rate because it is one out of 235 implants.

5 DR. JENSEN: Okay.

6 In terms of the patients who do not  
7 respond and have a permanent implant, what is the  
8 company's position on how to cancel those patients as  
9 to what to do with that explant -- with that implant?

10 Explant it or leave it in?

11 DR. RUDOLPH: You have two options. You  
12 can have it explanted. You can leave it in. If the  
13 device is left in, the general precautions that are  
14 communicated are those that are in our label regarding  
15 the risks of having this implant, permanent implant  
16 in, which have to do with MRI risk, full-body MRI, not  
17 head MRI but full-body MRI. And the risk of receiving  
18 diathermy.

19 DR. JENSEN: And the defibrillation risk?  
20 Anything? If they require defibrillation, that  
21 doesn't do anything?

22 DR. RUDOLPH: No.

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1 DR. JENSEN: Okay. All right. So you've  
2 got a group of people that are relatively young now  
3 but they have an implant in. And chances are at some  
4 point in their lifetime, they will require an MR.

5 And furthermore, they are depression  
6 patients so they will probably at some point in time  
7 get a brain MR, possibly a high field strength MR, so  
8 is it -- to me it looks like you may be precluding  
9 other forms of either treatment or at least evaluation  
10 of patients if the implant remains in since they now  
11 cannot have an MR with that.

12 DR. RUDOLPH: You can still have head MR.

13 DR. JENSEN: Even high field strength?  
14 When we go to three Ts?

15 DR. RUDOLPH: We're going to -- we'll get  
16 an imagine expert up here to answer this. This is --

17 PROFESSOR GEORGE: Hello, I'm Professor  
18 Mark George. I'm a professor of psychiatry,  
19 radiology, and neurology at the Medical University of  
20 South Carolina. And I did a research imaging  
21 fellowship here at the NIH and I'm in Charleston now.

22 And we've done extensive FMRI studies in

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1 these VNS patients. So it's not the case that they  
2 can't have the MRI scans. It's just that they can't  
3 have certain types. And those are whole body, where  
4 the gradient actually are the large whole body  
5 gradients and they cause heating of the electrodes.

6 So if you have a send/receive head coil,  
7 even at three tesla, then VNS is fine. So it's not  
8 the case that having the device in would preclude  
9 diagnostic MRI.

10 DR. JENSEN: Of the head.

11 PROFESSOR GEORGE: Of the head.

12 DR. JENSEN: But if they ever at some  
13 point down the road need a body MR, that could be  
14 problematic?

15 PROFESSOR GEORGE: Correct. And of the  
16 cervical spine, that could be a problem as well, yes.

17 DR. JENSEN: Okay.

18 So along those lines, there are other  
19 issues, too, just with operating in the carotid  
20 sheath, which is once you have fibrosis that's set up  
21 after surgery, you now make other operations, you  
22 know, redoes difficult, for example, the complication

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1 rate with carotid endarterectomies goes from 3 to 16  
2 percent when you're looking at patients with carotid  
3 redoes.

4 So again you have a relatively young group  
5 of patients right now who at some point in time might  
6 need to have carotid surgery and you may be precluding  
7 them from being able to have it if the device has  
8 caused some sort of fibrosis.

9 So do you have any long-term data on the  
10 patients who have had the device implanted for  
11 seizures in terms of battery corrosion, wire  
12 corrosion, vascular perforation, operative problems in  
13 the carotid sheath afterwards?

14 DR. RUDOLPH: I'm going to ask one of our  
15 engineers to come up and answer that technical  
16 question for you.

17 MR. ARMSTRONG: Hello, I'm Scott  
18 Armstrong, Director of Electrical Engineering,  
19 Cyberonics.

20 And as far as the corrosion, no we don't  
21 have any problems with the leads or the device or the  
22 battery. They're all -- the can it titanium, which is

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1 very stable. And all the materials are the same that  
2 are used in pacemakers and defibrillators so there is  
3 an extensive history of this same type material and  
4 have not seen any type of corrosion.

5 DR. JENSEN: Okay. But in terms of  
6 surgery, we don't really have any data on repeat  
7 carotid surgery? Got a surgeon in the group?

8 (Laughter.)

9 DR. RUDOLPH: Unfortunately we don't have  
10 a surgeon but one of my staff members is a clinical  
11 engineer and he spends a lot of time in the OR so --

12 MR. PARNIS: My name is Steve Parnis. I'm  
13 the Senior Manager of Clinical Engineering,  
14 Cyberonics.

15 No, we don't have specific data about the  
16 number of other surgeries that have been done but we  
17 do know of a lot of surgeries that have been done to  
18 remove the lead, to replace the lead in cases of lead  
19 breaks, or patients who want the device removed.

20 As you know, any operation, whether it is  
21 carotid endarterectomy, whether it's a patch graft  
22 that has to be put in the neck, surgeons do go back

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1 in. We do know of the complications. There's no  
2 difference in the complications between our device  
3 being in and a patient who has had previous carotid  
4 surgery.

5 DR. JENSEN: I'm sorry. Say that last  
6 line again.

7 MR. PARNIS: We've looked at the  
8 complication rates of patients who had carotid  
9 endarterectomies, especially redo carotid  
10 endarterectomies, and the complication rates for a  
11 replacement of our device has been no different than  
12 the replacement or a redo for a carotid  
13 endarterectomy.

14 DR. JENSEN: Okay. So you're not -- what  
15 you're saying is you're not seeing, for example, a  
16 higher recurrent laryngeal nerve palsy occur in  
17 removing your device versus those that occur with  
18 carotid endarterectomy redo? In other words, those  
19 are similar, the cranial nerve palsy is similar.

20 I would just submit though that if a  
21 patient has this device in has to have a carotid  
22 endarterectomy, they're already in the higher risk

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1 group, than that whose a virgin carotid. That's just  
2 my point.

3 MR. PARNIS: That's correct. And the redo  
4 rates for redo carotid endarterectomies do run up to  
5 28 percent. And we have looked at those numbers. And  
6 there hasn't been -- we don't have that high of a  
7 complication rate as we have seen in the literature  
8 for redo surgeries with our device. We haven't looked  
9 at other surgeries associated with vagus nerve  
10 stimulation.

11 DR. JENSEN: Okay.

12 My next question has to do with --

13 MEMBER JAYAM-TROUTH: Okay, can I follow  
14 through on that?

15 DR. JENSEN: Oh, yes, go ahead.

16 MEMBER JAYAM-TROUTH: I don't think that  
17 you answered it correctly. I mean I don't think it is  
18 still to the point. I think the question that was  
19 raised was not that the morbidity for your operation  
20 is, you know, as good as a carotid endarterectomy.  
21 The question was is the morbidity greater for a  
22 carotid endarterectomy after you've done your

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1 operation.

2 DR. JENSEN: Well, you're putting the  
3 patient in the higher risk category as opposed to the  
4 three percent group.

5 MEMBER JAYAM-TROUTH: Would you put a  
6 patient -- suppose in the future this patient needs a  
7 carotid endarterectomy then would this patient be in  
8 greater jeopardy doing a carotid endarterectomy after  
9 you have done this operation?

10 DR. RUDOLPH: We don't have data to bear  
11 on that but presumably yes.

12 DR. JENSEN: In terms of your training  
13 requirements, how are you choosing which surgeons are  
14 allowed to place the implant? Which physicians are  
15 allowed to program the implant?

16 And do you have any sort of program of  
17 proctoring for those new physicians who are  
18 programming the implant to be sort of overseen by a  
19 member of the -- a trained member of the company to  
20 make sure that the initial patients are done properly?

21 DR. RUDOLPH: Mr. Parnis has been working  
22 on developing our training program so he's best suited

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1 to answer that as soon as he comes -- we lost him --  
2 as soon as he comes back up here.

3 MR. PARNIS: Hi, Steve Parnis again. If I  
4 understand your question correctly, it's -- first of  
5 all what surgeons would be implanting our device?

6 DR. JENSEN: Yes, how do you pick your  
7 surgeons, yes. For example, in the NASDA trial,  
8 surgeons had to have a five percent or lower  
9 complication rate in order to be in the trial. So are  
10 you just saying anybody who is a neurosurgeon or  
11 vascular surgeon or do you have to have some criteria?

12 MR. PARNIS: Okay, slide up please. In  
13 our labeling, we do recommend that surgeons be  
14 experienced in surgery within the carotid sheath.  
15 That is in our current labeling and that will be --  
16 and it's in our depression labeling, in the draft  
17 labeling as it sits today.

18 Sixty-four percent of our surgeons are  
19 neurosurgeons today. We do have other surgeons.  
20 There's ENTs, general surgeons, vascular surgeons  
21 could do the procedures. So we do recommend that  
22 surgeons be experienced in working within the carotid

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1 sheath.

2 DR. JENSEN: But you're not going to have  
3 a minimum number of carotid procedures performed per  
4 year? It's just all that they can say is I'm  
5 experienced?

6 MR. PARNIS: No, no.

7 DR. JENSEN: Okay. All right. What about  
8 who can program it?

9 MR. PARNIS: T-21 please. As far as  
10 programming, we do have -- for psychiatrists, we will  
11 have a training program in place. The training will  
12 consist of the device overview as well as product  
13 labeling. Going over the experience that we do have  
14 in VNS and epilepsy as well as going over the training  
15 itself as far as the programming, diagnostics, and the  
16 experience that we have in the D-02 studies.

17 A member of Cyberonics, our therapeutic  
18 consultants, clinical engineers, clinical technical  
19 services do perform the training for psychiatrists.

20 DR. JENSEN: Okay. Is there any plan to  
21 have any sort of proctor program where you send  
22 somebody to the site for the first however many --

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1 DR. RUDOLPH: We do recommend that  
2 physicians do consult with an experienced VNS user  
3 before prescribing VNS. That's in our current  
4 labeling today as well as in the labeling for  
5 depression.

6 In addition to that, we do offer  
7 proctoring.

8 DR. JENSEN: Is there any plan for any  
9 sort of registry to follow up the first however many  
10 number of patients?

11 DR. RUDOLPH: Yes, definitely. We've been  
12 actively talking about and planning a depression -- a  
13 treatment-resistant depression registry.

14 DR. JENSEN: And do you have an idea of  
15 how many -- how many numbers of patients you would  
16 enroll in the registry and how long you would follow  
17 them for?

18 DR. RUDOLPH: We -- as you may or may not  
19 know, we have an epilepsy registry. And we're  
20 somewhat modeling it on that although we're trying to  
21 make it a new and improved version.

22 I'll ask Dr. Wingard to come up because

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1 she has the primary responsibility for developing the  
2 registry so she can give you the specific numbers.

3 DR. WINGARD: This is a draft form of the  
4 registry. But we actually do have a protocol for a  
5 TRD registry for the United States. And we're  
6 initially going to have a TRD registry so that  
7 patients who have VNS therapy as well as those who do  
8 not have VNS therapy will be allowed to come into the  
9 registry.

10 We're initially going to have it at 20  
11 sites. These are our sites that did our investigative  
12 studies in D-02 and then this will expand to about  
13 approximately 60 sites in the United States.

14 And when they are enrolled in the  
15 registry, we will be asking all kinds of demographic  
16 information, patient history as well as their  
17 psychiatric history, medical history.

18 And then we will be following them at  
19 least on a quarterly basis for approximately three  
20 years.

21 DR. RUDOLPH: How many total patients?

22 DR. WINGARD: In the end, we're planning

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1 to have about 9,000 patients in the TRD registry that  
2 we will be following.

3 DR. JENSEN: Thank you.

4 CHAIRPERSON BECKER: Dr. Ortiz?

5 MEMBER ORTIZ: As a follow up to that, I  
6 have another question. So -- and the purpose for the  
7 non -- the patients that are not going to receive the  
8 device, what will be the purpose of those people in  
9 the registry?

10 DR. RUDOLPH: To better understand the  
11 course of treatment-resistant depression. You know,  
12 as you probably appreciate this more, and actually the  
13 published literature is fairly scant on longer-term  
14 outcomes in treatment-resistant depression patients.

15 MEMBER ORTIZ: Okay. My questions are  
16 more clinical.

17 What can you tell us about the co-  
18 morbidity of the patients in your studies? I'm  
19 interested -- it seems like a number were on atypical  
20 antipsychotics. And I'm wondering if they had  
21 depression with psychotic features or they had  
22 concomitant psychotic problems?

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1 I'm also interested in a little bit more  
2 about the personality issues, cognitive issues. Can  
3 you elaborate a little on that?

4 DR. RUDOLPH: Yes, first of all, the use  
5 of the atypicals was as a treatment for treatment-  
6 resistant depression didn't represent a psychotic  
7 depression, there were some specific exclusions of  
8 patients in the D-02 protocol.

9 And those included patients with psychotic  
10 depression, patients with a drug or alcohol abuse, and  
11 patients with a schizoaffective disorder. And if I'm  
12 forgetting any, perhaps Dr. Rush could chime in.

13 DR. RUSH: Well, I just want to --

14 DR. RUDOLPH: And in terms of the Axis 2  
15 diagnosis, they were not specifically excluded.

16 DR. RUSH: And I just want to emphasize  
17 there were no patients with a current or lifetime  
18 history of psychotic depression in the trials. They,  
19 of course, could have bipolar 1 disorder in the  
20 depressed phase, not mixed, not manic, and not rapid  
21 cycling.

22 DR. RUDOLPH: Rapid cycling was the other

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1 category excluded. So I think I covered all of them.

2 Schizoaffective, rapid cycling, psychotic depression,  
3 and drug and alcohol abuse.

4 MEMBER ORTIZ: Schizoaffective was  
5 included or was not?

6 DR. RUDOLPH: Was excluded.

7 MEMBER ORTIZ: Excluded. Okay.

8 The other question I have is from the FDA  
9 presentation. On page 15, and again you seemed to  
10 address a couple of the variables. They have a list  
11 of variables that they were --they have a question  
12 mark about the -- if there were any notation about it.

13 But I guess this is more for the sponsor.

14 I'm interested if you did have -- I know  
15 you had thyroid up there that you showed us. Then you  
16 showed us some data on ethnicity. But premorbid  
17 personality, family history, other losses, was there  
18 any data on those areas as well?

19 DR. RUDOLPH: I'm sorry. We thought you  
20 were asking the FDA.

21 MEMBER ORTIZ: No, no.

22 DR. RUDOLPH: We were hoping to leave the

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1 table for a little while.

2 MEMBER ORTIZ: I was asking you. I wanted  
3 a follow up to the FDA question is what I want.

4 DR. RUSH: Sorry, no, no, we  
5 misunderstood.

6 Let me take them one at a time. With  
7 regard to personality disorders, there was no formal  
8 structured interview for personality disorders. And,  
9 therefore, we did not diagnose them. I would put in  
10 context that the consent form is a multi-page, single-  
11 spaced document which says something like you have  
12 received an implantable device, the safety and  
13 efficacy of which is unknown for your condition.

14 This tends to take certain personality  
15 disorders and move them to the side. But it's not a -  
16 - it's just a practical screener. So we really do not  
17 know the types of personality disorders that were  
18 included and certainly none were excluded.

19 Any social personality disorders tend not  
20 to sign up for this sort of thing. Borderline  
21 personality disorders, especially with the multiple  
22 baseline requirement and the complex consent tend to

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1 shy away from it. I'm just speaking clinically.

2 But we have no data for you. As you know,  
3 in TRD, the incidence, the prevalence of personality  
4 disorder is very high. It's high in chronic  
5 depression, over 60 percent from the Keller Study done  
6 a few years ago. Probably on the order of 75 to 80  
7 percent in treatment-resistant depression.

8 Some of that is actually due to the  
9 chronic nature of the depression. And as I mentioned  
10 this morning, when you treat the depression, you often  
11 -- it has been documented in trials, that some of the  
12 people with so-called personality disorders even  
13 diagnosed by structured interview, studied 12 to 14  
14 weeks later when not depressed, no longer meet those  
15 criteria for that personality disorder.

16 So we know from the work of Akiskal and  
17 others that the personality disorder range is very  
18 high but also fluid, highly dependent on the state of  
19 depression.

20 And finally from the work of Klerman and  
21 Hirshfield back in the 80s and replicated by others  
22 since, I'm sure that you recall that the reliability

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1 of personality diagnoses in the midst of significant  
2 depressive symptomatology that lasts for a time is  
3 really not very high.

4 So that was the reason to elect not to  
5 attempt to diagnosis these personality disorders. So  
6 that's one.

7 Family history of mood disorders, if I  
8 recall, we reported and I want to say it's around 50  
9 percent in first degree relative, something like that.

10 It's significant, as you would expect, in this kind  
11 of condition.

12 And the others?

13 MEMBER ORTIZ: They talked about -- they  
14 asked about losses and substance abuse.

15 DR. RUSH: No, we had no codification of  
16 losses. Our assumption here was that the chronicity  
17 and/or recurrent nature required. The two years or  
18 greater in the current episode or the four more  
19 episodes in the lifetime would identify people with  
20 serious depression that would be long lasting and,  
21 therefore, require an implantable kind of  
22 intervention.

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1           And that people that were suffering  
2 depression from losses alone would have recovered from  
3 the losses in the typical time, at six months, as you  
4 know, with DSM, or they would have -- the loss would  
5 have triggered a major depressive episode that now  
6 would meet those criteria, that is two years or more,  
7 or they would have multiple episodes, typically not  
8 all triggered by losses, as you know.

9           So we didn't codify losses and we don't  
10 have that.

11           What was the last one?

12           MEMBER ORTIZ: Substance abuse was the  
13 other one.

14           DR. RUDOLPH: That was excluded --

15           DR. RUSH: Drug and alcohol was excluded.

16           DR. RUDOLPH: -- by the protocol.

17           MEMBER ORTIZ: Okay.

18           DR. RUSH: Six months, I think, six or  
19 twelve months, one year. Thank you. Twelve months  
20 exclusion.

21           MEMBER ORTIZ: Okay. Thank you.

22           DR. RUDOLPH: It might be worth mentioning

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1 that these typically aren't measured in antidepressant  
2 drug trials either.

3 DR. RUSH: No, but often drug and alcohol  
4 is excluded.

5 DR. RUDOLPH: Yes, that's true. Usually I  
6 would say.

7 CHAIRPERSON BECKER: Dr. Malone?

8 MEMBER MALONE: I don't know how many  
9 questions I have but I have some general comments on  
10 design. But I don't know if it is appropriate to make  
11 them now.

12 CHAIRPERSON BECKER: Sure, go ahead.

13 MEMBER MALONE: I come from the  
14 psychopharm advisory committee, so we're used to  
15 looking at drug trials.

16 And in many ways, I think the same  
17 criteria should be used for judging this data because  
18 it is a treatment for a psychiatric disorder. So it's  
19 the kind of disorder we're usually used to looking at.

20 And most psychiatric -- and depression,  
21 like most psychiatric disorders, has spontaneous  
22 remissions, variable treatment responses, variable

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