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Quick Pulse

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FDA Panel Dubious about Devices for Treatment-Resistant Depression – and CMS Rejects Coverage of One Device

The FDA's Neurological Devices panel of the Medical Devices Advisory Committee met in Gaithersburg, MD, January 26, 2007, and it was a difficult day for three device companies: Neuronetics, Cyberonics, and Confluent Surgical.

The panel spent most of the day discussing and then ultimately giving a thumbs down to Neuronetics' NeuroStar TMS (transcranial magnetic stimulation) System, a magnetic pulse system. After that, panel members spent an hour reviewing post-approval studies for Cyberonics' Vagus Nerve Stimulator (VNS) for treatment-resistant depression (TRD) and Confluent's DuraSeal Dural Sealant System. They were concerned about both the efficacy of the devices and the use of interim analyses.

Just 10 days after the panel meeting, the Centers for Medicare and Medicaid Services (CMS) not only denied coverage of Cyberonics' VNS but also said, basically, that it doesn't work.

Neuronetics' NeuroStar TMS

Neuronetics is seeking 510(k) approval for NeuroStar TMS, which is designed to treat depression by zapping the brain with magnetic pulses, inducing electrical currents in the area of the brain associated with mood. The device is intended to be used by psychiatrists on an outpatient basis as an alternative to electro-convulsive therapy (ECT).

While the panel did not make a specific recommendation on whether or not NeuroStar TMS should be approved, it concluded that:

- The device seems to be safe.
- While there is some suggestion the device works, the effects are marginal, borderline, or questionable.

Two patients and a partner of one of the patients spoke on behalf of NeuroStar, saying that it changed their lives and that they are now able to live normal lives. A physician who said he suffered from acute depression for 15 years told the panel, "I did not work. I lived in my own world, excluded my family, and slept up to 18 hours a day…Within one week (of receiving NeuroStar therapy) I made measurable progress toward the cure that came in two weeks." A spokesperson for Families for Depression Awareness also made a plea for approval, saying, "There must be a new treatment for patients with TRD."

Dr. Peter Lurie, deputy director of Public Citizen's Health Research Group, criticized the Center for Devices and Radiological Health (CDRH) and spoke against Neuronetics' device, as well as the Confluent's DuraSeal and Cyberonics' VNS. He said, "Although the three devices to be discussed at (the) meeting either treat different conditions or use significantly different mechanisms of action to treat the same condition, they all share one characteristic; their path to approval is indicative of the lax standards currently employed by the CDRH."

Dr. Lurie criticized the FDA for "mistakenly allowing this application to proceed through the 510(k) shortcut, rather than through the more rigorous PMA process…We are perplexed as to why the principal study proffered in support of a device that would be approved based on its similarity to an existing device would compare the device to sham therapy rather than the existing device. It is no small irony, therefore, that the sponsor has been unable to even demonstrate that its device is superior to sham therapy."

Neuronetics, in its presentation, said that its device is safe and that the side effects, mostly headache, were not more common with TMS than with sham control.

Panel questions included:

- The panel chair, Dr. Thomas Brott, a neurologist at the Mayo Clinic in Jacksonville FL, asked about the integrity of the study blind and about how patients were scheduled during the trial. He wanted to know if there was one day a week when these patients would gather for treatment. A Neuronetics official responded that patients were scheduled on an individual basis.
- A panel member asked about the effects of frontal lobe dysfunction on measures of depression. A company official replied that frontal lobe dysfunction measures are among the most sensitive indicators of depression.
- A panel member was curious about whether patients who didn't respond to treatment had had any ECT, and a Neuronetics official said that many patients had been referred for ECT, but that most preferred not to get it.

Panel discussion of FDA questions

The FDA posed ten questions to the panel about NeuroStar, and the panel chair, Dr. Brott, summarized the panel opinions after each question was discussed.

QUESTION 1. Please discuss the results for the primary effectiveness endpoint, including the statistical and clinical significance of:

a. Results from the pre-specified per-protocol analysis.

b. The sponsor's post hoc adjustment and the results obtained.

Efficacy was not established.

Panel chair: "The consensus is the company did not establish efficacy. The clinical effect was marginal, borderline, questionable, perhaps a reasonable person could ask whether there was an effect at all."

QUESTION 2. The results for multiple secondary outcome measures were provided in the marketing submission. These included various analyses for several different clinician-rated and patient-rated severity scales. Please discuss:

a. The scientific validity of analyzing secondary outcomes as a measure of device effectiveness given that the per-protocol primary effectiveness endpoint did not achieve statistical significance and how the need to correct for multiplicity testing should be addressed.

b. The clinical significance and consistency among the secondary effectiveness endpoints at Week 4. The relative importance of clinician-rated versus patient-rated scales when assessing depression symptoms and responses to therapy.

There was no consensus on these issues.

QUESTION 3. Given that more than half of the evaluable population (n=156) exited Study 01 between Weeks 4 and 6, please discuss the effectiveness results from Week 6 and how, if at all, they contribute to the interpretation of the Week 4 data for the NeuroStar System.

Dropouts make interpretation difficult.

Panel chair: "With the number of patients who dropped out (in a non-random fashion), it minimized the result."

QUESTION 4. The sponsor conducted several analyses to assess differences in application site pain among treatment groups and the integrity of the study blind. Considering the information provided, please discuss the issue of blinding and any potential impact on the clinical data and results.

Blinding makes interpretation difficult.

Panel chair: "Blinding is not obligatory. When results are equivocal and placebo might be inferred, then the adequacy of blinding is a fundamental consideration. There was some concern that the numbers did not reflect the true degree of blinding."

QUESTION 5. Given that both Study 02 and Study 03 were open-label and had missing data, please discuss any conclusions that can be drawn from these studies.

These studies were helpful on safety but not efficacy.

Panel chair: "There is a consensus among panel members that these secondary studies are not helpful with regard to efficacy but were helpful in regards to safety and in generating hypotheses for future studies."

QUESTION 6. Please discuss the safety results reported in the clinical trials and whether they raise any concerns.

The device appears safe, but physicians would need to be trained in how to use the device.

Panel chair: "The safety data raised no important safety issues. Several panel members mentioned that the company did not use tests to rule out any neurocognitive deficits. Theoretically, energy delivered would not be expected to cause such problems, given knowledge of electroconvulsive therapy." He also said the panel expressed a need for physician training.

QUESTION 7. Based on the trial design, treatment with this device would require that subjects be withdrawn from antidepressant medications prior to treatment with the device. Please comment on whether removing medication therapy while instituting device therapy poses any clinical safety concerns.

While the device appears safe, stopping antidepressants was a concern.

Panel chair: "There was no consensus. The panel identified no safety concerns apparent in Study 01 during the brief wash-out period. But concerns were raised that efficacy was not demonstrated."

QUESTION 8. The mean number of ATHF level 3 exposures for subjects enrolled into Study 01 was 1.6. Over 50% of the subjects met the criteria for ATHF group (i.e., had failed only one antidepressant medication during the current episode). Please discuss your interpretation of the severity of the depressive episode of subjects enrolled in Study 01.

The data did not allow conclusions based on severity of depression.

Panel chair: "The panel has a consensus that severity of depression and treatment resistance are not the same, and the trial is not designed to stratify effects or stratify results by these categories. It appears that the population is less severely affected with regard to severity than the total ECT population, but when comparing the ECT population that would have qualified for trial 01, no major differences in the populations are apparent. Trying to draw conclusions when the overall p-value is in the range that it is, is done with great peril."

QUESTION 9. The sponsor has submitted the following indications for use (IFU) statement: The treatment of Major Depressive Disorder (MDD). Considering that the IFU statement should reflect the population that was studied, please discuss whether the sponsor's clinical trial supports this general indication. If not, please comment on the population which might be best considered for treatment with this device, based on the specific population enrolled and evaluated in the clinical trial.

The device should be limited to the type of patients studied.

Panel chair: "Widening the indication of the device to populations beyond populations tested in clinical trials should be done with great caution. With regard to this particular device and treatment, the panel was in consensus that the indication should be for that population studied in the trial, specifically the panel suggested that the indication be for patients who had not received benefit from at least one, but not more than four, adequate trials of an antidepressant in the current or past episode."

Other panelists commented:

- "This gets to one of our difficulties…We're talking about a treatment that has an effect, but it is a fairly small one."
- "To take questionable results from a specific subset and then generalize it to a very large group, I think (is a leap)…If you take the leap that it works in the group it was tested in – and I think there was still some question there – and apply it to the whole group including those on treatment and concomitant treatment…I think is an unreasonable leap of faith."
- "One of the exclusion criteria for the study was psychosis, so I would want to exclude…MDD without psychosis."
- "Was one failed trial part of the inclusion criteria for this study? Then I would have to agree with some of the panelists who said it might be harder to generalize the patients who didn't have a failed trial."

QUESTION 10. Overall risk:benefit: Taking into account your day's deliberations and your responses to the prior FDA questions, please discuss your interpretation of the overall risk:benefit profile for the NeuroStar System for the proposed indication for use as well as how that profile compares to that of ECT devices.

NeuroStar is safe, but efficacy wasn't proven.

Panel chair: "There was consensus that safety is much better established relative to ECT. With regard to benefit, the majority of the panel members thought there was an efficacy signal. No member of the panel indicated there was substantial equivalence between ECT and the NeuroStar System."

Other panelists commented:

- "We have a device sending a signal that has some efficacy. It looks like potentially something is there. But is it equivalent to ECT, which has efficacy and known side effects? At the present time, I can't say it is in the same ballpark risk:benefit ratio to ECT which has very well known benefits with some side effects. I currently can't say it is equivalent…Depression is a serious illness, and any new modalities are very much desired. I look forward to the next round of studies."
- *Statistician:* "I believe there is a modest signal. I am concerned about the clinical relevance of that signal, and it is a very sensitive situation to figure out how much efficacy you are willing to sacrifice for improved safety …I believe that the safety is favorable. I think I believe that there is a modest signal (of efficacy). I am concerned about the clinical relevance of that signal, and it is a very sensitive situation to figure out how much efficacy or effectiveness you are willing to sacrifice for…safety. That is a very difficult question, and I'm not sure I know the answer to it."
- *Patient advocate:* "I would like to see how long (the results) last – more studies. Five consecutive days of treatment may or may not be possible for a lot of people. I'd like to see a dose-response relationship for the study."
- *Industry representative:* "I don't think anyone would want to use this as a treatment of last resort. The word 'perilous' was used to describe statistical analyses. But positioning it (NeuroStar) as a therapy of last resort, especially for patients who are depressed and who might do away with themselves, is probably a bad idea. I would vote for approval, but certainly not as a therapy of last resort. The predicate device is ECT. The effect size is not as large as that of ECT, but it doesn't have to be. Equivalence and substantial equivalence in regulatory definition has nothing to do with the patients being the same identical patients, so this therapy is effective enough …Safety is comparably better than ECT – no general anesthesia, no muscle paralysis, no concerns about oxygenation, no seizures."
- "The risk:benefit ratio of ECT is well known. I have a problem in understanding the benefits of the (device) presented to us, although I understand the safety is much more beneficial."
- "All told, I'd say that the risk:benefit ratio is probably ***not*** acceptable. I don't have questions about safety, but I don't think that we have enough evidence of efficacy. So, without efficacy, you have an unacceptable ratio. We have clear evidence ECT works, and (we know the) side effect…I think it was a fairly low standard to show even that this would have an effect in one study. I know there has been a lot of talk about devices not being drugs, but I think treatments in general are treatments. And I think that the same criteria should be used for treatments for depression generally. I really think that the criteria is to have two controlled studies be positive. Here we set a lower standard with one study, and it was not positive, so it really peaks against efficacy."
- "My feeling is that, as the sponsor stated, we have 14 million or more patients in the U.S. with depression, many with MDD. This trial was completed in 18 months at only 23 sites. Many multicenter devices involve many more sites in conditions with much lower prevalence. I'd think, practically, one could design a trial where this floor effect is avoided, where the best primary endpoint could be decided upon based on these results, where blinding could be optimized further, and secondary endpoints could be part of the protocol…I think such a trial could be completed in less than 18 months."
- "During the meeting today, my confidence in ECT increased, and my confidence decreased in the efficacy of TMS. My conclusion is that the evidence so far doesn't support an equivalence of the risk:benefit ratio of the two agents."
- "This is a different population. The more modalities we have the better, though we'd like to see better figures (results)."
- "I would encourage the sponsors that they are close and an additional study would, hopefully, get them over the bar here."
- "Depression is a very serious illness…and I look forward to the next round of studies."
- *Patient advocate:* "I feel I needed more information in order to make an adequate decision."
- *Industry representative:* "I want to respectfully disagree with the non-substantially equivalent consensus in the chair's summary because I think that he may have misunderstood the regulatory definition of 'substantially equivalent'…I want to put on record that two members of the panel – neurosurgeons – were not able to make it, and missing members might be as important as missing data."
- "I think the question of whether it works against sham would still be an important question."

POST-MARKETING STUDY UPDATES

Susan Gardner, director of the FDA's Office of Surveillance and Biometrics, told the panel that the review of post-marketing studies of Cyberonics' VNS and Confluent's DuraSeal represented a "milestone" as a part of a new FDA initiative to improve quality and oversight of post-market studies, "The intention is not to revisit our decision to allow devices to market…Routinely now, there is going to be a post-market update." She added that such updates are going to be expected and said this first official post-market panel meeting was the trial run.

Panel members did not get into a long discussion of the efficacy of either device, but they expressed concern that neither has yet been proven to be effective. They also were astonished that interim data was released, and they warned of the potential consequences of that.

CYBERONICS' VNS Therapy System

Cyberonics' VNS (vagus nerve stimulator) device is a titanium disc about the size and thickness of a small stopwatch. It was approved for epilepsy in 1997, and in 2005 the FDA approved it for treating chronic treatment-resistant or recurring depression (TRD). As part of its approval in July 2005, the FDA ordered that the device carry a strong warning cautioning patients that VNS therapy is permanent. The FDA also asked for a post-marketing (Phase IV) trial as well as a patient registry.

An FDA official told the panel, "We had set up the ambitious six-month reporting schedule for Cyberonics to provide the agency with a progress status on their two study commitments. We specified that we would like the sponsor to provide general information but also study information, specify the study progress, any changes occurred, and any interpretation of the potential interim results…Very early in the review process, before the device was actually approved, we had a clear timeline that would help us later identify the study progress more efficiently."

The FDA's original decision to approve VNS for depression has been criticized by consumer advocates and was the target of a Senate Finance Committee investigation. Cyberonics also is involved in an accounting scandal and stock options probe and is searching for a new chief executive officer (CEO) and a new chief financial officer (CFO).

Public Citizen's Dr. Lurie said, "The history of the approval of this device remains an embarrassment to the FDA and to this committee specifically. As documented in the Senate Finance Committee's February 2006 report on the approval process for VNS, the CDRH director, who typically does not make device approval decisions, overruled at least 20 staff members who recommended against approval of this device on the grounds that efficacy had not been demonstrated. Not one staff member recommended approval. This committee came in for specific criticism in that report when the committee's Executive Secretary described the committee's June 15, 2004, meeting on VNS as 'very unusual, emotional, and not data-driven.'"

Dr. Lurie claimed the VNS approval – as well as the NeuroStar application – indicated there is "a dangerous double-standard within the FDA." He explained, "Whereas CDER (FDA's Center for Drug Evaluation and Research) requires randomized, placebo-controlled trials to approve antidepressants, the lax approval standard for devices ('reasonable assurance that the device is safe and effective' for devices, compared to 'substantial evidence of effectiveness for the claimed indications' for drugs) has been interpreted by CDRH to allow liberal use of historical controls. At least for devices that make a disease claim (e.g., 'treats depression'), it defies logic and endangers patients to have a lower approval standard for a device than a drug."

The panel allowed only 30 minutes for the discussion of the VNS post-marketing study and the registry. An FDA official said that the company was "on plan" with those studies. Cyberonics said it will pay for the device for about 250 patients in order to complete the study.

Dr. Richard Rudolph, vice president of clinical and medical affairs and chief medical officer for Cyberonics, told the panel that his company has made progress toward completing two post-market approval studies, and FDA reviewers concurred. An official with the FDA's Office of Surveillance and Biometrics said, "The company was tasked with submitting complete protocols for a 1-year, randomized, dose-ranging study as well as a five-year observational registry study. The (randomized) study, called D-21, is designed to compare the safety and efficacy of adjunctive VNS therapy administered at three different amounts of electrical charge among patients with TRD. That is a multicenter, double-blind, randomized study of 460 patients. The primary endpoint is QIDS-C change from baseline to Week 22. Secondary endpoints include change in scores and categorical outcomes based on IDS-C, IDAS-SR, MADRS, and CGI; adverse events; and frequency, intensity, and burden of side effects rating."

Phase IV study

Although enrollment in Study D-21 is low, an FDA official described the study as "on schedule." A Cyberonics official indicated this is due, at least in part, to the company deciding to start giving away the devices. The FDA…did have concern that there would be some difficulty meeting the future

Status of Study D-21 as of December 31, 2006

Sites/patients	Number planned	Actual number
Initiated Sites	30	26
Declining Sites	---	21
Enrolled patients	85-115	89
Withdrawn patients	---	5
Active patients	85-115	84
Implanted patients	---	51

Serious Adverse Events in Study D-21 as of December 31, 2006

Event description	Pre-implant	Post-implant
Worsening of depression	5	1
Suicide ideation	1	0
Urinary tract infection	1	0
Suicide attempt	0	1
Wound infection	0	1
Chest pain	0	1
Death (MV accident)	0	1
Carcinoma (thyroid)	0	1

enrollment under the current suboptimal coverage environment that exists. The studies were envisioned to enroll patients commercially implanted. Most payers will approve coverage on a case-by-case basis. This is not what was envisioned, so we were concerned, and we initiated a limited study. We acted as payer-of-last-resort for a limited number of patients, and that program is now expiring. (Cyberonics) has voluntarily initiated a new program which we're calling Device Donation and Surgical Program, in which (we) will cover implant costs for the remaining patients in the study."

An FDA official said, "The areas of concern were the high cost of the VNS procedure coupled with reimbursement issues. The sponsor early realized the problems with keeping to the schedule. Many sites declined participation. Several strategies were identified and, in order to shorten the approval process, the sponsor took a more active role working with clinical sites on IRB applications…The sponsor will work with insurance companies, and it submitted a request to CMS for a national coverage decision. It also covered the implantation cost and provided the device (free) for up to 250 patients." **She said she felt the FDA and company could work together to ensure timely completion of the study.**

A Cyberonics official gave the panel a peek at outcomes with VNS at three months, noting that the data has not yet been vetted with the FDA and has not been submitted for publication. He added that the company does not intend to submit it for publication until there is more patient experience.

Registry

Though enrollment in the registry also is low, the FDA said it, too, is "on schedule." A Cyberonics official said that a large number of sites are participating in the study because "it is not as rigorous a study as a randomized dosing study, and we can use some sites that have access to large pools of patients."

TRD Registry as of December 31, 2006

Sites/Patients	Number planned	Actual number
Initiated Sites	35	46
Declining Sites	---	87
Enrolled patients	200-450	267
Withdrawn patients	---	3
Active patients	200-450	264
VNS	---	223
Non-VNS	---	41

Preliminary Efficacy Data from TRD Registry

Measurement	Improvement in VNS patients n=57	Improvement in non-VNS patients n=15
QIDS-SR	21%	9%
MADRS	21%	11%

Only one panel member made a negative comment about VNS, saying that there was no difference in efficacy between VNS and sham therapy.

Members of the public who spoke earlier in the day made brief comments about VNS:

➢ **PRO:** Dr. Jeffrey Cousins, an Illinois neurosurgeon representing the American Association of Neurological Surgeons and the Congress of Neurological Surgeons, made a plea in favor of the devices. He said that his organizations were voicing support for the use of VNS for treatment of TRD in patients deemed appropriate candidates for the device, "VNS has proven to be very safe, useful, and effective in treatment of epilepsy, and we think it will be useful in TRD."

➢ **CON:** Dr. Lurie said Public Citizen opposes the approval of VNS on the grounds that it has not been proven to be efficacious. He said, "It's nice to see data, but there are much more fundamental questions…such as, Does it work?"

Panel discussion

- *Panel chair:* "Can I ask for some examples? As I looked at this, I was impressed that we are hearing about the challenges of these studies, the difficulties with the centers, and the numbers. How many centers accepted and declined? How many patients are in this group and that? Are those okay from your point of view?"
- *Statistician:* "I think most of those are relatively benign. I think when we get to endpoint information and data are broken down by treatment (it is troublesome). Does the information that we show create an operational bias? Does it affect the way patients and investigators behave in the trial? If it does, it is jeopardizing the integrity of the trial, but if it isn't, that's fine."
- *FDA official:* "We don't usually ask for interim reports. We ask for current status of the study. Because this is the first official presentation, we wanted to explore what opportunities we have."
- "I don't think anyone except a data safety monitoring committee should see the interim outcome data on any blinded or even unblinded trial as we have today. I would think about applying that standard to the registry. I think you've been extremely lucky. Often early in a trial grave inequalities can occur."
- "The original study for VNS failed to show a difference between sham and VNS. Is there a no-treatment arm in the dosing study? Because if all the doses are the same, you don't know whether all the doses did nothing or all the doses equally treat?"
- *FDA official:* "There was consideration, but we decided to go with the three (electrical) charge amounts, and this is the final recommendation that was made (for the study design)."
- *Statistician:* He voiced his general concern about making interim data available to the public, saying, "I strongly suggest developing policies of what data can be made public without jeopardizing the scientific integrity of the study…A lot of the data shown today are benign, but

some data would be more appropriate in closed session…I realize this is an evolving initiative, but it's really important that you think about that issue."

- *Industry representative:* "The objective of the dosing study was…to look at differences or comparisons between the safety of different doses; it wasn't designed for effectiveness. That was determined when the FDA approved the therapy. The two PMA studies were to answer unanswered questions from the original program: one is the optimal dosing program and the second is what the outcome is in the real world and, secondarily, what are the moderators of that response."

The CMS rejection

Just 10 days after the FDA panel, CMS indicated it plans to do what many other insurers have done – reject coverage of VNS for depression. CMS issued a draft decision that it "does not believe there is a treatment effect directly attributable to VNS therapy based on the current evidence."

Cyberonics has had trouble convincing insurers to pay for the device, which costs more than $10,000, in patients with depression, though most if not all cover it for epilepsy. In 2006 Blue Cross/Blue Shield rejected national coverage of VNS, saying the most rigorous studies showed it is no better than placebo at reducing depression.

CMS currently pays for VNS for certain types of epilepsy but not for depression. Last fall Cyberonics asked Medicare to issue a National Coverage Decision, initially asking Medicare to cover VNS for the broader category of adjunctive long-term treatment of chronic or recurrent depression for patients over the age of 18 who are experiencing a major depressive episode and have not had an adequate response to four or more adequate depression treatments. The company later amended the coverage request to just TRD patients who have been either (a) previously treated with ECT or (b) previously hospitalized for depression. About 103,000 Americans are estimated to have this type of severe depression.

At the FDA panel meeting, panel members and FDA officials had no comments on the outlook for CMS coverage of VNS for depression, but Dr. Lurie said, "We…petitioned the FDA to reverse its approval and have also asked CMS to deny Cyberonics' application for a favorable National Coverage Determination. We expect they will. As of September 6, 2006, 10 individual CMS contractors in 19 separate applications had turned down the company's application for a favorable Local Coverage Determination. None had issued a favorable Determination."

Indeed, CMS's analysis found that the pivotal VNS trial failed, noting there is "little weight" to support its use. VNS is "not reasonable or necessary," the agency said. CMS stated that the "concept of treatment-resistant depression is vaguely defined, subject to varying determination, and until a scientifically valid definition exists is of little help in treatment selection for individual patients."

After the CMS announcement, Dr. Lurie commented, "The agency correctly found that the device 'is not reasonable and necessary for treatment of resistant depression,' a decision that is very likely to result in the denial of reimbursement for implantation of this device in Medicare patients…It is high time for the FDA to admit that it erred and get this high-tech placebo off the market."

Cyberonics officials said they were "extremely disappointed" in the CMS decision and urged supporters of the therapy to send in their responses during the agency's 30-day public comment period before a final ruling is issued.

CONFLUENT'S DuraSeal Dural Sealant System

Erick Ankerud, vice president of Confluent Surgical, described the post-approval study that his company is doing with DuraSeal. He said that the purpose of the study was to further characterize the use of DuraSeal compared to standard of care.

The study will enroll 111 patients. In the preliminary analysis of the first 78 patients, 98.2% were free of neurological complications related to unplanned intervention or return to the operating room (OR), which was the primary endpoint. The infection rate was 8.1%, with the majority of these being deep surgical site infections.

Post-Approval Study Interim Results

Complication	DuraSeal n=39	Control n=39
CSF leak	0	2
Surgical site infection	1	1
Poor wound healing	1	0
Return to OR	1	0

The panel's statistician questioned the company on the study's power, asking, "What are you powered to do in this study? It is questionable whether you have enough power to find significant results at the end of the trial." He also asked if more information is available on how the study was powered, saying, "I'm a little uncomfortable with whether you have enough patients to delineate between two treatment arms with rare events. It seems like that should be known."

Other panel members said they want to see more data and questioned the value of interim analyses. One said, "To me it is unusual to see a public presentation of interim results. Scientifically, for you as a company, it takes a long time to understand the variabilities that can show up here. So far you might have been pretty lucky. Sometimes interim results can be very misleading. It takes a great deal of courage to have

the ***Wall Street Journal*** looking at these results." A company official responded, "It is a pilot program that we are pleased to be a part of, and we haven't drawn any conclusions at this time."

A panelist who was on the advisory committee which originally considered DuraSeal asked about imaging. A Confluent official told the surprised panel that it had shared some imaging/radiology data with the FDA as part of the PMA approval process. Several panelists suggested that it would be a good idea for them as well as centers involved in the studies to see the data, too.

Public Citizen's Dr. Lurie was critical of this product as well. He said, "The preliminary data from the post-approval randomized, controlled trial of DuraSeal do not yet permit assessment of whether this device is associated with increased rates of cerebrospinal fluid leaks or infections, the concerns raised in the uncontrolled trial which was the basis for the device's approval on April 7, 2005…The regulatory history of this device is literally upside-down with a randomized, controlled trial being used post-approval to support an approval decision based on uncontrolled data. In the mean-time, patients are being exposed to this inadequately tested device."

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