

1 depressed. So as you improve, your scores go down on  
2 the scales.

3 Here are some examples. I'll just provide  
4 some further detail on the Hamilton rating scale for  
5 depression. On the lefthand side of the slide, you  
6 see the various domains that are assessed by the  
7 scale: Mood, feelings of guilt, suicide, sleep, work,  
8 activities, psychomotor retardation and agitation,  
9 anxiety, somatic symptoms and weight loss.

10 A sample item from the scale is up here,  
11 and a clinical interpretation, and this is only a  
12 rough clinical guideline. This is not standardized  
13 through research, but here is a rough clinical  
14 interpretation of how you interpret the total scores  
15 and equate it to how severely ill the patient is.

16 Here is a similar representation for the  
17 Inventory of Depressive Symptomatology Self-report.  
18 It assesses some of the same symptoms and some  
19 symptoms not assessed by the Hamilton scale. Here is  
20 a sample item, and here is the clinical interpretation  
21 of the total scores.

22 One thing to note as I start to show the

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1 effectiveness results from the VNS studies is you will  
2 find that the baseline scores for the patients entered  
3 in our trial fall -- as a mean fall into the severe  
4 range on both scales.

5 Broadly speaking, the types of analyses  
6 that you will be seeing fall into two categories,  
7 either continuous measures or categorical outcomes  
8 analyses. The continuous outcomes analyses measure --  
9 Probably the most prominent we used was a repeated  
10 measures linea regression. These continuous measures  
11 generally measure a change from baseline.

12 The categorical outcomes measure discrete  
13 categories of outcome. Commonly, these include  
14 response. Response is generally defined in the field  
15 as a 50 percent or greater improvement on the multi-  
16 dimensional scales or on the CGI, the Licher type  
17 scale, response is defined as a one or two, which  
18 corresponds to a clinician rating of Very Much or Much  
19 Improved from baseline.

20 We also use categorical outcomes of  
21 complete response or sometimes called remission. This  
22 equates with a patient who is well or almost

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1 completely well, and those are defined by absolute  
2 cutoff scores on the scales.

3 Finally, because we were concerned with  
4 this particular population that these standard  
5 definitions might underestimate the true benefit for  
6 the patients, we also included a categorization of  
7 clinical benefit derived from the literature, which  
8 categorizes different levels of improvement from the  
9 Hamilton scale. I will be presenting data from this  
10 particular categorical outcome mostly in the form of  
11 looking at the durability of response for patients in  
12 the D-01 and D-02 studies.

13 Now, of course, with the multiplicity of  
14 scales, it is important to identify one single primary  
15 outcome, and this slide shows you the primary analyses  
16 that were prespecified in our various statistical  
17 plans for each of the important studies I will be  
18 talking about today.

19 In the D-02 acute study the primary  
20 analyses were response rates after 12 weeks of therapy  
21 determined from the Hamilton rating scale. So that is  
22 the 50 percent or greater improvement.

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1           For the D-02 long term study the primary  
2 analysis was the repeated measures linear regression  
3 analysis of the Hamilton scores over 12 months,  
4 estimating the change over time.

5           For the D-02 versus D-04 comparison, the  
6 primary analysis was a repeated measures linear  
7 regression analysis of the IDS scores over 12 months,  
8 estimating the monthly difference between the D-02 and  
9 D-04 patients, in other words a linear study effect.

10           You may be wondering why we had this  
11 transition through different scales and different  
12 types of analysis. So let me explain that up front.

13           When we had the opportunity to revise the  
14 statistical plan, which was necessitated by the  
15 finding in the acute study that there were trends and  
16 some positive findings on secondary outcomes, but the  
17 primary outcome failed to reach statistical  
18 significance, we then moved to a repeated measures  
19 rather than a categorical outcome, primarily because  
20 in prior communications with the FDA they had  
21 expressed some preference for that as an outcome, and  
22 also because it is a more sensitive measure for

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1 finding differences between treatment groups.

2 Then when we moved on to the D-02 and D-04  
3 comparison, having committed ourselves to the repeated  
4 measures linear regression approach, we were kind of  
5 forced into using the IDS as the primary scale,  
6 because the D-02 study only had a baseline and a 12-  
7 month measurement on the Hamilton, and the repeated  
8 measures approach requires multiple observations over  
9 time, which were present for the IDS but not for the  
10 Hamilton. Therefore, we chose the IDS for those  
11 particular set of analyses or at least for the primary  
12 analysis.

13 So with that as background, let me move on  
14 to a review of the primary data that supports an  
15 effectiveness claim for VNS for the TRD indication. I  
16 am going to start with the most important evidence.  
17 That comes from a comparison of the D-02 results  
18 versus the D-04 results over 12 months of treatment.

19 Let's start by looking at the flow of the  
20 D-02 study participants through the long term phase.  
21 You will recall that I said 235 patients were  
22 initially implanted in the D-02 acute study; 233 of

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1 those patients continued into the long term phase and  
2 constitute our long term safety population.

3 Our statistical plan prespecified that  
4 analyses would be done primarily using an evaluable  
5 efficacy subset of patients, and that included 205 of  
6 those 233 patients. The reason for excluding 28  
7 patients are shown in the middle box here on the  
8 slide.

9 The majority of those patients are: 21  
10 were patients in the sham control group that were  
11 excluded, because after the sham period, their  
12 Hamilton score was no longer above 18, which was a  
13 prespecified criteria.

14 Now I would like to point out -- I know in  
15 the FDA review material that you received, there was a  
16 mention that 20 percent of the patients had a placebo  
17 effect, and I want to distinguish that from a placebo  
18 response, that it was an effect based on patients  
19 falling below 18, but that should not be confused with  
20 a placebo response which would require the definition  
21 that a patient improve 50 percent or more. In fact,  
22 only 10 percent of the patients improved to the extent

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1 that they could be called a placebo responder.

2 The other seven patients were excluded  
3 from the treatment group, and they were excluded  
4 either because they didn't have long term data or  
5 because three did not meet acute phase continuation  
6 criteria that were also prespecified in the  
7 statistical plan.

8 For the D-04 study there were 127 patients  
9 that were enrolled. Three were excluded from the  
10 evaluable efficacy analyses for the reasons shown on  
11 this slide.

12 When we analyzed the patients for their  
13 baseline characteristics, we found that they were  
14 quite comparable. This is just one of several slides.

15 All told, we analyzed about 20 different baseline  
16 characteristics. Only three of them were  
17 statistically different between the two groups, and  
18 those are shown on this slide in yellow highlighting,  
19 along with some of the additional 19 characteristics  
20 which I thought would be of most interest to the Panel  
21 members.

22 So let's start with the ones that were

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1 statistically different. The first one was ethnic  
2 distribution. There was a higher percentage of  
3 Caucasians in the D-02 group, but this is probably  
4 clinically irrelevant, since as you can see in both  
5 groups, they were at least 90 percent Caucasian.

6 The second difference was in the number of  
7 lifetime episodes of depression. The D-04 group had a  
8 higher proportion of patients in the category of more  
9 than 10 lifetime episodes.

10 Then the third area of difference was in  
11 the percentage of patients that had had exposure to  
12 ECT, and both in the current episode and lifetime  
13 there was a higher percentage of patients with ECT  
14 exposure in the D-02 group.

15 So one take-home message from this slide  
16 and the other information I have given you is that  
17 these patients are very comparable at baseline. Also  
18 a take-home point from this slide is some indication  
19 of just how extraordinarily severely ill and treatment  
20 resistant these patients are.

21 For instance, you can see in terms of the  
22 average duration of illness over the lifetime and in

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1 the current episode, these are very lengthy illnesses.

2 Patients as a mean had been sick for at least 25  
3 years in their lifetime, and at least four years in  
4 the current episode. In fact, fully two-thirds of the  
5 patients were actually in a chronic major depressive  
6 episode, defined as an episode lasting continuously  
7 two or more years.

8 The primary analysis for comparing the D-  
9 02 and D-04 outcomes was a repeated measures linear  
10 regression of the IDS scores. That is illustrated on  
11 this slide. Now for point of clarity, I should say  
12 that the actual graph is drawn from actual raw scores  
13 and not from the repeated measures model. I did that  
14 for the sake of presentation clarity, but the  
15 statistical comparison comes from the primary repeated  
16 measures model.

17 What you will note is the D-04 patients  
18 shown in the light blue dotted line improved very  
19 little during the course of 12 months of treatment  
20 with access to every accepted therapy, every legal  
21 therapy, and a lot of churning through therapies.

22 By contrast, the patients in the D-02

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1 group receiving adjunctive VNS, shown in the solid  
2 burnt orange color, improved to a greater degree.  
3 That improvement increases. That is the difference  
4 between not only the absolute improvement but also the  
5 difference between the two groups improves as time  
6 marches on through the year, and the comparison is  
7 highly statistically significant with a p-value of  
8 less than 0.001.

9 We did a series of alternate methodologic  
10 approaches to the data to test the robustness of the  
11 data. These included doing the primary analysis on  
12 the intent to treat population rather than this  
13 efficacy evaluable population. So all patients were  
14 included in this analysis, all 235 D-02 patients, all  
15 127 D-04 patients, and that analysis retained  
16 statistical significance at the less than 0.001 level.

17 We also did an analysis where we looked at  
18 just the overlapping sites, so just the common sites  
19 to both D-02 and D-04, patients from those sites.  
20 Again, statistical significance was retained, in this  
21 case at a level of 0.002.

22 The results from the primary analysis were

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1 confirmed by a variety of secondary analyses. Here we  
2 are looking at the secondary analysis that examines  
3 the change in Hamilton scores from baseline to 12  
4 months. Remember, we just had a baseline in the 12  
5 month scores available on the Hamilton.

6 What one observes is that in the D-02  
7 group there is about an eight-point decrease in the  
8 Hamilton score over the course of a year. Again,  
9 decreases signify improvement, versus about a five-  
10 point improvement in the D-04 patients. That result  
11 is statistically significant.

12 On a variety of secondary outcomes looking  
13 at response rates and complete response or remission  
14 rates, we find the following. Results from the IDS  
15 scale are shown here, from the Hamilton scale here.  
16 First we look at response, and then we look at  
17 complete response.

18 So response based on the IDS scale was 22  
19 percent for the D-02 group and 12 percent for the D-04  
20 group. Complete response was 15 versus 4 percent. on  
21 the Hamilton scale, the response in the treated group  
22 with adjunctive VNS was 30 percent. For the D-04

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1 group it was 13 percent. In terms of complete  
2 response it was 17 versus 7 percent. All these  
3 comparisons are statistically significant.

4 One more, using the Clinical Global  
5 Impressions as a measure of response where a 1 or 2  
6 corresponding to a clinician rating of Much or Very  
7 Much Improved equates with response, we found almost a  
8 threefold difference between the groups, with 37  
9 percent of the D-02 patients and only 12 percent of  
10 the D-04 patients reaching the response criteria, a  
11 result that was statistically significant at a robust  
12 level.

13 So in summary for this section of slides,  
14 what we found were comparable, highly treatment  
15 resistant groups at baseline, a statistically  
16 significant result favoring adjunctive VNS therapy on  
17 the primary analysis, statistical significance in both  
18 evaluable efficacy analyses and ITT analyses, and  
19 statistical significance retained in the subset of  
20 patients that come only from the overlapping sites  
21 enrolling both D-02 and D-04 patients, and we found  
22 that statistically and clinically significant

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1 differences were confirmed by secondary analyses using  
2 multiple outcome measures, the categorical outcomes  
3 being a more appropriate way to assess clinical  
4 outcome.

5 Now because our control was a  
6 nonrandomized one, we were very concerned about  
7 potential sources of bias or other explanations for  
8 the outcome other than the VNS was contributing to the  
9 better improvement in the D-02 patients. This slide  
10 in a picture way tries to give you what we were most  
11 concerned about.

12 We were certainly concerned about the  
13 influence of baseline differences on patients, the  
14 influence of medications and electroconvulsive  
15 therapy, and I am going to deal with those three right  
16 now and show you why those are not the explanations  
17 for why the D-02 patients are getting better, and then  
18 i am going to address the issue of placebo response a  
19 little later in my presentation.

20 So let's start with baseline  
21 characteristics. Baseline characteristics do not  
22 explain why the D-02 patients are doing better. Why

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1 is that? Well, first of all, there were few  
2 significant differences between the D-02 and D-04 on  
3 baseline characteristics, as I have already  
4 demonstrated. However, we did take an additional  
5 measure that was prespecified in our statistical plan.

6 That was to incorporate a propensity  
7 adjustment strategy to provide additional insurance  
8 that potential bias associated with the imbalance of  
9 measured baseline covariates was removed. For  
10 nonstatisticians, such as me, let me try to give you a  
11 one-slide lesson on what propensity is all about,  
12 because it may be a new concept for some of you.

13 It is a technique that is particularly  
14 suitable for adjusting nonrandom treatment assignment.

15 So it is particularly suitable for this comparison  
16 with the D-04 group.

17 In this particular strategy, you calculate  
18 a propensity score, and that score represents a  
19 conditional probability of assignment to a group,  
20 given a set of measured covariates. So it is a way of  
21 encompassing a whole large variety of different  
22 characteristics in a single score.

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1           The way we used it was to incorporate it  
2 in all analyses of effectiveness and, when we did so,  
3 we found that the propensity score did not contribute  
4 to the primary repeated measures analysis' statistical  
5 significance.

6           Now the limitation of propensity analysis  
7 is that it can only address measured covariates or  
8 measured characteristics. It cannot address those  
9 that are unmeasured. We do not think, however, that  
10 unmeasured covariates are likely to account for the  
11 differences either, and the reasons for that are that,  
12 first of all, all or nearly all of the covariates that  
13 have a well established literature behind them were  
14 things that we measured and accounted for.

15           Furthermore, we think that, to the extent  
16 unmeasured covariates might be present, they are very  
17 likely to be equally distributed between the D-02 and  
18 D-04 groups, because the sample sizes for both D-02  
19 and D-04 are quite large or, if they are not equally  
20 distributed, that would probably be because they are  
21 so rare that they would be unimportant in terms of  
22 affecting outcome.

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1           The second issue that I would like to  
2 address is the influence of medications and  
3 electroconvulsive therapy. Obviously, this was a  
4 major consideration for us, because the way the trials  
5 were set up is patients in both groups could have  
6 access to virtually every therapy that was legally  
7 marketed.

8           That raises the question of whether, in  
9 the end, in fact, the treatment that the patients  
10 received as adjunctive treatment for the D-02 and the  
11 standard of care treatment for D-04 are indeed  
12 comparable.

13           So we have done a number of analysis to  
14 address that issue. The first thing we did was simply  
15 to look at the use of new treatments during the 12-  
16 month outcome. That is, the addition of a new  
17 medication or significant increase in an existing  
18 medication, based on those ATHF criteria.

19           What we found was that, among D-02  
20 responders, 56 percent of the patients added or  
21 increased a medication during the 12 months. In  
22 contrast, 77 percent of the nonresponders and 81

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1 percent of the D-04 responders did so, differences  
2 both of which were statistically different from the D-  
3 02 responders.

4 So this is highly suggestive that the  
5 benefit the D-02 responders are deriving is coming  
6 from VNS, because they are actually using less  
7 medication as time goes on.

8 That wasn't enough for us, however. We  
9 wanted to address this even further. So we undertook  
10 a series of censored analyses which we felt would be a  
11 rather conservative way to address this potential area  
12 of bias.

13 The censored analysis that I will be  
14 sharing with you this morning was the most  
15 conservative of a set that we did. In this analysis  
16 the D-02 patient scores are censored at the first  
17 significant increase or addition of an antidepressant  
18 medication.

19 At that point, what we do is drag forward  
20 the last score prior to censoring for those patients  
21 into the subsequent observation periods used in the  
22 repeated measures in your regression analysis of its

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1 scores.

2 This has the effect of truncating the VNS  
3 benefit. So it is somewhat unfair to the VNS. Even  
4 in the absence of medication, it is unfair to the VNS  
5 group, because it truncates any ongoing or increasing  
6 benefit they might obtain from VNS to, in this case,  
7 an average of seven months out of the 12 months of  
8 treatment.

9 At the same time, the D-04 patient scores  
10 are uncensored. They get the benefit of the full 12  
11 months of treatment with unlimited treatment changes.

12 This slide shows you the results from that  
13 censored analysis. First of all, in the blue line  
14 were the results we saw before on an earlier slide for  
15 the D-04 patients on the repeated measures linear  
16 regression analysis of its scores. The bottom burnt  
17 orange line are the scores or the line that we saw  
18 before for the D-02 patients uncensored.

19 The censored line for the D-02 patients is  
20 shown in the line in the middle in the yellow color.  
21 So not surprisingly, once censored, the D-02 scores  
22 aren't as good, and yet there still is a good amount

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1 of change.

2 You can see as a change per month from  
3 baseline, uncensored is here, and for the D-02  
4 censored scores it is still a good amount of change,  
5 and as a change from baseline both are statistically  
6 significant.

7 More importantly, if we look at the  
8 average difference per month versus the D-04 groups,  
9 here are the uncensored values that we looked at  
10 before. The average change per month on the IDS was a  
11 difference of .397 which, as we saw, was statistically  
12 significant.

13 Censored, actually somewhat to our  
14 surprise because we didn't expect this in this  
15 sensitivity analysis, didn't reach statistical  
16 significance, but it came awfully close at .052.

17 So we conclude that differences in  
18 outcomes between the D-02 and D-04 patients are not  
19 attributable to baseline characteristics. In fact,  
20 the results were the same with and without propensity  
21 adjustment, nor are they attributable to concomitant  
22 antidepressant medication or ECT, and I should mention

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1 that in the censored analysis medication changes  
2 always preceded an attempt at ECT. So they are  
3 accounted for in the censored analysis.

4 So the differences in outcomes between the  
5 two groups are also not attributed to concomitant  
6 antidepressant medication or ECT. The D-02 responders  
7 had fewer medication changes, and the D-02 patients,  
8 even censored for concomitant treatment changes, still  
9 improved more than the D-04 patients, uncensored, but  
10 didn't quite reach statistical significance.

11 Additional evidence for the effectiveness  
12 of VNS therapy comes from a number of datasets  
13 indicated on this slide. First, let me talk about the  
14 findings from the D-02 acute study. That was the  
15 randomized control of VNS versus sham treatment. The  
16 primary outcome measure was a response on the  
17 Hamilton. That is a 50 percent improvement.

18 There was a numerical trend for the  
19 treated group shown in orange to be better than the  
20 sham group of 15 versus 10 percent. This numerical  
21 trend held up through all the analyses, but it rarely  
22 reached statistical significance.

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1           It did not reach statistical significance  
2 on the primary outcome. It did occasionally reach  
3 statistical significance on secondary outcomes such as  
4 the response from the IDS where the slightly larger  
5 differential of 17 versus 8 percent in response rates  
6 was statistically significant.

7           In the long term, you won't be surprised  
8 if I tell you on the repeated measures of the Hamilton  
9 scores compared to baseline, that was statistically  
10 significant. Here I have chosen to display the longer  
11 term results in terms of the categorical outcomes.  
12 What you will note is that, regardless of what scale  
13 is used, whether the IDS, the Hamilton scale or  
14 Montgomery Asberg scale, there is an accruing response  
15 over time as the patients continue from three months  
16 out to one year.

17           AS I indicated before, for these very  
18 treatment resistant patients these traditional  
19 research definitions may understate the true benefit  
20 to the patient. That is consistent with other very  
21 chronic and intransigent disorders such as obsessive  
22 compulsive disorder or schizophrenia. We sometimes

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1 accept a lower threshold for response. So we did use  
2 the clinical benefit categories that I showed you on  
3 an earlier study.

4 If you do that, in addition to the 30  
5 percent of patients that were responders based on the  
6 Hamilton scale using the traditional research  
7 definition, you can pick up maybe another 25 percent  
8 of patients that fall into this category of a 25 to 49  
9 percent improvement in the Hamilton, which could be  
10 meaningful in terms of producing some significant  
11 benefit for the patient, even in terms of functional  
12 outcomes.

13 So all told, when you add all those  
14 categories together, maybe up to slightly more than  
15 half of the patients do achieve some at least  
16 meaningful benefit during 12 months of VNS therapy.

17 Now, of course, those types of analyses,  
18 particularly when you are going from three to 12  
19 months, do beg the question of which are those  
20 patients in 12 months? Are they the same patients at  
21 three months, and you are just adding more patients to  
22 it or is it a total different group of patients?

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1            Obviously, what we would most like to see  
2            is that we are adding patients, and the patients that  
3            do benefit initially continue to benefit. This is a  
4            very important point with VNS therapy, as you have  
5            already probably come to appreciate from Dr. Rush's  
6            presentation and from hearing from some of the  
7            patients.

8            In this TRD population it is very unlikely  
9            that patients are going to respond, but even more  
10            stunning it is extremely unlikely that, once having  
11            responded, they are going to retain it. So while not  
12            controlled, I think these are some of the most  
13            persuasive data as to VNS's long term effectiveness.

14            So for instance, using the categories on  
15            the previous slide we found at the end of three months  
16            in the D-02 study there were 56 patients that fell  
17            into the extraordinary, highly meaningful or what was  
18            labeled meaningful clinical benefit, those patients  
19            that had at least a 25 percent improvement on the  
20            Hamilton score.

21            So after an additional nine months of  
22            therapy, what happens to those patients? Well, 41 of

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1 those patients continue to be maintained in one of  
2 these categories, and only 15 patients fall out of  
3 that category. So 73 percent of the patients all told  
4 maintained at least a meaningful clinical benefit from  
5 three to 12 months with continued adjunctive VNS  
6 therapy.

7 We can use these same type of analyses,  
8 which we refer to as SHIF tables, and this is just a  
9 pictorial form of that, to ask what happens to the  
10 patients that don't benefit after three months. You  
11 already heard from the patients that in some cases it  
12 takes a long time to derive benefit, and that is  
13 illustrated here.

14 There were 118 patients that after three  
15 months did not fall into those more desirable  
16 categories of extraordinary, highly meaningful or  
17 meaningful clinical benefit, and after an additional  
18 nine months of therapy 56 of the 118, or nearly half,  
19 did transition into at least the meaningful category  
20 of clinical benefit.

21 So there is some value-- There appears to  
22 be some value in continuing VNS therapy even beyond

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1 three months in patients that don't initially respond.

2 Then finally for the effectiveness data, I  
3 want to end with results from the D-01 feasibility  
4 study, so we don't shortchange that. The primary  
5 outcome identified in that protocol was response rate  
6 on the Hamilton.

7 After three months of therapy you see that  
8 31 percent of the patients were responders, Fifteen  
9 percent were in complete response, and at the 12 month  
10 point 45 percent of the D-01 patients were responders,  
11 and 27 percent were complete responders.

12 Again, we can do that type of SHIF table  
13 analysis, and here are the results for the D-01 study,  
14 again using the same categories of clinical benefit.  
15 There were 30 patients after three months that were in  
16 those desirable categories, and after an additional  
17 nine months of therapy 23 of those 30 patients  
18 maintained at least a meaningful clinical benefit, and  
19 that was 77 percent of the patients.

20 I promised before that I would address the  
21 issue of placebo response. For those of you that are  
22 very familiar with depression studies, you know this

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1 is a major issue in doing clinical trials in drugs, at  
2 least with the more common type of depression.  
3 Hopefully, you are already getting an appreciation  
4 that it is not as much of an issue with treatment  
5 resistant depression, and I will show you why.

6 There are a number of reasons why  
7 improvements in the D-02 patients are not readily  
8 attributable to a placebo effect. First of all, I  
9 personally think the most persuasive is that we did  
10 show statistically significant differences in the D-  
11 02-D-04 comparison where we are actually comparing two  
12 active treatment regimens.

13 Moreover, just some general considerations  
14 lead us down the road that placebo response is a very  
15 unlikely explanation for the D-02 patients' outcomes.

16 First of all, published literature tells us that  
17 placebo response rate in this treatment resistant  
18 group, unlike more common depression, is very low and  
19 the numbers that are cited in the literature are  
20 generally between zero and ten percent.

21 I think more compelling is that placebo  
22 response by nature is not usually sustained for 12

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1 months, even in more common depression. There is a  
2 good literature now characterizing the pattern of  
3 placebo response, and what that literature tells us is  
4 that placebo response tends to occur early and is not  
5 persistent or sustained.

6 Then, too, consider that as you saw in  
7 some of the data that Dr. Rush presented, even in  
8 active treatment maintenance of patients -- and he  
9 showed you data from the ECT responders. Even when  
10 those patients are not on placebo but in active  
11 treatment, their maintenance of response is very poor,  
12 and this is another view of data that Dr. Rush showed  
13 you earlier, just a simpler presentation using bars  
14 rather than survival analysis curves.

15 Again, to remind you of the findings,  
16 following successful ECTs -- these are all ECT  
17 responders -- and then following patients in Dr.  
18 Sackheim's study out to one year in a naturalistic  
19 setting, 68 percent of the patients who had a prior  
20 history of medication resistance, and that could be as  
21 little as resistance to one drug -- 68 percent of  
22 those patients relapsed over the year, which was twice

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1 as high as the relapse rate in patients without an  
2 adequate medication trial prior to ECT.

3 We used those observations to do one  
4 exploratory analysis that I would like to share with  
5 you. There is no statistical values here, because it  
6 was just an exploratory analysis, and we didn't do  
7 statistical testing. But we asked ourselves what  
8 would happen if we just looked at the chronic subset  
9 of patients from D-02 and D-04?

10 Remember, two-thirds of the patients were  
11 in a chronic episode, and that is defined as a  
12 continuous episode of two or more years. These are  
13 the patients you would expect are the least likely to  
14 be subject to some type of placebo response. So we  
15 wanted to see if their overall response was similar to  
16 the total group.

17 That is indeed what we found. Here you  
18 see the overall response on the Hamilton scale was 29  
19 percent for this group and 10 percent for the D-04  
20 group, and complete response was 14 versus 3 percent.

21 So percentages very similar to the overall group.

22 So in summary for this section, we found

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1 consistent numerical advantages for acute VNS therapy  
2 over sham control. Although it didn't reach  
3 statistical significance on the primary outcome, it  
4 was statistically significant on a few of the  
5 secondary outcomes. So it lends at least supporting  
6 evidence for VNS's effectiveness.

7 We saw increasing improvement of  
8 responders and complete responders over time, and  
9 probably most importantly, we saw improvements during  
10 adjunctive VNS therapy that were sustained at a high  
11 rate.

12 By contrast, placebo response in  
13 depression studies or depression in general tends to  
14 occur early and is not sustained. And even in  
15 medication resistant ECT responders, relapse is very  
16 high, even during active continuation therapy.

17 Next I would like to provide a very quick  
18 summary of the safety data that was in our  
19 application. Our safety database consisted of a pool  
20 of patients from the D-01, D-02 and D-03 groups or  
21 studies. That encompassed 342 patients and, I think,  
22 importantly, 689 total patient years of exposure.

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1           The common adverse events that were  
2 obtained in the depression studies are similar to what  
3 we experienced in the epilepsy studies and epilepsy  
4 clinical use. They are listed here on this slide as  
5 defined by those events that occurred at least at a  
6 five percent incidence during acute treatment in the  
7 D-02 group and at a rate at least one and a half times  
8 that in the sham control, a sort of convention that  
9 helps sort out treatment related side effects from  
10 those that aren't treatment related.

11           The most common side effect that we  
12 observed was voice alteration in 68 percent of the  
13 therapy group, and the other very common effects,  
14 cough increase, shortness of breath, and swallowing  
15 difficulties, as well as some discomfort at the site  
16 of stimulation, whether that is pain or peresthesias,  
17 are all commonly known to occur with VNS therapy when  
18 it is used for the treatment of epilepsy.

19           These different side effects are generally  
20 mild to moderate, and most often, particularly the  
21 ones on the top of the list, are effects that only  
22 occur when the stimulator is actually on. So they may

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1 only be experienced by the patient during the 30  
2 seconds that the stimulator is typically on, and then  
3 they don't experience them for the five minutes that  
4 it is off.

5 Also, the events tend to decrease over  
6 time, or at least the reporting of the events decrease  
7 over time, as illustrated by this analysis. Here we  
8 are looking at a cohort of patients that report these  
9 more frequent adverse events during the first three  
10 months of therapy, and then have continuous  
11 observations over 12 months of therapy so we can track  
12 the persistence of disappearance of that event over 12  
13 months.

14 So for example, if we just look at the  
15 first one here, cough increase, what we found was that  
16 there were 55 patients -- you probably can't see the  
17 numbers too well, but there were 55 patients that  
18 reported this particular adverse event in the D-02  
19 study during the first three months of stimulation,  
20 and then over the course of the next nine months their  
21 reporting of that side effect decreases, so that by  
22 the period nine to 12 months only 11 of the original

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1 55 patients are still reporting that adverse event.

2 You see a similar pattern throughout all  
3 these common side effects, although some decrease to a  
4 lesser extent than others, like there still is a fair  
5 degree of persistence on the voice alteration. Not  
6 too surprising, since it is a direct effect of  
7 stimulating the vagus nerve.

8 Overall, I think very importantly, these  
9 adverse events are very well tolerated, and that is as  
10 evidence by this slide. Here we are looking at  
11 adverse event related discontinuation rates from the  
12 D-01 and D-02 studies at the time of our data cutoff  
13 for the submission.

14 That encompassed at least two years of  
15 experience for all the D-01 patients and at least one  
16 year for the D-02 patients. You will observe that  
17 only three percent in each of those two studies had  
18 discontinued during that time period specifically  
19 related to an adverse event.

20 This, I think, compares very favorably  
21 with what you see in typical drug trials where maybe  
22 10 or even more than 10 percent of patients will

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1       discontinue for adverse events even over a short term  
2       trial lasting eight to 12 weeks.

3                 In our review of safety, we were  
4       particularly focused on some issues that might be  
5       specific to depressed patients or the disorder of  
6       depression, and the one that we were most focused on  
7       was suicide.

8                 Now probably all the Panel members are  
9       very sensitive to this, because there has been a lot  
10       in the public press recently about concerns that  
11       antidepressant drugs may very rarely provoke suicidal  
12       type thinking in patients, particularly pediatric  
13       patients, which has been the recent focus.

14                So we looked at this very carefully.  
15       First, here is the results for the pool of the D-01,  
16       02 and 03 studies, 342 patients. We have the  
17       incidence of suicide attempts per patient year here.  
18       That works out to 3.5 percent, and actual suicide 0.4  
19       percent.

20                The first thing we did was compare that to  
21       published literature. There is a nice review by Khan  
22       and Co-Workers. It is a very large review, as you can

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1 see. It encompasses almost 20,000 patients. Those  
2 patients are derived from the FDA summary bases of  
3 approval for seven different antidepressant drugs.

4 What Khan and Co-Workers found in a less  
5 treatment resistant group was suicide attempt rates of  
6 2.9 percent, and actual suicide of 0.8 percent per  
7 patient year in the combined active treatment groups,  
8 and here are data also for the placebo group.

9 So we think the rates for the VNS group  
10 compare quite favorably with this. We also had the  
11 ability to look specifically at suicide ideation in  
12 the form of the third item of the Hamilton scale,  
13 which measures suicidal ideation.

14 What we were able to do here is use a  
15 standard definition that the pharmaceutical  
16 manufacturers or sponsors use, which is to look for  
17 the percentage of patients that have a two-point  
18 increase from baseline in their third score on the  
19 Hamilton.

20 We compared the experience in the VNS  
21 group to two control groups. First, in the acute D-02  
22 trial, we compared the VNS group with the sham control

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1 group, and you can see similar rates. Two percent of  
2 the actively treated VNS patient and three percent of  
3 the sham treated patients had these two-point  
4 increases.

5 Then for more long term exposure we were  
6 able to compare the D-02 long term experience at 12  
7 months with the D-04 experience at 12 months when we  
8 did have that Hamilton rating. Again you see similar  
9 rates, three and two percent respectively.

10 We should not forget that VNS therapy has  
11 been on the market for seven years. We have  
12 accumulated a lot of safety data from the epilepsy  
13 experience, most of which, obviously, is directly  
14 relevant to the depression experience also.

15 As you heard earlier, we now have more  
16 than 22,000 implanted patients and over 56,000 patient  
17 years of experience. In that experience, we found the  
18 VNS implant procedure to be a relatively low risk  
19 procedure.

20 The most important and common adverse  
21 associated with the procedure itself are infection  
22 necessitating explant in about one percent of

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1 patients, nerve damage in about less than half a  
2 percent of patients, either in the form of damage to  
3 the vagus nerve or the facial nerve, and a phenomenon  
4 of transient asystole in the operating room when the  
5 device is first turned on for testing that occurs in  
6 somewhere between one and two patients in 1,000.

7 As with the depression data, most of the  
8 adverse events in the epilepsy clinical experience and  
9 the clinical trials has proved -- most of the adverse  
10 events have proved to be minor and stimulation  
11 related.

12 There are few serious simulation related  
13 events associated with VNS therapy, and patients -- As  
14 a measure of how well tolerated the therapy is,  
15 patients in our pool of epilepsy trials continued  
16 therapy at a very high rate, about 72 percent after  
17 three years.

18 So in summary, our safety data from the  
19 depression studies has shown us that adverse events  
20 are mainly stimulation related and not troublesome.  
21 There is a low rate of treatment related  
22 discontinuation.

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1           There is no signal for treatment related  
2 emergence of suicidal ideation or behavior and,  
3 obviously, we have to hasten to acknowledge that this  
4 is at best a very rare event. So the ability of our  
5 dataset to actually detect such a signal would be  
6 rather limited, but at least what we can say is, based  
7 on the data that we have looked at, there is no signal  
8 for emergent suicidal ideation or behavior.

9           Also data that I didn't show you this  
10 morning, another potential adverse event peculiar or  
11 specific to depression that we looked at was the rate  
12 of emergent mania or hypomania.

13           About ten percent of the patients in the  
14 D-02 and D-04 studies were bipolar patients, and in  
15 this group you do worry about the emergence of mania,  
16 which can be a side effect either of treatment, and in  
17 fact, it is taken by most clinicians to be a sign they  
18 have an effective treatment, or it can be due to the  
19 underlying disease.

20           So we looked at that one carefully, too,  
21 and we found that the incidence of emergent mania or  
22 hypomania was in the range that you would expect for

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1 an effective antidepressant. We have data we can show  
2 you later, if you are more interested in that.

3 So overall, VNS therapy was very well  
4 tolerated and safe in our clinical trials.

5 There are also some unique benefits for  
6 VNS therapy, as it is a unique approach to treating  
7 depression. So from this device based approach, some  
8 benefits that you wouldn't get from drugs and, in some  
9 cases, from ECT.

10 For example, Mr. Totah alluded to early in  
11 his presentation that patients can acutely disable the  
12 device if necessary, to temporarily stop side effects.

13 That is a unique advantage of this therapy.

14 Also, published data that I didn't present  
15 this morning shows that there is an absence of  
16 cognitive and psychomotor effects with VNS, and as you  
17 have already heard, cognitive and psychomotor effects  
18 can be a significant problem with drugs and especially  
19 electroconvulsive therapy.

20 Of course, as a device based approach,  
21 there is an absence of overdose toxicity, which is a  
22 major problem with antidepressant drugs.

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1 Additionally, since it is not a drug therapy, you have  
2 the ability to add VNS therapy to other drugs without  
3 a concern for a drug-drug interaction.

4 Not to be overlooked, because VNS doesn't  
5 require active participation by the patient in the  
6 form of taking a pill every day, treatment compliance  
7 is obviously high with this particular therapy. And  
8 as you are all aware of, treatment compliance is a  
9 major, major problem with all chronic disorders, but  
10 particularly psychiatric disorders.

11 So a lot of patients never get their  
12 prescriptions filled. if they get them filled, they  
13 don't take them. If they take their pills, they don't  
14 take all of them. So this alone, I think, is a  
15 significant benefit for VNS therapy.

16 In conclusion, data that I have shown you  
17 this morning shows us that VNS effects on brain  
18 structures and neurotransmitters associated with mood  
19 regulation provide a biological rationale for the use  
20 of VNS therapy in treatment resistant depression.

21 Adjunctive long term VNS therapy was more  
22 effective than a standard of care treatment alone, and

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1 the p-value for that was less than 0.001 in the  
2 primary analysis.

3 The differences versus standard of care  
4 are not explained by differences in the baseline  
5 patient or disease characteristics, concomitant  
6 treatments or a placebo effect.

7 The improvements observed with adjunctive  
8 VNS therapy are largely sustained during long term  
9 treatment. VNS therapy is well tolerated and safe in  
10 depression clinical trials and clinical use in  
11 epilepsy, and finally, VNS therapy has additional  
12 device related benefits versus standard of care.

13 At this point I would like to invite Dr.  
14 Rush to come back up and just give a few closing  
15 remarks, and we will try to put these clinical data  
16 into a clinical perspective.

17 DR. RUSH: Thank you, Richard. I will be  
18 very brief. You have had to listen to a long series  
19 of presentations.

20 I want to just address the data and the  
21 information from the point of view of a clinician. I  
22 have been doing clinical work for 30 years and trial

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1 work for the same period of time.

2 It is important to put into context again,  
3 as we tried to do at the beginning, to remind you who  
4 it is that we are talking about that we are treating.

5 These individuals, more than half had previously had  
6 ECT, and it had not produced a sustained benefit.  
7 Many had just not even had a response to it at all.

8 So these are really the most treatment  
9 resistant, the most difficult and disabled depressed  
10 patients that I have ever put into a trial anywhere  
11 and, as I mentioned earlier, half would not have --  
12 half of the ECT community sample would not be eligible  
13 for our study.

14 To give you a sense of how we recruited  
15 patients for this, it might give more of a clinical  
16 feel. At least in Dallas, we went out to the well  
17 known psychopharmacology masters, if you will, the  
18 people that do advanced, complex medication management  
19 where treatment resistant patients go.

20 We asked them each to give us two, your  
21 very two worst, most difficult depressed patients.  
22 That is how we recruited the patients. So these are

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1 really very, very difficult patients for whom we don't  
2 have an alternative.

3 The second question is: Are the clinical  
4 effects meaningful? I think, to gauge the value of  
5 the clinical effects, you have to keep in mind three  
6 things. One is the population itself.

7 This, as we have discussed, is a  
8 population where we really don't have much going, and  
9 especially in the long run. So if we can help one in  
10 four or one in five to actually achieve a response or  
11 better -- and notice that some of our responders  
12 actually hit remission, and some of the patients today  
13 are in remission -- that is a home run in a patient  
14 population where we just don't see it in the long run.

15 It just doesn't happen.

16 So given the severity of the illness and  
17 its treatment resistant nature, and the standard high  
18 threshold for benefit, 50 percent, we are looking at  
19 37 percent versus 12 percent using the CGI. So you are  
20 looking at a number needed to treat of 4 or a number  
21 needed to treat of 5, if you use the Hamilton.

22 Those are very significant benefits,

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1 especially when we are not looking at short term. We  
2 are looking at the end of the year, when we should, in  
3 fact, have lost territory, if you look at all the  
4 other treatments that we have.

5 We should have done better in the sort run  
6 and worse in the long run. In fact, we did not so  
7 great on the short run, but really terrifically with  
8 this population in the long run. That is the  
9 "Duracell bunny keeps on working" for most, not for  
10 everybody, as you saw from Dr. Rudolph's presentation,  
11 but for most people there is a benefit that largely is  
12 sustained at a year.

13 The good news is some people who aren't  
14 benefitted early seem to come up with a benefit later.

15 We have looked at that even over two years, and that  
16 seems to be a fact.

17 Could this really be a placebo? I think,  
18 looking at the population just per se, this is so  
19 unlikely it would be a miracle to have a placebo of  
20 this magnitude that works for this long and that  
21 consistently over time. It just would, I think, be  
22 looking at it as a clinician, very, very unlikely.

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1           Typically, placebos, when they work, work  
2 early. Well, we don't have as much early as we have  
3 later. So the timing is all wrong. Secondly, they  
4 wear off. Well, we seem to have an increasing benefit  
5 over time. That would be a very unique placebo.  
6 Finally, those that benefit seem to have a sustained  
7 benefit, by and large. That also is unique, would not  
8 be easily attributed to placebo.

9           Finally, the induction of hypomania:  
10 While it was an adverse event here, it was more  
11 common, as you heard, in bipolar disorder patients.  
12 We often look at that clinically in antidepressant  
13 trials as an indicator that we have antidepressant  
14 activity.

15           Then finally, we have the experiment in  
16 nature, not conducted in any of the D series, but  
17 several patients you heard who lost efficacy when  
18 their battery ran down and achieved a recapture when  
19 the battery was replaced. Not an experiment that we  
20 could have done early on, but one that is going on by  
21 nature.

22           Just to put a final face on it and a

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1 comment on public health significance. I'll be quiet.

2 I told you about this graduate student at the  
3 beginning. That individual entered the VNS study, and  
4 he did very well. Within about two months, he  
5 achieved remission. So this is unusual. It is one of  
6 the earlier responders.

7 He has stayed in remission now for five  
8 years. He finished his graduate school, got married,  
9 and has a child.

10 The other comment I want to make is about  
11 the category of response. We are very used to the 50  
12 percent, because it comes from the nontreatment  
13 resistant world. Some of the patients mentioned that  
14 any benefit to some degree is better than what we have  
15 now, and you saw Dr. Rudolph talk a little about the  
16 25 to 49 percent group, and I just want to give you  
17 one patient in this regard.

18 This is a lady who actually was not a  
19 responder, but she was a lady who was full time  
20 employed, in her mid-forties, married with two  
21 children, one just about to graduate from high school.

22 She had had depression, really, since her early

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1 twenties, largely on, sometimes off, and the last  
2 several years more time -- roughly an eight-year  
3 episode, last episode.

4 She had received 80 ECT treatments. She  
5 was in maintenance ECT. She was brought in by her  
6 husband who said, the ECT is really helping her; it's  
7 the only way we can keep her out of the hospital, but  
8 she is having these long term cognitive difficulties  
9 and I really -- I can't allow her to go on and she,  
10 too, is complaining of it.

11 So we gave her the VNS treatment. It took  
12 a while, probably about three to four months. We kept  
13 her medication. So it's past the end of -- Well, at  
14 the end of the study, in the three months where  
15 medications were fixed, she had a 48 percent reduction  
16 in her Hamilton.

17 Then we followed her out, medications  
18 largely fixed. We were very loathe to change  
19 medicine. She had been so fragile. She had been in  
20 and out of hospital many, many times in the prior  
21 several years. So we left her where we were, adjusted  
22 the parameters. She never hit response. She never

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1 hit a 50 percent reduction. She was always in the  
2 forties..

3 So she comes up as not a beneficiary in  
4 the classical definition. Good news is she had been  
5 fired from her job because she couldn't function as a  
6 computer program or information technology person  
7 about a year and a half before we started. She wasn't  
8 able to be rehired there. She worked for a large IT  
9 company, a famous name you know. But she started a  
10 business in her own home and was partially employed.

11 The most important thing she said was, I  
12 got to see my son graduate from high school. Excuse  
13 me. So even though we don't call them responders,  
14 there are a number of people that actually really do  
15 quite well with this. Not perfect, but a lot better  
16 than what they had.

17 Then finally, just let me make one comment  
18 about the public health perspective. I did these  
19 numbers, and I thought about it, and it's so shocking  
20 to me, I thought I would share it with you.

21 Thirty thousand people per year commit  
22 suicide. Eighty percent are due to depression. That

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1 is 24,000 people. Treatment resistant depression is  
2 known to be the most lethal form of depression. Let's  
3 say half of those individuals that commit suicide from  
4 depression have treatment resistant depression.  
5 That's 12,000 suicides a year. That is 1,000 suicides  
6 a month. That is one suicide every 45 minutes. That  
7 means we lost four of these individuals in the last  
8 two and a half hours due to treatment resistant  
9 depression.

10 This is not a panacea, obviously, but it  
11 is a high need and, if we can help one out of five of  
12 these people with this treatment, I think it would be  
13 a tremendous contribution. Thank you.

14 CHAIRPERSON BECKER: Thank you. I would  
15 like to thank the sponsor for their presentation.

16 Given the fact that we all have been  
17 sitting here for quite some period of time, I think  
18 maybe it is appropriate to take a break now and  
19 reconvene in 15 minutes, say at ten after eleven.  
20 Thank you.

21 (Whereupon, the foregoing matter went off  
22 the record at 10:56 a.m. and went back on the record

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1 at 11:14 a.m.)

2 CHAIRPERSON BECKER: If I could get  
3 everyone to take their seats, we'll get the meeting  
4 restarted. Alright, thank you. It's now 11:15 and  
5 we'll resume the meeting. And we'll start with the  
6 FDA presentations on this PMA. The first FDA  
7 presenter is Carlos L. Pena, Ph.D. Dr. Pena?

8 DR. PENA: Good morning panel members. My  
9 name is Carlos Pena, and I am here today from FDA to  
10 present to you the PMA application for the Vagus Nerve  
11 Stimulation Therapy System proposed to treatment of  
12 resistant depression. I'm accompanied by Dr.  
13 Schlosser, medical officer, who will be sharing with  
14 you safety data contained in the application, and Dr.  
15 Lao, statistical officer, who will be sharing with you  
16 statistical data contained in the application. And  
17 I'll be providing the regulatory history of the VNS  
18 Therapy System, an overview of VNS studies including  
19 efficacy data, and a closing summary.

20 The sponsor has described the VNS Therapy  
21 System in some detail, which includes an implantable  
22 pulse generator, lead, and external programming

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1 system. The sponsor seeks commercial approval for the  
2 injunctive long-term treatment of chronic or recurring  
3 depression for patients over the age of 18 who are  
4 experiencing a major depressive episode that has not  
5 had an adequate response to two or more antidepressant  
6 treatments. VNS has previously been approved for use  
7 as an injunctive therapy in reducing seizures in  
8 patients refractory to epileptic medications.

9           Regarding the mechanism of action, no  
10 definitive mechanism of action has been reported for  
11 the proposed indication for the injunctive long-term  
12 treatment of chronic or recurrent depression.

13           I will now discuss the regulatory history  
14 of the VNS Therapy System. Following FDA approval for  
15 epilepsy in 1997, anecdotal reports of mood alteration  
16 were noted for some epilepsy patients. And the  
17 sponsor conducted a 30-patient, later expanded to 60-  
18 patient, pilot study called D01. The pilot results  
19 led to the development of the D02 study. The D02  
20 pivotal study included an acute, randomized, placebo-  
21 controlled phase -- the only randomized placebo-  
22 controlled portion involving VNS studies discussed

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1 today -- as well as long-term follow-up. The sponsor  
2 un-blinded the acute phase of D02 in 2002, and found  
3 that the study failed to demonstrate a statistically  
4 significant difference between responders in the  
5 treatment arm and sham treatment control arm, the  
6 study's primary efficacy endpoint.

7           Despite the failed outcome, the sponsor  
8 claimed a pattern of increasing treatment effect over  
9 time, and suggested that the full antidepressant  
10 effect of VNS therapy might take longer. The sponsor  
11 proposed to use a non-significant risk study, D04, as  
12 a reference group for comparing to D02, long-term  
13 clinical data. And FDA advised the sponsor of the  
14 serious concerns regarding the ability of this  
15 comparison to demonstrate safety and effectiveness of  
16 their device due to lack of a randomized subject data  
17 set. The sponsor submitted their application in  
18 October of 2003.

19           In all, there are six studies that will be  
20 discussed today. During the first part of FDA's  
21 presentation I will focus on the first three studies,  
22 called D01:, the pilot study, D02: the pivotal study,

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1 and D04: the observation of control study. Other  
2 trials include D03 and D06, both of which will be  
3 discussed further by Dr. Schlosser, and D05, which was  
4 a videotape assessment of D02 study subjects only to  
5 ensure interrater reliability in assessments. Which  
6 takes us to a description of each study.

7 In the D01 pilot study, this study was an  
8 open label, non-randomized, single treatment arm,  
9 multi-center study. The primary efficacy endpoint was  
10 the proportion of subjects that responded to therapy,  
11 response defined as a 50 percent or more decrease  
12 reported as improvement in the HAM-D score at post-  
13 treatment compared with the baseline. The HAM-D, the  
14 Hamilton Rating Scale for Depression, is a clinician's  
15 tool to rate depression.

16 Out of a total of 71 subjects, 11  
17 discontinued prior to implantation, 60 were implanted,  
18 and 59 completed the acute phase. Across various  
19 times during the pilot study, several subjects had  
20 concomitant treatment changes. Six subjects had  
21 changes in concomitant treatments during the four  
22 weeks prior to their first visit post-implantation,

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1 twelve subjects had changes in concomitant treatments  
2 during the acute phase, and three subjects received  
3 ECTs during the long-term study, and a total of 77  
4 serious adverse events were reported. And Dr.  
5 Schlosser will discuss these events shortly.

6 At the acute phase exit, 18 of 59 patients  
7 were responders, 25 of 55 patients were responders at  
8 one year, and 18 of 42 patients were responders at two  
9 years. Response defined by a greater than 50 percent  
10 decrease in the HAM-D score compared with baseline.

11 The pilot results led to the development  
12 of the D02 pivotal study. And the D02 pivotal study  
13 was comprised of two phases, including a randomized  
14 controlled 12-week acute phase, and a 12-month follow-  
15 up evaluation period. During the randomized  
16 controlled acute phase, subjects were required to  
17 maintain a stable medication regimen, and during the  
18 long-term phase, changes to the mood disorder  
19 treatments and ECT were allowed, and no concomitant  
20 treatment criteria was provided in the clinical  
21 protocol. The primary efficacy endpoint of the acute  
22 phase was the proportion of subjects who had greater

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1 than a 50 percent decrease in the HAM-D at acute phase  
2 exit compared to baseline. And responders in the  
3 treatment group were compared to the proportion of  
4 responders in the control group.

5 A total of 266 subjects enrolled, 31  
6 discontinued prior to implantation, leaving 235  
7 patients that were implanted. The second yellow box,  
8 green box on the left-hand side. And 222 patients  
9 were considered evaluable for efficacy analyses. Of  
10 the 222 evaluable subjects, 112 were randomized to  
11 treatment and 110 were randomized to sham treatment  
12 control. And regarding the long-term phase of  
13 enrollment, of the 235 subjects who were implanted,  
14 233 subjects were identified as the safety population,  
15 205 were considered evaluable subjects, and 177  
16 subjects were 12-month completers.

17 During the acute phase, nine subjects had  
18 changes in concomitant treatments and noise to use was  
19 reported. During the long-term phase, changes in  
20 concomitant treatments were allowed, and 169 patients  
21 of the 205 evaluable subjects added or increased  
22 antidepressant medications. In addition, 14 subjects

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1 received ECT. Of those 14 subjects, eight subjects  
2 were 12-month completers, four subjects were  
3 categorized as responders, and two subjects were  
4 categorized as complete responders. And I would like  
5 to remind you that one of our panel questions is  
6 related to the use of concomitant antidepressant  
7 treatment changes, permissible in the treatment group,  
8 over the course of 12 months.

9 The sponsor reported implantation related  
10 adverse events, stimulation related adverse events,  
11 and other events from the D02 study. These results  
12 will also be discussed by Dr. Schlosser shortly.

13 The primary efficacy endpoint failed to  
14 show a significant difference between treatment  
15 subjects, those who received VNS, and sham treatment  
16 control subjects, those who received regular care for  
17 treatment-resistant depression. In other words, the  
18 amount of improvement for patients with VNS was not  
19 statistically significantly greater than the amount of  
20 improvement when receiving standard care. And other  
21 psychiatric measurement tools reported similar  
22 outcomes during the acute phase.

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1           Despite the outcome of the acute phase,  
2 the sponsor submitted a revised statistical plan with  
3 new primary efficacy endpoints, and employed an  
4 observational control study for comparison. And the  
5 revised statistical plan introduced the D04 control  
6 study.

7           The design of the D04 study was to collect  
8 long-term clinical quality of life, productivity, and  
9 health care utilization data on patients with  
10 depression. The D04 study began towards the end of  
11 the D02 study, and was a non-significant risk study  
12 conducted under local IRB jurisdiction. Up to 130  
13 patients enrolled, and standard of care was defined in  
14 the clinical protocol as whatever treatment strategy  
15 the physician and the subject chose to follow.

16           Which takes us to the D02/D04 comparison.

17           The objective of the D02/D04 comparison was to  
18 demonstrate that there is a difference in the  
19 improvement of patients with VNS therapy plus  
20 treatment compared to treatment as usual. The design,  
21 schedule, sample size, concomitant treatments have all  
22 been described previously. There was a total of 22

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1 sites enrolling patients in either D02, D04, or both.

2 And of those 22 sites, eight sites enrolled patients  
3 for D02 only, and one site enrolled patients for D04  
4 only. And Dr. Lao will discuss statistical outcomes  
5 associated with the use of overlapping and non-  
6 overlapping investigational sites.

7 The majority of D04 subjects enrolled  
8 after D02 was closed. And sites that enrolled both  
9 the D02 and D04 patients usually screened and offered  
10 patients enrollment into D02 prior to enrollment into  
11 D04, because D02 offered a new treatment as opposed to  
12 standard of care, and sites were more focused on the  
13 treatment study rather than a naturalistic  
14 observational study, D04.

15 During the six months of overlap between  
16 D02 and D04, 83 percent of the patients who met the  
17 enrollment criteria for the D02 study enrolled into  
18 D02. And 17 patients who met the enrollment criteria  
19 for the D04 study enrolled into D04. After D02  
20 closed, clinical sites had a pool of subjects  
21 interested in D02 that were also eligible for D04.  
22 And subjects that could not enroll in D02 typically

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1 enrolled into D04. And I would like to remind you  
2 that another panel question you will discuss is  
3 related to the enrollment outcomes of an  
4 investigational study versus an observational control  
5 study.

6 The primary efficacy endpoint was a  
7 repeated measure of linear regression analysis  
8 performed on raw IDS-SR scores of D02 and D04  
9 patients. The IDS-SR is a self-assessment tool for  
10 depression. And the HAM-D, the primary efficacy  
11 assessment tool for D02 during the acute and long-term  
12 phase, was only included as a baseline D04 assessment,  
13 and therefore was not adequate for D02/D04 comparative  
14 analyses.

15 The D02 study also collected safety data.

16 However, the D04 study did not prospectively or  
17 systematically collect any safety data while studying  
18 treatment-resistant depression, and is an issue  
19 determining whether the VNS Therapy System is safe for  
20 the proposed indication.

21 Evaluable patient baseline demographics  
22 between D02 and D04 were for the most part comparable.

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1       However, there were significant differences in  
2 baseline demographics between D02 and D04, including  
3 those patients who received ECT during their  
4 lifetimes, patients who received ECT during the  
5 current major depressive episode, and patients in the  
6 control population with greater than 10 lifetime  
7 episodes of depression. In addition, there are  
8 several patient variables for which no information was  
9 collected, and have been reported in published  
10 literature to influence treatment responsiveness. And  
11 unmeasured patient variables are also an issue that we  
12 have provided as a question for your deliberations  
13 later today.

14               Now, if we turn to the primary analysis  
15 comparing long-term outcomes between D02 and D04, a  
16 statistically significant difference was observed in  
17 the estimated IDS-SR raw scores per month between D02  
18 and D04 at 12 months.

19               To further evaluate the permissive use of  
20 concomitant treatments during the long-term, the  
21 sponsor performed a second analysis, not specified in  
22 the original or revised clinical protocols, and

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1 compensating for concomitant treatment use. Namely,  
2 if a subject added or increased antidepressant  
3 treatment, and their subsequent IDS-SR scores prior to  
4 the change in concomitant treatments, last observation  
5 carryforward approach was used. The difference  
6 observed in the primary efficacy analysis was not  
7 statistically different from improvement observed  
8 under standard of care. In other words, there was no  
9 improvement difference between patients who improved  
10 with VNS and those patients receiving standard of  
11 care. And this is another issue that we have posed to  
12 you in the form of a panel question.

13           Aside from the statistical numerical  
14 outcomes of one analysis over another, more  
15 importantly, the overall permissive use of concomitant  
16 treatments during the long-term study is an issue in  
17 determining the effectiveness of this device.

18           And now I'd like to turn the presentation  
19 over to Dr. Schlosser, who will be discussing with you  
20 the safety data and the PMA.

21           DR. SCHLOSSER: Good morning. I'm Dr.  
22 Michael Schlosser. I'm a medical officer in the

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1 division reviewing this device. And I'm going to  
2 briefly talk about some of the safety data and the  
3 PMA.

4 I'm going to start by clarifying some of  
5 the terms. The sponsor purported the data, the safety  
6 data, looking at adverse events, and then also looking  
7 at treatment-emergent or stimulation related adverse  
8 events. And so I'm going to talk about those two  
9 categories. And then as a third category there were  
10 these serious adverse events. And so, throughout the  
11 slides I'm going to be talking about each of those  
12 three different groups, and I'll try to explain  
13 exactly which group we're looking at at the time.

14 Because a lot of the events we're talking  
15 about were stimulation related adverse events, I  
16 wanted to talk briefly about the stimulation  
17 parameters that were used in the protocol, just to  
18 start with. Specifically, I'm just going to focus on  
19 the current output. Current output was limited to  
20 0.25 to 3.5 milliamps by protocol in the IDE. The  
21 adjustment protocol called for increasing this output  
22 by 0.25 milliamps in steps until a maximum tolerable

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1 level was achieved. Programmers were specifically  
2 instructed to warn patients that higher level of  
3 stimulation and stimulation related adverse events did  
4 not necessarily correspond to higher efficacy. In the  
5 protocol, it was listed that this was based on  
6 experience with the epilepsy patients, and therefore  
7 the programmers were instructed to tell the patients  
8 not to tolerate events that they really would normally  
9 not tolerate because they thought it was going to  
10 improve their efficacy.

11 Stimulation was to be decreased any time a  
12 patient reported that there was a painful or troubling  
13 adverse event. And the programmers were instructed to  
14 continue to increase the current during the  
15 programming phase in order to try to reach that  
16 maximum tolerable level during the two-week  
17 programming phase of the acute phase of the study. It  
18 was also noted in the protocol, and in the  
19 instructions to the programmers that any individual  
20 patient may have very different responses to different  
21 current levels, and they even went as far as to say  
22 that there may be some patients for who 0.25 milliamps

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1 would be the maximum tolerable setting, and that that  
2 should be expected and not an area of concern.

3 In April, 2005, Cyberonics sent a letter  
4 to the D02 investigators instructing a new stimulation  
5 protocol. This was to be implemented in patients who  
6 had a HAM-D score of greater than 10, which was their  
7 definition for non-responders at that point in the  
8 chronic study. This protocol specified a ramp-up  
9 period of six weeks during which, and this is a quote  
10 from the letter, several attempts should be made to  
11 increase output current to a level of 1.5 milliamps.  
12 It was also recommended that patients undergoing the  
13 ramp-up procedure be seen more frequently, every two  
14 weeks, but as frequently as every week, during the  
15 ramp-up period. And it was additionally recommended  
16 that if patients couldn't tolerate 1.5 milliamps, that  
17 an adjustment be made to -- I'm sorry, an adjustment  
18 be made to the pulse width in order to decrease it to  
19 250 milliseconds, which may facilitate an increase in  
20 current levels.

21 So, now moving more specifically to the  
22 safety data. I'm just going to go through the

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1 different studies that we've already heard about this  
2 morning and talk about the safety data presented for  
3 each. There were 60 subjects in D01. Every subject  
4 reported at least one adverse event. The most common  
5 adverse events, which were reported in at least 10  
6 subjects, were device site pain, headache, incisional  
7 pain, neck pain, dysphasia, increased cough, dyspnea,  
8 and voice alteration. These are kind of the common  
9 adverse events that we're going to see though the rest  
10 of the slides. They're also similar to the events  
11 known to occur during stimulation in epilepsy  
12 patients.

13 There were 77 serious adverse events  
14 reported across 38 of the patients. So greater than  
15 50 percent of the patients had a serious adverse  
16 event. The most common being 12 suicide attempts or  
17 overdose events, and 34 cases of worsening depression.

18 These are incidences of events, not number of  
19 patients. There was one death as a complication of  
20 surgery due to rectal prolapse.

21 In the acute study, now looking just at  
22 the acute D02 phase, 235 implanted patients. There

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1 were 233 reporting an adverse event. So, again,  
2 nearly every patient reporting adverse events. The  
3 events were classified in the PMA as mild, moderate,  
4 or severe. Mild was defined as easily tolerated and  
5 transient. Moderate as caused discomfort and  
6 interrupted usual activities. And severe,  
7 considerable interference with usual activities.

8 As you can see, there was a very large  
9 number of adverse events in both groups. It's  
10 important that we obviously look at the adverse events  
11 in both of these groups since they both had the  
12 surgical procedure and the implant. They were both  
13 exposed to risk. There was 61 severe adverse events  
14 in the treatment group and 73 severe adverse events in  
15 the sham control group. The difference between the  
16 adverse event rates to the treatment in sham control  
17 group probably relates to stimulation related adverse  
18 events, which I'm going to come to.

19 This is now just looking, again, at just  
20 all adverse events in the D02 acute phase. So these  
21 are not graded in any way as to their relationship to  
22 the device or to stimulation. And we can see the most

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1 common adverse event was clearly voice alteration,  
2 which was very common. Eighty-one patients, 68  
3 percent of the treatment group; 44 patients, 37  
4 percent in the sham control group. And then again,  
5 these are those adverse events that I read in that  
6 first slide that are going to be the ones we're going  
7 to see over and over again: device site reaction,  
8 device site pain, incisional pain, dysphasia, incision  
9 site reaction, cough, dyspnea. Similar events that  
10 you would expect given the direct stimulation to the  
11 Vagus nerve.

12 This slide now kind of focuses in a little  
13 bit on events. These are treatment-emergent adverse  
14 events that were rated as possibly, probably, or  
15 definitely related to stimulation. So this was a cut  
16 made by the investigators in the study. When they  
17 reported the events, they would then report whether  
18 they thought the event was related to stimulation. So  
19 you can see, it's the same type of list. It's really  
20 the same adverse events. There are very few of these  
21 events listed in the sham control group, which makes  
22 sense because these were events that the investigators

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1 determined were related to stimulation. So it's  
2 obvious that the investigators were able to pick up  
3 which events were related to stimulation and which  
4 patients weren't getting stimulation.

5 We've heard this morning that these events  
6 are similar in their frequency and in their nature to  
7 the events seen in the epilepsy study. I'm going to  
8 come back to that in one of my last slides. But I'll  
9 just make the point at this point that in this  
10 situation, we're comparing the adverse events and  
11 risks seen in patients with depression, to the benefit  
12 of this device in depression. And the safety of the  
13 device in another population doesn't necessarily mean  
14 that that device is safe in this different population.

15 And the risk/benefit ratio must be looked at  
16 separately.

17 Moving on to serious adverse events. Just  
18 as a reminder, the definition of a serious adverse  
19 event is an event that resulted in death, a life-  
20 threatening event, hospitalization, prolongation of a  
21 current hospitalization, or a persistent disability.  
22 There were 39 such events. Nine occurred prior to

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1 implantation in the acute phase. So there were a  
2 total of 30 adverse events occurring between  
3 implantation and acute phase exit, 16 in the treatment  
4 control group and 14 in the sham control group.

5 If we look at these events individually,  
6 again, we have the most common is depression. I'm  
7 going to mention some things about the depression as  
8 an adverse event in a study of depression in another  
9 slide. But that was the most common serious adverse  
10 event. There was one suicide in the treatment group,  
11 none in the sham group. There were two cardiac events  
12 of note, an asystole and a bradycardia, both of which  
13 rose to the level of a serious adverse event. And  
14 then one wound infection. And then you can just go  
15 down the list, noticing that these numbers are small  
16 and there's one or two patients on either side. So  
17 there really are no statistical differences to be  
18 examined between treatment and sham control groups.  
19 And again, both groups were exposed to the device, and  
20 so, really, adverse events in both groups should  
21 really be included in the safety profile.

22 If we look now at the chronic phase of the

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1 D02 study, again, this is just serious adverse events.

2 We see seven suicide attempts in six patients, four  
3 episodes of syncope in three patients, and then  
4 gastrointestinal disorder, convulsion, one episode of  
5 sudden death. I'm going to come back to sudden death  
6 at the end. And then by far and away the most common  
7 reported serious adverse event in the chronic phase  
8 was depression, 62 instances in 31 patients. The  
9 sponsor in the PMA explains that this probably  
10 represents a lack of efficacy of device rather than a  
11 true adverse event of the device.

12 Moving on to the D03 study. We haven't  
13 looked at the D03 study in the FDA presentation yet,  
14 so I'm just going to review the clinical protocol  
15 quickly. This was an open label, non-randomized,  
16 single arm, longitudinal study. It's the post-market  
17 study in Europe. It actually began before the CE  
18 mark, but the majority of the study has actually  
19 occurred afterwards. So it became a post-marketing  
20 study. Antidepressant treatment changes were allowed  
21 in this study, and the primary efficacy endpoint was a  
22 portion of subjects with a 50 percent response on the

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1 Hamilton rating scale at 12 weeks compared to  
2 baseline.

3 Safety data was collected in this study,  
4 and provided to us. Looking at just, again, the  
5 serious adverse events, 47 subjects implanted, 14  
6 serious adverse events in those 47 subjects. Again,  
7 the most common, four cases of worsening depression.  
8 There were two suicides, which were also the only two  
9 deaths in the study. And then down the list,  
10 bacterial infection, accidental overdose, accidental  
11 injury, one case of syncope, and then gallstones,  
12 kidney stones, and kidney pain.

13 I won't go over specifically what the  
14 stimulation related non-serious adverse events were  
15 for D03. But as per the sponsor's submission, they  
16 were similar to those seen in D02 and D01 and in  
17 epilepsy studies.

18 The D06 clinical protocol. This was a  
19 pilot study of safety and efficacy in rapid cycling  
20 bipolar, as we heard. Standard bipolar disorder  
21 patients were included in D02, but rapid cycling  
22 patients were not. This was a separate study looking

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1 at that population by itself. It was again an open  
2 label, non-randomized, single arm study, so it was not  
3 designed to be an efficacy study, but did collect  
4 safety data, which we have. There were 11 subjects  
5 enrolled. Only seven actually implanted. And two  
6 subjects had one-year follow-up only, so we don't  
7 really have long follow-up on these patients.

8 We do have safety results. Again, I'm  
9 focused on serious adverse events. There was one  
10 suicide, three suicide attempts, one prior to  
11 implantation, two cases of worsening depression, and  
12 one case of manic reaction. So seven events in seven  
13 patients, though two subjects reported two events  
14 each.

15 Now we heard this morning about the  
16 specific focus on suicide. Obviously, published  
17 literature and recent experience has taught us that in  
18 very rare cases, antidepressant medications can  
19 precipitate suicidal behavior. There were 12 suicide  
20 attempts or overdoses in D01. The D02 acute phase had  
21 one suicide in the treatment group, none in the  
22 control. The long-term phase of D02 had seven suicide

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1 attempts in six patients. That was by the cutoff date  
2 for submission of the PMA. Since then there have been  
3 two more attempts in two additional patients. D03  
4 study had two suicides. We don't have the report of  
5 attempts. And D06 had one suicide and two attempts in  
6 seven patients. So enough to make us concerned that  
7 there might be something to precipitation of suicide  
8 by this device, or at least to look at it more  
9 carefully. Again, a reminder that safety data was not  
10 collected in D04 for comparison.

11 This is kind of a busy slide, but what  
12 we're looking at here is the D02 acute phase on the  
13 top, and then comparative data, which includes a  
14 combined D01, D02, and D03 group on the bottom. So  
15 treatment group versus sham control group. Very small  
16 n here, only one suicide in the treatment group, none  
17 in the sham group, and no attempts. So tough to make  
18 a comparison, though, 4.3 percent versus zero percent.

19 But the numbers are small.

20 In the larger comparative data we're  
21 looking now at a larger group, 342 patients in the  
22 combined analysis. And we see, as the sponsor showed

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1 this morning, if we look at instances of suicide per  
2 year, 0.4 percent. This is, again, comparison to this  
3 Khan Study, which was this very large meta-analysis of  
4 drug studies used for approval. And there we had a  
5 0.8 percent rate in the treatment group, and a 0.4  
6 percent rate in the placebo group. So similar numbers  
7 of instances of suicides per year and suicide attempts  
8 per year between the D01, D02, D03 combined and the  
9 meta-analysis.

10 Now, I mentioned I would come back to the  
11 epilepsy data. This is a chart that represents the  
12 stimulation related adverse events in the E-05 study,  
13 which was the pivotal study for VNS for treatment of  
14 epilepsy. And again, you see this very similar list  
15 of adverse events that we've seen on all the previous  
16 slides: cough, dyspnea, hoarseness and voice  
17 alteration being the common events. This was a  
18 comparison between baseline and then high levels of  
19 stimulation. So these are actually patients compared  
20 to themselves. And we see, you know, they all reach  
21 levels of statistical significance. So these are all  
22 adverse events that are related to the stimulation,

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1 and they can be bothersome to the patient.

2 But again, I'll just restate that the  
3 determination of safety is not done in a vacuum. It's  
4 done as a risk/benefit analysis, comparing to the  
5 benefit or the efficacy of the device. And so the  
6 safety in the epilepsy population does not necessarily  
7 mean safety in the depression population. The adverse  
8 events must be weighed in relationship to the benefit  
9 shown by the efficacy studies.

10 And then finally I'm just going to finish  
11 by talking about cardiovascular events. I mentioned  
12 the one sudden death in the D02 study. There were  
13 also, I believe, two cases of sudden death in the  
14 epilepsy studies, and cases reported in the MDRs as  
15 well, very rare incidence of sudden death. There is a  
16 concern that this might be due to cardiac events due  
17 to the direct vagal nerve stimulation. Could this be  
18 causing a cardiac event that led to sudden death?

19 So we looked just kind of specifically at  
20 what cardiovascular events were seen. The events in  
21 red are the serious adverse events. This whole column  
22 is in red, even the zeroes, because I have not

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1 included the non-serious adverse events for the  
2 chronic phase. There were many, and in many cases  
3 they were the same patient reporting the same adverse  
4 event at each visit. For example, bradycardia. But  
5 there was no action taken. There was no action  
6 needed. And so those numbers were very large, but not  
7 necessarily meaningful. So the serious adverse events  
8 in the chronic phase: four cases of syncope, one case  
9 of dizziness. And then when we look at the acute  
10 phase, the case of asystole and bradycardia which I've  
11 already mentioned, and then several other cases of  
12 arrhythmia, hypertension, 10 cases of palpitation, 21  
13 cases of dizziness. I should mention that of course  
14 there are many causes for dizziness, so while we lump  
15 this under cardiovascular events, there obviously can  
16 be other reasons why people can be dizzy.  
17 Vasodilatation and syncope.

18 So there were cardiac events. We don't  
19 have any evidence of sudden death due to a cardiac  
20 event from vagal nerve stimulation, but it's just  
21 something to keep in mind in terms of the safety  
22 profile of the device.

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1                   Now I'm going to turn it back over to Dr.  
2                   Pena for a review.

3                   DR. PENA: So in review, regarding safety,  
4                   the absence of systematically collected safety data in  
5                   the observational control study for comparison to the  
6                   investigational study is an issue in determining  
7                   whether the clinical data in the PMA provides  
8                   reasonable assurance that the device is safe for the  
9                   proposed indication.

10                  And regarding efficacy, FDA has identified  
11                  the following issues, including first, the chief  
12                  limitation that the long-term D02/D04 comparative  
13                  analysis is not derived from a randomized subject data  
14                  set, but rather a comparison of outcomes from an  
15                  investigational device study and observational control  
16                  study. And a propensity adjustment strategy used to  
17                  reduce potential bias in the comparative analysis is  
18                  not able to address the problems of potential bias due  
19                  to other unmeasured patient variables.

20                  I would also mention that the sponsor  
21                  noted in correspondence to FDA that both the D02 and  
22                  D04 population would not differ on measured factors

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1 upon submitting their revised analysis, and that if  
2 they did, one could not be as confident in their  
3 statistical adjustment for baseline differences.  
4 FDA's uncertain whether one can reconcile the  
5 sponsor's statement in their own submission concerning  
6 there were relevant measured patient variables found  
7 to be significantly different between groups.

8           Second, FDA's concerned with the potential  
9 placebo effect rates for patients with VNS. The  
10 sponsor has discussed in some detail reasons why long-  
11 term outcomes from VNS patients are not due to  
12 placebo. Data provided in the submission identifies a  
13 placebo response rate of 10 percent, as defined by the  
14 clinician's measurement scale HAM-D, which persisted  
15 to the exit of the acute phase, namely 12 weeks.

16           Also, although both D02 and D04 were  
17 available to enrolled subjects at similar time  
18 periods, almost all D04 subjects enrolled into the  
19 study after D02 was closed for enrollment. Only 10  
20 D04 subjects enrolled into D04 while D02 was open.  
21 And the sponsor has indicated that sites were more  
22 focused on the treatment study rather than the

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1 naturalistic observational control study.

2           And third, moving past the insignificant  
3 numerical outcomes upon censoring scores of VNS  
4 patients with concomitant treatments, and using their  
5 last observation carried forward, FDA is concerned  
6 that concomitant medications an ECT use were not  
7 standardized in either the D02 long-term study or the  
8 D04 observational control study. And I would also  
9 mention that when a patient adds or increases  
10 treatment, one can reasonably expect that patients are  
11 not responding, or poorly responding to their current  
12 therapy regimen. And one would be unsure of the cause  
13 of the patient's improvement to subsequent additions  
14 or increases in antidepressant treatments.

15           At this time, I would now like to turn it  
16 over to Dr. Lao, who will be presenting the  
17 statistical data contained in the PMA submission.

18           DR. LAO: Good morning, my name is Chang  
19 Lao, Division of Biostatistics, FDA. Today I am going  
20 to present a comparison between D02 and D04. D02 is  
21 the VNS plus standard care. D04 is standard care  
22 only. And the primary/secondary efficacy endpoint is

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1 HRSD-24, is the Hamilton Rating Scale for depression,  
2 24 items. Maximum score 74. IDS-SR is maximum 84.

3 In the multi-center study, 22 sites, and  
4 overlapping Site 12. I'm going to talk overlapping  
5 sites later on. And then talk about propensity score  
6 analysis, try to test covariates in pairings. And  
7 then repeat a measure in the concordance study, try to  
8 predict an HRSD from IDS-SR. Then there is a  
9 statistical conclusion.

10 This is a D02, a brief summary on all 22  
11 sites combined. In the three-month actual study,  
12 which is double-blind, randomized, VNS was a sham  
13 control. Primary HRSD, parameter, and IDSS-SR is  
14 secondary. And primary endpoint is the comparison to  
15 response proportion. The final result based on three-  
16 month actual study, the significant difference was  
17 found for the IDSS-SR, which is 17 percent, VNS was  
18 7.5 percent sham, 0.03 based on psych test. No  
19 significant differences were found for the HRSD.

20 Then after three months, every patient was  
21 switched into VNS. So the primary endpoint for D02  
22 only is HRSD. Try to estimate a slope for every radar

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1 change, scope must -- we try to estimate a mean  
2 response score when you study. The slope average  
3 amounts of change in HR score 0.45 per month. Which  
4 is standard endpoint of 0.05/95 company's interval.

5 D02 and D04, long-term comparison, the  
6 endpoint is average rate of change, which is slope  
7 estimate average mean score per quarter by repeated  
8 measure and integration. And the longitudinal data  
9 for the HRSD, D02 yes, D04 no. Because it only had a  
10 baseline and 12 months data only. So the sponsor  
11 switches to IDSS now because they had both  
12 longitudinal data. And to do the repeated measure of  
13 lineal regression.

14 Secondary endpoints is a proportional  
15 response based on the 50 percent reduction in score  
16 from baseline. This is a sample size table for the --  
17 all the 22 sites, overlapping sites. Overlapping site  
18 means some site had both D02 and D04. As you can see,  
19 this sample size here, in the overlapping site the  
20 sample size is much smaller than the other 22 sites  
21 combined. By the way, sample size was based on the  
22 secondary endpoint. Compare the proportion of the

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1 response between the two groups. Not based on the  
2 primary endpoint.

3 This chart illustrates the patient by  
4 study and center for the D02 and D04 comparison. As  
5 you can see, about nine sites which had a D02, but no  
6 D04 study, and one site had D04 and no D02 studies.  
7 So overall, 10 sites out of 22 sites, which are  
8 roughly about 45 percent, no comparison group for  
9 those sites. The study design is incomplete and  
10 unbalanced. And it's hard to evaluate a true  
11 homogenous cross center. A true center interaction  
12 effect cannot be evaluated.

13 Propensity score analysis, which is when  
14 you have many, many confounding covariates present.  
15 Then the propensity score actually is overall  
16 composite scalar, sure to intend to reduce by  
17 comparison between D02 and D04. It took the best  
18 covariate only. Propensity score is a condition of  
19 probability of individual patients receiving D02.  
20 Condition even a set of IS patients, of best  
21 covariate, XI. We have total 17 covariates. Before  
22 after propensity score adjustment, use of logistic

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1 regression, which is a logit. Logit is a proportion  
2 of success to no success, probability of no success.  
3 Logit, log of that, actually is a probability assigned  
4 to D02 conditioned on a set of covariates. Vector X  
5 for the IS patient. The furnishing of the vector for  
6 a covariate for IS patient. So some basis of logistic  
7 regression.

8 Primary effectiveness analysis and  
9 repeated measure analysis, which its purpose is to  
10 estimate every radar change per month, or to estimate  
11 the mean response at 12 months, which is general mean  
12 response mode. We are interested in only comparing  
13 the mean, scope, from baseline between D02, D04, at 12  
14 months, not individual patients performance, which  
15 were required for random effect mode. So the  
16 dependent variable here, IDSS, independent variable is  
17 the baseline IDSS-SR, treatment in either D02 or D04,  
18 or time, four quarters. And the PS quantum five level  
19 group by the Propensity Scale for each individual  
20 patient. Nine pool sites from 22 sites. And measured  
21 by time interaction and the special power correlation  
22 which allowed the correlation to change over time.

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1 And so missing random. Probably we are missing data  
2 in future. All absent data is independent, missing  
3 data independent from the future of this issue. Next.

4 Concordance study shows how good are the  
5 ideas of particular HRSD. And the statistics uses a  
6 correlation of linear regression. Outcome is a  
7 correlation coefficient intercept slope R-square. R-  
8 square is a percent variable, about a mean of HRSD,  
9 explained by the future regression model. How much  
10 can explain by the independent variable, IDS-SR?

11 A range of R squares, zero to one. Zero  
12 is the worst fate. One is perfect fate. So if R  
13 squared equals one, that means the IDSS-SR can predict  
14 HR very well. If zero, then no prediction at all.

15 This is a value, the top number is the  
16 repeated measure linear regression result. All the 22  
17 sites combined. And top of the graph, the number  
18 there is each quarter observed predictive value of  
19 mean score, at each quarter for D02 and D04. At the  
20 bottom of the chart, there, you see the difference.  
21 D02 minus D04, observed at -6.6, which is not adjusted  
22 for any patient covariate, individual patient baseline

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1 data, or propensity score.

2 The predicted value after one year is  
3 minus 4.8, which is a reduced improvement at one year.

4 This is for all 22 sites combined. If we look only  
5 for the 12 overlapping sites, the 12 have both D02 and  
6 D04. Then the improvement, at the bottom of the chart  
7 you can see that at one year, the improvement --  
8 difference about 1.4 points. And the 95 confidence  
9 even before that difference, D02 minus D04, minus  
10 3.82, minus 0.5. That's based on 12 overlapping  
11 sites.

12 This is a result for the concordance  
13 study, as I talked before. R-square, the position of  
14 R-square by this histogram. You would like to see the  
15 R-square equal close to one as possible best  
16 prediction. If close to zero, no prediction at all.  
17 The mean of this distribution of 235 evaluable  
18 patients, D02 study, of 0.55. Which means about 55  
19 percent variability, and above the mean of the HRSD  
20 data, explained by IDSS-SR. So I would say it is, R-  
21 square is kind of in the middle. So concordance  
22 study, also you can look at the correlation

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1 coefficient and the slope. The mean correlation is  
2 about 0.70. And undefined of 0.67 to 0.73. And the  
3 slope, we use the average rate of change for the HRSD,  
4 for every unit change of IDS-SR.

5 Second endpoint is a definition of IDS-SR  
6 or HRSD score larger than 50 percent reduction from  
7 baseline. Statistics have several concerns here.  
8 Treat it like all the 22 sites as one site because the  
9 sponsor combined all the responses and non-response by  
10 D02, D04, combined together from those 22 sites. So  
11 it looks like the data all comes from one site. So no  
12 treatment in the baseline interaction was considered  
13 here. And supposed to talk about logistic regression  
14 for the response rate comparison to response  
15 proportion. But I don't see it. The covariate only  
16 appear in the linear regression analysis. So no  
17 pooling of the data, no modern approach, no covariate  
18 adjustment, like a baseline IDSS or HRSD site ECT RX  
19 used.

20 One reminder. IDSS is a baseline which  
21 was highly significant in the repeated measure  
22 regression. And also pool site is highly significant.

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1 So the unclear why to compare two proportion  
2 responses.

3 Summary. Three months double-blind  
4 randomized provided most for VNS. You know, this  
5 provisional study kind of weak in variable patients,  
6 all 22 sites. HRSD and the PY 0.3 second IDS-SR,  
7 which is 0.039 second. Based on two-sided exact  
8 test.

9 So the switch from primary HR to the two  
10 second endpoints, IDS-SR, in long-term study.

11 Summary. In a way, the D02/D04 study is non-  
12 randomized, un-blinded. Propensity score were used  
13 for balance of a measured covariate only.  
14 Approximately the balance seemed to have achieved.  
15 Look at the difference of propensity score between the  
16 D02 and D04. Reasonable balance in PS quintiles. PS  
17 balance individual patient covariate, which is good.  
18 But, PS propensity score cannot balance unmeasured  
19 covariates selected by -- not accounted for by  
20 covariate, regression to the mean providing a placebo  
21 effect.

22 Summary. Data one can follow. If

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1 antidepressant resistant ratings score increased,  
2 and/or ECT was applied, the prior IDS-SR HRSD score  
3 was carried forward to the place subsequent. Now  
4 we're missing observation. Unclear effect of analysis  
5 in preparation of these for censored analysis, which  
6 we based on definition above. It's kind of not easy.

7 Now, over to D02/D04 site. Nine sites  
8 they had at D02, one site at D04. No D04. Only 12.  
9 Reduce the sample size by one-third. PS used nine  
10 pooled sites in the repeated measure. So it only  
11 partly accounts for the imbalance. And also used only  
12 12 over the sites. Show a last effect.

13 This is the difference D02/D04 in repeated  
14 measure regression for IDS after one year. We have  
15 different end result here. Covariate -- observe just  
16 for covariate, based on raw data. The average  
17 difference after one year, about 6.6. Ninety-five  
18 confidence interval, about -10 to the -3.2. And it's  
19 just by covariate. All the 22 sites are about 4.8,  
20 with a 95 confidence interval. But if we use the  
21 overlapping site, we censor data. Then implement only  
22 cut it down to 2.1 points. And the 95 confidence

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1 interval minus 3.842, minus 0.54.

2 Always think of the 95 confidence interval  
3 rather than P value is more meaningful. Because P  
4 value only tests low hypothesis. The true difference  
5 equals zero. Equals zero doesn't equivalent -- may  
6 not be equivalent to the true clinical difference.

7 Summary. Unclear concordance study. Ask  
8 why 235 patients, about 0.55, which is kind of, you  
9 know, it's hard to say. It is not perfect predictor,  
10 anyway. And the way we estimate a mean difference  
11 IDS-SR, D02 minus D04, minus 2.1 unit to 4.8 unit,  
12 depending on which data you use, minus 2.1 with  
13 baseline of 12 overlapping sites of 4.8 points with  
14 all 22 sites. This improvement is clinically  
15 meaningful.

16 So this is based on the second endpoint,  
17 based on 12 months proportion of response based on 12  
18 overlapping sites only. The only significant  
19 difference for the nine site data and all the 22 sites  
20 was 0.001. The main comparison source of data for the  
21 12 overlapping sites didn't show any significant  
22 difference between the D02 and D04, for the second

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1 endpoint.

2 This ends my talk. Thank you.

3 DR. PENA: Panel members. The management  
4 of treatment-resistant depression is a therapeutic  
5 challenge to clinicians, and many such patients  
6 continue to lack adequate treatment options. However,  
7 any proposed device would need to have balanced  
8 scientific evidence to establish reasonable assurance  
9 of the safety and effectiveness of its use. Thus FDA  
10 has drafted five panel questions for your discussions  
11 in the afternoon session. At this time, FDA has  
12 completed its presentation, and we wait for  
13 instructions by the chairperson.

14 CHAIRPERSON BECKER: Thank you. We have  
15 about 45 minutes until the lunch break, so I think I'd  
16 like to open the session up for questions by the panel  
17 to the FDA presenters initially. Does anybody on the  
18 panel have a question for the FDA presenters?

19 DR. ELLENBERG: Yes, I wonder if you would  
20 mind bringing up the slide again for the covariate  
21 adjustment. I believe it was the third from the end  
22 in the statistical analysis. I'm afraid I didn't

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1 understand the presentation.

2 DR. PENA: Which slide did you refer to?

3 DR. ELLENBERG: It's the third from the  
4 end. It's titled Difference D02 minus D04 in IDS-SR  
5 improvement by one year.

6 DR. LAO: If you don't observe -- it's  
7 just based on observed only. And the sponsor's  
8 presentation shows after one year the difference,  
9 about 6.6 point difference with 95 confidence interval  
10 -10 to the -3.2. That's didn't use any statistics,  
11 just use the raw data, observed data. But --

12 DR. ELLENBERG: So that is not with any  
13 propensity score adjustment? Is that what you're  
14 saying, that's the first row?

15 DR. LAO: Yes. You are right.

16 DR. ELLENBERG: And then the second row  
17 is?

18 DR. LAO: Use the repeated measure linear  
19 regression, which use the propensity score adjustment.  
20 Also, individual patients' IDS-SR score. And the  
21 ninth --

22 DR. ELLENBERG: Wait, wait. So the second

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1 one is -- they're both done through the IDS-SR?

2 DR. LAO: Yes.

3 DR. ELLENBERG: Both rows?

4 DR. LAO: Yes.

5 DR. ELLENBERG: Alright. And the second  
6 row includes the PS adjustment. I believe the sponsor  
7 indicated that in the linear regression modeling, that  
8 the propensity score adjustment was not significant.

9 DR. LAO: That's right.

10 DR. ELLENBERG: Is that clear? Okay. So,  
11 in the second row you are presenting this data, and  
12 you're doing it for all 22 sites, and then for the 12  
13 sites that are overlapping.

14 DR. LAO: Yes.

15 DR. ELLENBERG: So you give two results.  
16 And what is the point you're making?

17 DR. LAO: Making is because total 22 site.

18 Ten site incomplete, missing, that didn't have the  
19 both D02/D04 study. So there's no comparison can be  
20 made for those 10 sites. So I would think you're  
21 using 12 sites which you had both D02/D04 study can do  
22 a meaningful comparison with each site.

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1 DR. ELLENBERG: So you believe that using  
2 the overlapping sites only is a more legitimate  
3 comparison than 22 sites?

4 DR. LAO: Yes.

5 DR. ELLENBERG: Okay. I understand that.  
6 And then, in terms of differences between what the  
7 sponsor presented on the first row and what you're  
8 showing for the 12 overlapping sites, they're both  
9 below zero. The confidence interval are both below  
10 zero. So, are you making a claim that there is a  
11 difference in the differences here?

12 DR. LAO: You have some difference here.  
13 But the confidence interval leaves some clinical  
14 decision here.

15 DR. ELLENBERG: Right. So you're just  
16 stating that the company's interval is different from  
17 the interval you get with the 12 overlapping sites.

18 DR. LAO: Yes.

19 DR. ELLENBERG: And also -- I'm not sure  
20 why that's important if the propensity score wasn't  
21 statistically significant.

22 DR. LAO: The propensity score is only one

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1 of the covariates used in the linear regression.  
2 There are some other nine pooled sites, or individual  
3 IDS-SR baseline data which is highly significant.

4 DR. ELLENBERG: I'm sorry, I'm not  
5 following that at all. Start again?

6 DR. LAO: Patient baseline data, IDS-SR.

7 DR. ELLENBERG: That was not included in  
8 the propensity score?

9 DR. LAO: That was included in the  
10 repeated measure linear regression.

11 DR. ELLENBERG: In addition to the  
12 propensity score?

13 DR. LAO: Yes. Yes.

14 DR. ELLENBERG: And so this analysis with  
15 the 12 overlapping sites includes those baseline  
16 scores?

17 DR. LAO: Yes.

18 DR. ELLENBERG: And the first row for the  
19 sponsor submission did not include those covariate  
20 baseline scores?

21 DR. LAO: First row -6.6 didn't use any  
22 covariate adjustment, didn't use any repeated measure

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1 linear regression, just --

2 DR. ELLENBERG: Okay, thank you. I  
3 understand.

4 CHAIRPERSON BECKER: Are there any other  
5 questions for the FDA presenters?

6 DR. ELLENBERG: Yes, I'm sorry. An  
7 additional question. Another statistical question.  
8 Can you explain to panel why it's important that if  
9 you're using all of the sites in an analysis as was  
10 done by the sponsor, you thereby, since you don't have  
11 complete overlap, are eliminating the possibility of  
12 looking at any differences in the results by site. In  
13 other words, the more technical term, the site by  
14 treatment interaction can't be estimated.

15 Can you explain to the panel why for this  
16 particular PMA looking at the site by interaction  
17 would be extremely important, moderately important,  
18 very important. Are their hints in what you've seen  
19 in the data that it's really critical to look at the  
20 site by treatment interaction, or are you just making  
21 a statement that one always looks at the site by  
22 treatment interaction because there may be differences

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1 and we would want to see that?

2 DR. LAO: The idea that you would like to  
3 see the treatment effect D02 minus D04 difference is  
4 homogenous across center. So then you can try to use  
5 the statistical model to pool data, get overall  
6 evidence, summary evidence from all the sites. But if  
7 you have the 10 sites without a comparison group then  
8 the statistical model would be very difficult to the  
9 pooling of the data.

10 DR. ELLENBERG: I understand that, but is  
11 there something in the data that you've seen for what  
12 the D02 minus D04 difference is looking at them by  
13 site that would hint to you that this is something we  
14 should be concerned with?

15 DR. LAO: Yes. Hopefully they go the same  
16 direction. D02 is always superior to D04 for most of  
17 the sites. Not necessarily for all the sites, but for  
18 most of the sites. If you see the opposite direction,  
19 if you saw within some site D04 superior than D02, or  
20 other way around, then you wonder is it a correlative  
21 interaction there. You wonder how can you combine the  
22 data. Is something going on there that's not only due

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1 to treatment effect, maybe due to site effect.

2 DR. ELLENBERG: But are you presenting a  
3 hypothetical, or are you seeing the data in a way that  
4 indicates --

5 DR. LAO: No, I didn't see the data.

6 DR. ELLENBERG: Alright, so let me restate  
7 what I think your point is. In general, there could  
8 be an interaction between the treatment and the sites,  
9 which in lay terms simply means that the treatment  
10 effect might be different by sites. The treatment  
11 effect could be different by sites in two major ways.

12 One way is that it's -- the treatment effect is  
13 considerably less in some sites than in other sites.  
14 Another way is that the treatment effect is entirely  
15 different in some sites than other sites. So it's  
16 useful to, at a minimum, review the site differences,  
17 and at a maximum be able to model through using a  
18 technical term, an interaction term, in the model.  
19 But there's no evidence that you've seen from the data  
20 that indicates that there is a treatment by site  
21 interaction of either sort. Has that made your point  
22 correctly?

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1 DR. LAO: Yes, you are right.

2 DR. ELLENBERG: Thank you.

3 DR. LAO: The difficult point is here this  
4 is not a randomized trial. So the sample size for  
5 some sites is very small. You really cannot make a  
6 meaningful comparison for those sites with small  
7 sample size. Not enough power.

8 CHAIRPERSON BECKER: There's another  
9 question for the FDA presenters. Dr. Wang?

10 DR. WANG: What I'm interested in is your  
11 possible reasons for that discrepancy in the acute  
12 phase D02 results depending on which measure is used.

13 Maybe actually if you can go back to Dr. Lao's slide,  
14 it's the one, D02 Brief Summary. It shows the acute  
15 phase results. There it is. What's your -- you've  
16 shown us that the correlation is moderate at best  
17 between the HAM-D and the IDS. What is your  
18 suggestion here? Is it that the -- someone suggested  
19 the IDS is maybe a more relevant modern measure of the  
20 depression constructs. Or potentially this is a self-  
21 report measure and you could imagine maybe being more  
22 prone to bias or a placebo effect? What's your sort

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1 of reasoning here?

2 DR. PENA: Well, we have concerns  
3 regarding the various psychometric tools that were  
4 used to measure effectiveness during the acute phase.

5 So, while the IDS-SR demonstrates statistical  
6 significance between the viable patient population,  
7 there were other psychometric measurement tools that  
8 did not demonstrate statistical significance. So that  
9 makes us wonder if the outcomes, really how strong  
10 those outcomes are across different measurement tools.

11 Some of those measurement tools include  
12 the HAM-D, the BDI, the SF-36, and the MADRS,  
13 Montgomery Ashberg Depression Rating Scale.

14 DR. WANG: What is your sort of suggested  
15 or proposed weakness of the IDS-SR?

16 DR. PENA: Well, you would want -- we  
17 haven't arrived at a conclusion. We have serious  
18 concerns, though, with only one scale able to  
19 demonstrate statistical significance in acute phase  
20 period.

21 DR. LAO: If you look at the histogram for  
22 the R-square, the prediction varies from patient to

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1 patient. That's the point there. Some patients  
2 predict very well. Some patients no prediction at  
3 all.

4 DR. PENA: I'd just like to add one  
5 comment. And it's one of the reserve slides that we  
6 do have. During the acute phase, in both the  
7 treatment group and the sham treatment control group,  
8 there were four subjects that were categorized as a  
9 responder, but neither were in either the HAM-D or the  
10 IDS-SR. They were responders in one, not the other.  
11 So it's further concerns regarding the concordance and  
12 the outcomes of one tool over another, and the  
13 strength of the data.

14 DR. WITTEN: I think you also might want  
15 to note that it's not -- there's not the same totals.

16 If you look at the slide that you were referring to  
17 for Dr. Lao, there's not the same total of patients.  
18 It's a relatively small number that aren't in both  
19 groups. But it's a small number that's a difference.

20 Numerically, they were successful in both groups.

21 DR. WANG: The non-responders might be an  
22 extreme.

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1 CHAIRPERSON BECKER: Any further questions  
2 for the FDA? Dr. Malone?

3 DR. MALONE: On the D02 acute, I think you  
4 did have a slide that said it was a failed study  
5 because the primary efficacy measure was not met? Is  
6 that right?

7 DR. PENA: Right. The acute phase data,  
8 the outcome of that acute phase failed to reach its  
9 primary efficacy endpoint. So it failed to reach that  
10 prospective outcome.

11 DR. MALONE: So my understanding would be  
12 if you want to do all these other tests, you have to  
13 start doing corrections for them. Because you're  
14 doing multiple tests. I mean, but regardless of that,  
15 it's a failed study. Is that right? If you take the  
16 primary outcome measure?

17 DR. PENA: Correct.

18 CHAIRPERSON BECKER: If there are no  
19 further questions for the FDS, perhaps we can start  
20 taking some questions for the sponsor at this time  
21 before we break for lunch.

22 Actually, I'll get things rolling by just

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