

UNITED STATES OF AMERICA  
FOOD AND DRUG ADMINISTRATION

\* \* \* \* \*

NEUROLOGICAL DEVICES PANEL

\* \* \* \* \*

18<sup>th</sup> MEETING

\* \* \* \* \*

OPEN SESSION

\* \* \* \* \*

TUESDAY, NOVEMBER 30, 2004

\* \* \* \* \*

The meeting was convened at 8:45 a.m., in Salon A of the Hilton Washington, D.C. North, 620 Perry Parkway, Gaithersburg, Maryland, Kyra J. Becker, M.D., Chairperson, presiding.

PRESENT:

Kyra J. Becker, M.D. Chair

Jonas H. Ellenberg, Ph.D., Voting member

Steven J. Haines, M.D. Voting Member

Annapurrni Jayam-Trouth Voting Member

Mary Lee Jensen, M.D. Voting Member

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PRESENT (Continued):

Christopher Loftus, M.D. Voting Member

Alexa I. Canady, M.D. Deputized Voting Member

Michael Egnor, M.D. Deputized Voting Member

Isabelle Germano, M.D. Deputized Voting Member

David T. MacLaughlin, Ph.D., Deputized Voting Member

Andrew K. Balo Industry Representative

Crissy E. Wells Consumer Representative

Janet Scudiero Executive Secretary

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

ALSO PRESENT:

Peter Hudson, Ph.D. FDA

CDR Stephen Rhodes FDA

Michael J. Schlosser, M.D. FDA

Amar Sawhney, Ph.D. Sponsor

Eric Ankerud, J.D. Sponsor

Patrick Campbell, Ph.D. Sponsor

John Tew, M.D. Sponsor

G. Rees Cosgrove, M.D. Sponsor

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Harry van Loveren, M.D.

Sponsor

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C O N T E N T S

	<u>PAGE</u>
Conflict of Interest Statement .....	4
Introductions .....	9
Update Since the June 15, 2004 Meeting .....	12
Open Public Hearing .....	14
Sponsor's Presentation:	
Eric Ankerud .....	16
Dr. Eric Campbell .....	18
Dr. John M. Tew, Jr. ....	26
Dr. G. Rees Cosgrove .....	31
Dr. Harry van Loveren .....	45
FDA Presentation:	
Dr. Peter Hudson .....	113
Dr. Michael J. Schlosser .....	125
Lead Panel Reviewer Presentations:	
Dr. David T. MacLaughlin .....	176
Dr. Alexa I. Canady .....	204
Questions to the Panel .....	224
Summation by the Sponsor .....	277
Panel Vote .....	289

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

(8:45 a.m.)

MS. SCUDIERO: Good morning, everyone.

We're ready to begin the 18th meeting of the Neurological Devices Panel. I'm Jan Scudiero, the Executive Secretary of this panel and a reviewer in the Division of General Neurological and restorative devices.

There are the usual housekeeping matters.

If you haven't signed in at the door, please do so.

There is agenda information at the door, and also Advisory Panel Website information about how to get summary minutes and transcripts.

Before I turn the meeting over to Dr. Becker, I'm required to read into the record the deputization of temporary voting members statement and the conflict of interest statement that was prepared for this meeting.

This is the appointment to temporary voting status statement.

Pursuant to the authority granted under the Medical Devices Advisory Committee charter, dated

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1       October 27th, 1990, and amended on April 20th, 1995, I  
2       appoint the following as voting members of the  
3       Neurological Devices Panel for the duration of this  
4       meeting on November 30th, 2004:

5                     Alexa I. Canady, M.D.

6                     Michael R. Egnor, M.D.

7                     Isabelle M. Germano, M.D.

8                     David T. MacLaughlin, Ph.D.

9                     For the record, these people are special  
10       government employees, and are consultants to this  
11       panel or another panel under the Medical Devices  
12       Advisory Committee. They have undergone the customary  
13       conflict of interest review and have reviewed the  
14       material to be considered at this meeting.

15                     Signed by Daniel G. Schultz, M.D.,  
16       Director, Center for Devices and Radiological Health,  
17       on November 18th, 2004.

18                     And this is the conflict of interest  
19       statement.

20                     The following announcement addresses  
21       conflict of interest issues associated with this  
22       meeting and is made part of the record to preclude

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1 even the appearance of an impropriety. To determine  
2 if any conflict existed, the agency reviewed the  
3 submitted agenda for this meeting and all financial  
4 interests reported by the panel participants.

5 The conflict of interest statutes prohibit  
6 special government employees from participating in  
7 matters that could affect their or their employer's  
8 financial interests. However, the agency has  
9 determined that the participation of certain members  
10 and consultants, the need for whose services outweighs  
11 the potential conflict of interest involved, is in the  
12 best interest of the government.

13 Therefore, waivers were granted for Dr.  
14 Mary Jensen and David MacLaughlin for their interest  
15 in firms at issue that could potentially be affected  
16 by the panel's recommendations. The waivers for Drs.  
17 Jensen and MacLaughlin involve a grant to their  
18 institution for their sponsor's study.

19 These panelists had no knowledge of the  
20 funding and had no involvement in the data generation  
21 or analysis. The waivers allow these individuals to  
22 participate fully in today's deliberations.

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1                   Copies of these waivers may be obtained  
2 from the agency's Freedom of Information Office, Room  
3 12A-15 of the Parklawn Building.

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

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

15                  I would like to mention that Ms. Crissy  
16 Wells, the consumer representative, is participating  
17 by telephone this morning, and I'd also like to  
18 announce that the scheduling information for the year  
19 2005 will be made public in January in the Federal  
20 Register and on our Website.

21                  Dr. Witten.

22                  DR. WITTEN: Yes, thank you.

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1           We have a couple of panel members who are  
2 going to be rotating off the panel after this meeting,  
3 and I'd like to take this opportunity to thank them.

4           And those are Dr. Becker, Ms. Wells, Mr.  
5 Balo, and Dr. Diaz, who unfortunately couldn't be here  
6 today.

7           FDA relies on its panel members to provide  
8 us with input and advice on our scientific matters for  
9 the devices that we regulate, and we appreciate the  
10 time and expertise that the panel members give us.

11           So I'd like to thank Dr. Becker, Ms.  
12 Wells, and Mr. Balo for their service here today and  
13 at the prior panel meetings during their tenure.

14           Thank you.

15           MS. SCUDIERO: Thank you.

16           I'd now like to turn over the meeting to  
17 our Chair, Dr. Kyra Becker.

18           CHAIRPERSON BECKER: Thank you.

19           Good morning. As Ms. Scudiero said, my  
20 name is Kyra Becker. I'm the Chairperson of the  
21 Neurological Devices Panel, and I'm a neurologist at  
22 the University of Washington in Seattle.

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1                   At this meeting, the panel will be making  
2 a recommendation to the Food and Drug Administration  
3 on the approvability of premarket approval application  
4 P040034 for the Confluent Surgical DuraSeal Sealant  
5 System, a bit of a tongue twister, intended for uses  
6 in adjunct sutured dural repair during cranial surgery  
7 to provide watertight closure.

8                   Before we begin this meeting, I'd like to  
9 ask our distinguished panel members who are generously  
10 giving their time to help the FDA in the matter being  
11 discussed today and the other FDA staff seated around  
12 this table to introduce themselves. Please state your  
13 name, your area of expertise, your position and  
14 affiliation.

15                   We'll start with Mr. Balo and go around  
16 the table.

17                   MR. BALO:           Andy Balo, industry  
18 representative. I'm Vice President of Regulatory and  
19 Clinical at DexCom in San Diego, California.

20                   DR. LOFTUS:       Hello. My name is  
21 Christopher Loftus. I'm a neurosurgeon. I'm Chief of  
22 Neurosurgery at Temple University in Philadelphia.

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1 DR. EGNOR: My name is Michael Egnor. I  
2 am a pediatric neurosurgeon. I am Vice Chairman of  
3 Neurosurgery at the State University of New York at  
4 Stonybrook.

5 DR. ELLENBERG: Good morning. My name is  
6 Jonas Ellenberg. I'm a biostatistician. I am  
7 currently employed at Westat in Rockville, Maryland.  
8 As of December 13th, I will be Professor of  
9 Biostatistics at the School of Medicine at the  
10 University of Pennsylvania.

11 DR. JENSEN: I'm Lee Jensen. I'm an  
12 interventional neuroradiologist. I'm Director of  
13 Interventional Neuroradiology at the University of  
14 Virginia in Charlottesville.

15 DR. CANADY: I'm Alexa Canady. I'm a  
16 pediatric neurosurgeon in Pensacola, Florida, and  
17 formerly Chief at the Children's Hospital in Michigan.

18 DR. HAINES: Steve Haines. I'm a  
19 neurosurgeon at the University of Minnesota.

20 DR. MacLAUGHLIN: Dave MacLaughlin. I'm  
21 Associate Director of Pediatric Surgical Research Labs  
22 at the Mass. General Hospital and a biochemist with a

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1 background in toxicology.

2 DR. JAYAM-TROUTH: Annapurrni Trouth. I'm  
3 a pediatric neurologist and the Chair of Neurology at  
4 Howard University Hospital, Washington, D.C.

5 DR. GERMANO: I'm Isabelle Germano,  
6 neurosurgeon. I'm Chief of the stereotactic  
7 functional and brain tumor problem at the Mt. Sinai  
8 School of Medicine, New York, New York.

9 DR. WITTEN: I'm Celia Witten, the  
10 Division Director of the reviewing division for these  
11 products at FDA.

12 CHAIRPERSON BECKER: And, Crissy, I don't  
13 know if you can hear us or not. Crissy Wells, are you  
14 there?

15 (No response.)

16 CHAIRPERSON BECKER: I guess she doesn't  
17 hear us by her telephone link-in.

18 So I guess at this point I'd like to note  
19 for the record that the voting members present  
20 constitute a quorum as required by 21 CFR Part 14.

21 Next Commander Stephen Rhodes, Chief,  
22 Plastic and Reconstructive Surgery Devices Branch,

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1 will update the panel on several matters that have  
2 occurred since the last meeting of the panel on June  
3 15th, 2004.

4 Commander Rhodes.

5 CDR. RHODES: Thank you, Dr. Becker.

6 I am Commander Stephen Rhodes, the Chief  
7 of the Plastic and Reconstructive Surgery Devices  
8 Branch here at the FDA, one of the branches that  
9 regulates neurological devices in the Division of  
10 General Restorative and Neurological Devices.

11 Welcome, members of the panel, members of  
12 the public, and manufacturers, to this one-day meeting  
13 of the Neurological Devices Panel.

14 This panel --

15 CHAIRPERSON BECKER: Hi, Crissy. We're  
16 just starting the update. We'll get back with you.

17 DR. WELLS: I'm having difficulty hearing  
18 you.

19 CHAIRPERSON BECKER: Crissy, we're just  
20 starting the update. Before Stephen gets going, would  
21 you like to just introduce yourself as the consumer  
22 rep.?

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1 MS. WELLS: Good morning. My name is  
2 Chris Wells, and I'm calling in from Phoenix, Arizona.  
3 I'm the consumer rep. for this panel.

4 CHAIRPERSON BECKER: Thanks, Crissy.

5 CDR. RHODES: This panel last met on June  
6 15th of this year, at which time you made  
7 recommendations on the premarket approval application  
8 for the Cyberonics Vagus Nerve Stimulator Therapy  
9 System intended for the adjunctive long-term treatment  
10 of chronic or recurrent depression.

11 The panel also met on February 23rd of  
12 this year to make recommendations on Concentric  
13 Medical's premarket notification for the MERCI  
14 Retriever.

15 On August 11th, the agency cleared the  
16 MERCI Retriever for restoring blood flow in the  
17 neurovasculature by removing thrombus in patients  
18 experiencing ischemic stroke. The MERIC Retriever is  
19 also indicated for use in the retrieval of foreign  
20 bodies misplaced during interventional radiological  
21 procedures in the neuro, peripheral, and coronary  
22 vasculature.

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1 More recently, on October 24th, the agency  
2 issued a guidance document entitled "Clinical Trial  
3 Considerations: Vertebral Augmentation Devices to  
4 Treat Spinal Insufficiency Fractures."

5 Additionally, one regulation action that  
6 this panel recommended in previous meetings is  
7 undergoing final review and clearance in the agency.  
8 The guidance document and the final rule reclassifying  
9 the neuro embolization device and the vascular  
10 embolization device from Class III to Class II should  
11 issue within the next few months.

12 And today you will make a recommendation  
13 on a premarket approval application from Confluent  
14 Surgical for the DuraSeal Dura Sealant System intended  
15 as an adjunct to sutured repair during cranial surgery  
16 to provide a watertight closure.

17 That concludes the update. We appreciate  
18 the commitment to public health of the panel members.

19 We value the comments of the members of the public  
20 who have requested time to address the panel. And we  
21 appreciate the PMA sponsor's presentation to the panel  
22 this morning and responses to questions that the panel

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1 may have.

2 Thank you for your attention.

3 CHAIRPERSON BECKER: Thank you, Commander  
4 Rhodes.

5 So we will now proceed with the open  
6 public hearing portion of the meeting, and prior to  
7 the meeting there were no requests for the public to  
8 speak. I think I'd just like to ask if there's  
9 anybody in the audience now who would like to make an  
10 address to the panel.

11 (No response.)

12 CHAIRPERSON BECKER: No. Well, if that's  
13 the case, then we'll move on to the sponsor's  
14 presentation, and Confluent Surgical will be  
15 presenting their information for the DuraSeal Dura  
16 Sealant System intended for use as an adjunct to  
17 sutured dural repair during cranial surgery to provide  
18 watertight closure.

19 After this presentation we'll have a short  
20 break and then proceed with the FDA presentation  
21 before lunch. After lunch, the panel will deliberate  
22 on the approvability of the PMA.

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1           Before the panel votes for the  
2           approvability of the PMA, there will be another open  
3           public hearing and a time for FDA and sponsor  
4           summations.

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

9           We'll begin with the sponsor presentation.

10          The first Confluent Surgical speaker is Mr. Eric P.  
11          Ankerud -- I hope I pronounced that correctly -- VP  
12          for Clinical, Regulatory and Quality. He'll introduce  
13          the other Confluent Surgical speakers as time goes on.

14          Mr. Ankerud.

15          MR. ANKERUD: Thank you, Dr. Becker, and  
16          good morning, distinguished members of the Advisory  
17          Panel, FDA, and guests of this meeting.

18          Confluent Surgical today will present to  
19          you the DuraSeal Dura Sealant System. Our presenters  
20          will include Patrick Campbell, Vice President of R&D  
21          at Confluent Surgical; Dr. Tew from the Mayfield  
22          Clinic; Dr. Cosgrove from Massachusetts General

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1 Hospital; and Dr. van Loveren from Tampa General  
2 Hospital.

3 In our presentation, we will provide to  
4 you an overview of our technology for the device,  
5 discuss the study design that was executed in the U.S.  
6 pivotal trial, and address safety questions that were  
7 provided to the panel.

8 Our company was founded in 1998 by Dr.  
9 Amar Sawhney, who has innovated this technology over  
10 the last decade. The mission of the company is to  
11 address unmet needs of surgical wound healing with in  
12 situ polymerized biomaterials.

13 Our country is based in a suburb of  
14 Boston, Massachusetts, and we are a small company.

15 The DuraSeal Dura Sealant System is  
16 commercialized in Europe in select markets, as well as  
17 registered in Australia.

18 The project that will be presented to you  
19 today began with a formal pre-IDE submission to FDA in  
20 March of 2002. Initially submitted as a study that  
21 was seeing input from FDA on the design for clinical  
22 trial to study the DuraSeal device.

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1           During the discussions with FDA, FDA did  
2 seek input from an advisory panel member before this  
3 trial design was finalized in an IDE submission in  
4 February 2003.

5           Upon approval of that IDE with input from  
6 the advisory panel member, we executed a pivotal trial  
7 in the U.S. at ten clinical sites and one European  
8 site.

9           In May 2004, the study follow-up was  
10 completed. We treated 111 patients in this pivotal  
11 trial, following those patients out to three months.  
12 A modular PMA submission was initiated in January of  
13 this year, and in July of 2004, the final clinical  
14 results from the pivotal trial were submitted to FDA,  
15 and it is those results that we will discuss in this  
16 meeting today.

17           I would like to welcome to the podium Pat  
18 Campbell. Dr. Campbell is Vice President of Research  
19 and Development at Confluent Surgical.

20           DR. CAMPBELL: Thank you, Eric.

21           Before I discuss the DuraSeal hydrogel  
22 technology and preclinical tests, I'd like to review

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1 some of the properties for an ideal Dura Sealant.

2 First and foremost, the sealant needs to  
3 be biocompatible. DuraSeal consists over 90 percent  
4 of water. The solids that are there, that remain, are  
5 mostly polyethylene glycol, a molecule which is widely  
6 known and used in the pharmaceutical industry and  
7 recognized as nontoxic.

8 Polyethylene glycol is also synthetic,  
9 which means there's no potential for viral  
10 transmission in the product.

11 DuraSeal, when formed, contains water  
12 sensitive linkages that allow it to break down into  
13 small molecules and be fully absorbed in the body.  
14 When it's applied on tissue, it reacts very quickly.,  
15 and this quick reaction allows it to adhere very well,  
16 and that good adherence with inherent cohesive  
17 strength of the material allow it to function well as  
18 a dural sealant to withstand elevated CSF pressures.

19 As I mentioned, the material goes onto the  
20 tissue as a liquid and polymerizes so that it's very  
21 easy to apply and spray onto tissue, and it contains a  
22 dilute blue dye that allows it to be visualized and to

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1 determine thickness and coverage of the product.

2           Prior to application, DuraSeal consists of  
3 two liquids. One liquid contains a small molecular  
4 weight amine, as shown in the top box. The other  
5 liquid contains an end modified polyethylene glycol  
6 molecule. That molecule contains a water sensitive  
7 linkage, as shown in the yellow, that allow it to  
8 break apart in time.

9           It also contains an end modification that  
10 allows it to react with the amine when it comes into  
11 contact with that. When those liquids are sprayed  
12 onto tissue, they rapidly polymerize, forming a  
13 hydrogel network that then has interspersed in that  
14 network water sensitive linkages that then allow it to  
15 break back down over a period of one to two months  
16 into small molecules which are absorbed and cleared  
17 from the body.

18           This is the DuraSeal kit as supplied. You  
19 see it contains two liquid syringes. The top syringe  
20 is injected into the powder vial that contains the  
21 polyethylene glycol and the blue dye. When that  
22 powder dissolves, the blue liquid is drawn back into

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1 the syringe, and the entire device is assembled as  
2 shown on the bottom frame.

3 This is a movie that shows the application  
4 of DuraSeal just on a hand. The surgeon advances the  
5 syringes, sprays the liquids. The rapid  
6 polymerization allows it to coat surfaces that are  
7 even tilted without significant runoff, and the blue  
8 coloration allows the surgeon to determine the extent  
9 of coverage and the thickness.

10 DuraSeal has undergone all of the  
11 biocompatibility tests as mandated in ISO 10993. The  
12 only test I'll mention here is the subchronic toxicity  
13 test where the material was evaluated in rats at a  
14 dose of 40 times the human dose, and there was no  
15 noted systemic toxicity.

16 DuraSeal has also been evaluated in canine  
17 craniectomy model where a durotomy was created, as you  
18 can see in the top left frame, that was two to three  
19 millimeters wide by two centimeters long. Animals  
20 were then randomized to either receive DuraSeal  
21 application, as in the right panel, or to remain as  
22 controls with no sealant application.

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1                   Animals then had the bone flaps removed  
2 and were recovered from surgery. They were then  
3 evaluated at four different postoperative time points,  
4 and at the time of evaluation animals were  
5 anesthetized. The bone flaps were removed, and the  
6 Valsalva maneuver was performed in an attempt to  
7 determine what pressure the Dura leaked.

8                   You can see the left-hand picture on the  
9 lower panel. That's at day one. The blue dye rapidly  
10 diffuses out of the sealant after application and so  
11 you can see the gel is still present. It's clear, and  
12 you can see under the Valsalva maneuver the Dura is  
13 straining, but the sealant is withholding the  
14 pressure.

15                   At day four there's a very similar  
16 picture. At 56 days the material was fully absorbed.

17                   The dura was completely healed, and I'll show you  
18 some histology in a moment.

19                   This is the data obtained of the actual  
20 leak pressures measured in the DuraSeal and test  
21 animals at the different postoperative time points.  
22 You can see at day one all of the control animals

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1 leaked at five centimeters of water, which was the  
2 resting CSF pressure in that model.

3 So upon immediate bone flap removal there  
4 was a leak. Well, all of the DuraSeal animals  
5 withstood at least 50 centimeters of water. Two of  
6 those animals made it to 55 without leaking.

7 A similar difference in test and control  
8 persisted at four days. At seven days you can see a  
9 slight increase in the control ability to resist  
10 pressure, and interestingly, at seven and 56 days it  
11 was noted that in the test animals the bone flap was  
12 easy to remove. There were no adhesions between the  
13 dura and the bone flat, whereas the controls had  
14 significant adhesions or scar tissue, as you would  
15 expect in this model, between the bone flap and the  
16 dura.

17 And interestingly, at 56 days, there was  
18 still a difference in the test and control leak  
19 pressures.

20 The picture on the left is what I showed  
21 earlier with the gross image of the 56 time point with  
22 the dura smooth, healed in plane. The picture on the

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1 right is the histology in this model. You can see the  
2 bone flap, the thickened dura underneath. The dura  
3 appeared very similar in histology as it did to  
4 controls. There's no signs of neurotoxicity or local  
5 mass effect in this model.

6 DuraSeal was also evaluated for absorption  
7 using two different techniques. The top panel of  
8 pictures is a canine imaging study where DuraSeal was  
9 implanted and then imaged using MRI at T2 weighted.  
10 At three days you can see the light area on the top  
11 left right there. DuraSeal is very visible at two  
12 weeks. Four weeks it's getting a little bit thinner.  
13 Six weeks there's a trace, and by ten and eight  
14 weeks, it's rapidly absorbed.

15 A similar study was performed in the rat  
16 subcutaneous model where plugs of gel were implanted  
17 and that were harvested every two weeks and evaluated.

18 At two weeks the physical properties of the gel were  
19 very similar to what they were at time zero. The  
20 material then rapidly degraded and was completely  
21 absorbed. The pockets were empty by eight weeks.

22 DuraSeal has also been evaluated in

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1 neurotoxicity studies where pieces of gel were  
2 implanted into rat brain parenchyma. The picture on  
3 the left is a histology slide from four days with no  
4 neurotoxicity, no reaction shown. The square in the  
5 middle is the void where the gel was. It doesn't  
6 withstand the histological processing well.

7 The six weeks had a very similar non-  
8 neurotoxic response with a decrease in volume  
9 associated with the absorption of the gel.

10 So in summary, DuraSeal has undergone a  
11 battery of tests. It has been shown to be nontoxic.  
12 It's not neurotoxic when in contact with brain tissue,  
13 and it has been shown to be safe at high doses in  
14 preclinical models.

15 It effectively seals the dura, allowing it  
16 to heal underneath, and then the material end life can  
17 be imaged using MRI imaging, and it is completely  
18 absorbed over eight weeks.

19 It is my pleasure now to introduce Dr.  
20 John Tew, a professor in the Department of  
21 Neurosurgery at the University of Cincinnati in  
22 Mayfield Clinic.

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1 DR. TEW: Thank you, Pat.

2 Good morning, ladies and gentlemen, Madam  
3 Chair. My name is John Tew from the University of  
4 Cincinnati, Mayfield Clinic, and it's my pleasure to  
5 be here today as a neurosurgeon for 35 years and to  
6 disclose to you that I do own stock options in this  
7 company; that I am a member of the Scientific Advisory  
8 Board; and that I've been involved as an investigator  
9 in the process and am paid to be here today to explain  
10 to you the project rationale.

11 As a neurosurgeon for 35 years, I am well  
12 aware that watertight dural closure has been an  
13 illusive objective for neurosurgery for that time and  
14 much, much longer. Achieving a watertight dural  
15 closure is a basic objective of all who are in  
16 neurosurgical practice, particularly in some parts of  
17 neurosurgical closure, such as the post dura fossa and  
18 in spinal operations because controlling  
19 intraoperative leakage is very important to preventing  
20 CSF leakage and the development of serious  
21 postoperative complications.

22 The strata of these complication go from

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1 minute pinholes, either between suture lines or  
2 pinholes made in the performance of tacking up the  
3 dura for getting it out of the way, and these small  
4 holes may act as a one-way valve in which the fluid is  
5 allowed to get out of the dural compartment and  
6 collect as a pressurized system in the extra dural  
7 space.

8 In addition, extra dural and subcutaneous  
9 collections of CSF may develop into what are called  
10 pseudomeningoceles or enclosed meningoceles and other  
11 collections of CSF which may lead to acute and chronic  
12 problems of wound healage.

13 Overt leakage of CSF has perhaps even more  
14 potential serious postoperative complications and lead  
15 to not only compression of the neurological tissues,  
16 brain, spinal cord, but serious interference with  
17 wound healing, leading to dehiscence or breaking down  
18 of the wound which may be complicated by meningitis,  
19 infections, and a requirement for surgical  
20 intervention which leads to prolonged hospitalization  
21 and marked increase in medical cost.

22 So in my opinion as a surgeon for 35

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1 years, there continues to be a major unmet need for  
2 product that creates a watertight dural closure.

3           Sealing sutured dural closure is a current  
4 method which is in search of an appropriate device.  
5 There are no FDA approved devices at the present time,  
6 but yet neurological surgeons use a variety of  
7 products off label. There's no standard of care for  
8 the use of these products. They fall basically into  
9 three types: hemostasis agents, such as surgical or  
10 gelfoam, which are approved as hemostatic agents, but  
11 I suppose in our experience are used principally as  
12 space fillers to attempt to result in some type of  
13 sealant of the dura; adhesives, such as fibrin glues,  
14 cryoprecipitates, albumin gluteraldehydes,  
15 cryanoathacrylates, all of which have some potential  
16 toxic issues and have no approval for this particular  
17 objective; and finally, dural substitutes, such as  
18 DuraGen.

19           I'd like to show you one representative  
20 case which illustrates the intraoperative  
21 effectiveness of DuraSeal and the ease of application  
22 and the intraoperative effectiveness.

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1                   This is a 69 year old female who is  
2                   undergoing a craniotomy for a tumor in the left  
3                   frontal area, a so-called supratentorial craniotomy,  
4                   in which the durotomy is seven centimeters in total  
5                   length. Three, point, two milliliters of DuraSeal is  
6                   applied.

7                   And you see this is a movie which shows  
8                   the craniotomy in this area. And there's an overt  
9                   leak at the one o'clock area, and the DuraSeal is  
10                  applied. The polymerization time is three to five  
11                  seconds. You can see the rapid set-up, the  
12                  polymerization, and then the testing with a Valsalva  
13                  maneuver for up to 20 centimeters of water in the  
14                  immediate polymerization.

15                  The testing shows visibly that there's now  
16                  no leakage at the site of what was previously an overt  
17                  leakage in a hole two millimeters in size.

18                  Thereafter the DuraSeal pilot study was  
19                  performed in Europe at Nijmegen Medical Center by a  
20                  single principal investigator, Dr. Andre Grotenhuis,  
21                  who performed in a period of eight months craniotomies  
22                  for operative procedures on the brain, 45, and two

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1 spinal procedures reflecting the principal cranial  
2 nature of his surgical practice.

3 The objective of this study was to  
4 evaluate safety and efficacy of DuraSeal as an  
5 adjuvant to standard surgical dural repair techniques  
6 in cranial and spinal procedures.

7 It was a single arm, non-randomized,  
8 single center trial performed by one surgeon. The  
9 intraoperative sealing endpoint was no CSF leakage  
10 during a Valsalva maneuver after application of  
11 DuraSeal.

12 The results were as follows. There was  
13 100 percent intraoperative sealing success after a  
14 Valsalva is performed in the previous representative  
15 case. The results documented a 6.4 percent incidence  
16 of CSF leak, one incisional leak which was through the  
17 incision, and one was through the nose, reflecting an  
18 unsuspected or unidentified intraoperative leakage or  
19 potential opening into a nasal sinus, and one  
20 pseudomeningocele.

21 There was a 4.3 percent incidence of  
22 infection, one deep and one superficial. There were

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1 no device related adverse events, and the general  
2 impression of the investigator was that of excellent  
3 wound healing. Adverse events were consistent with  
4 the complexity of the operations that were included in  
5 the study. The results of this study were felt to be  
6 adequate to serve as a basis for a U.S. pivotal trial.

7 I would now like to introduce my  
8 colleague, Dr. Rees Cosgrove, who is Associate  
9 Professor of Surgery at Harvard Medical School and the  
10 Massachusetts General Hospital, who is the principal  
11 study investigator.

12 Thank you very much.

13 DR. COSGROVE: Thank you, John.

14 My name is Dr. Rees Cosgrove. I'm a  
15 neurosurgeon at Massachusetts General Hospital and the  
16 principal study investigator.

17 I have been compensated for my time and  
18 travel here today. I serve on the Scientific Advisory  
19 Board and, as Dr. Tew has mentioned, I am the  
20 principal study investigator.

21 As you've heard, the objective of this  
22 study was to see if the DuraSeal product would provide

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1 us with a watertight closure after primary dural  
2 sutured repair in craniotomies.

3 We used some of the information from the  
4 Nijmegen or the European trial in order to design an  
5 appropriate study to test this objective, and I have  
6 to say this was a very difficult study to design, and  
7 there are a variety of reasons.

8 We deliberated internally. We brought in  
9 experts, consultants to discuss expert groups of  
10 neurosurgeons to discuss an appropriate study design.

11 We had communication with the FDA throughout this  
12 process. We had input from the FDA and input from one  
13 of the panel members here to try and develop an  
14 appropriate study design.

15 Part of the problem and some of the big  
16 problems is that in terms of achieving watertight  
17 dural closure is there is no standard of care.  
18 Neurosurgeons across this country use an absolute  
19 mishmash of materials. Some people prefer surgical  
20 and gelfoam over the durotomy. Some people prefer  
21 dural substitutes over a primary dural closure. Other  
22 people prefer fibrin glue sprayed over the durotomy.

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1                   So we all agree that a watertight closure  
2                   is an important objective of our standard wound  
3                   closure, but there is absolutely no standard of care  
4                   in this country.

5                   And as Dr. Tew has pointed out, none of  
6                   the devices we use are FDA approved for this  
7                   application. So this presented us with a problem, and  
8                   we deliberated on having a control arm of using fibrin  
9                   glue which is one of the commonly utilized materials,  
10                  but you know, this is an unapproved device, and in our  
11                  communications and deliberations with the FDA, we were  
12                  told that this was inappropriate to do a trial  
13                  comparing it to an unapproved device, especially when  
14                  the efficacy and safety profile of that device is not  
15                  known in this application. So that was not  
16                  appropriate.

17                  And then the concept of having no  
18                  treatment at all as the control arm was also neither  
19                  medically or ethically acceptable, and because no  
20                  neurosurgeon that I know of would not supplement their  
21                  dural closure in some way in an attempt to achieve a  
22                  watertight closure.

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1           So with the FDA input, with the panel  
2 members' input, we arrived at a study that chose an  
3 intraoperative endpoint as its outcome.

4           The study was a prospective study at  
5 multiple centers and had a nonrandomized, single arm.

6           We did use a prospective objective performance  
7 criteria for the primary endpoint and had 11  
8 participating sites, ten in the United States and one  
9 in Europe.

10           The single European site was a Nijmegen,  
11 as has been previously mentioned, and then as you can  
12 see, there are ten other major academic medical  
13 centers in this country, and what these major academic  
14 medical center tend to attract is a very complex and  
15 complicated subject population, typically sicker  
16 patients.

17           So we actually gave ourselves quite a  
18 challenging study population. Key inclusion criteria  
19 included adults who were to undergo an elective  
20 craniotomy or craniectomy and classified as a clean  
21 procedure per the CDC guidelines, and there were a  
22 variety of exclusion criteria, including penetration

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1 into an air sinus of the mastoid air cells which would  
2 make it a clean contaminated procedure; prior surgery  
3 in the area; previous radiation or chemotherapy or  
4 even plant chemotherapy or radiation, preexisting  
5 hydrocephalus, and then a variety of serious medical  
6 exclusion criteria.

7 Intraoperatively, the eligibility criteria  
8 included a durotomy of at least two centimeters in  
9 length. The durotomy had to be at least three  
10 millimeters from the craniotomy margin. The gap could  
11 not be greater than two millimeters if after the  
12 neurosurgeon made his best efforts to close the dural  
13 opening. If there was a gap of greater than two  
14 millimeters, that these patients were excluded. We  
15 allowed only autologous duraplasty materials to be  
16 used, and importantly, the patients have to  
17 demonstrate either a spontaneous leak of CSF after the  
18 neurosurgeon had done his absolute best to get his  
19 closure, what he considered his optimal closure, or  
20 they have to leak spontaneously, or they have to leak  
21 upon a Valsalva maneuver.

22 So our primary efficacy endpoint was,

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1 indeed, interoperative sealing, and we termed it  
2 successful if there was no evidence of CSF leak after  
3 the dural repair, after up to two DuraSeal product  
4 applications, and tested during a Valsalva maneuver,  
5 taking the intracranial pressure up to 20 centimeters  
6 of water and holding it there for at least five to ten  
7 seconds.

8 And we used prospective objective  
9 performance criteria of 80 percent success rate at  
10 doing that.

11 And in order to justify and in order to  
12 demonstrate that for statistical purposes that our 95  
13 percent confidence interval for intraoperative ceiling  
14 would be greater than 80 percent, we concluded that at  
15 least 70 patients needed to be enrolled and for safety  
16 purposes, we targeted a full 100 patients, assuming  
17 that about ten percent of these might drop out.

18 So for the entire study we planned on  
19 enrolling 110 patients.

20 The safety evaluations and the endpoints  
21 used were typical for a study of this nature, and  
22 included everything that is demonstrated up there. We

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1 defined a postoperative CS leak inclusively, and any  
2 obvious CSF leak that required some sort of surgical  
3 intervention, i.e., breaking of the skin, either  
4 suturing, over suturing of the incision, needle  
5 aspiration of a collection, placement of a lumbar  
6 drain or a ventricular drain or reoperation, that's  
7 clearly a significant CSF leak, and that was one  
8 definition.

9 Any time that fluid was collected outside  
10 the head that could be confirmed with tau-transferrin  
11 as being CSF, that was clearly a CSF leak.

12 And finally, at any time that the  
13 principal site investigator deemed either clinically  
14 or on his physical examination that there was  
15 suspicion for a CSF leak, that was also determined to  
16 be a CSF leak.

17 The protocol was designed to be with a  
18 detailed preoperative baseline testing and appropriate  
19 follow-up periods in seven days, six weeks, and three  
20 months to the conclusion of the study.

21 It is important to note that adverse  
22 events were collected at every time point in this

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1 study.

2 All centers were mandated to maintain a  
3 screening log, and a total of 303 patients were  
4 screened for entrance into the study. One hundred and  
5 five of those did not meet preoperative eligibility  
6 primarily because of coexistent medical illnesses,  
7 prior surgery in an area, long-term steroid use which  
8 we excluded.

9 Twelve patients actually were enrolled and  
10 signed consent, but then in terms of some of the  
11 metabolic work-up, their abnormalities of BUN and  
12 creatinine that excluded them from actually entering,  
13 and 54 patients refused participation primarily for  
14 social reasons. These are big academic medical  
15 centers where people are attracted from around the  
16 country and for different reasons. They wouldn't be  
17 willing to come back at different time points and  
18 complete the requirements of the study.

19 So a total of 132 patients were enrolled,  
20 and at surgery 111 of these were treated with  
21 DuraSeal. There were 21 intraoperative screen  
22 failures, i.e., an inadvertent entry into a sinus,

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1 recognition that the durotomy wasn't far enough away  
2 from the craniotomy margins or the fact that the  
3 neurosurgeon used nonautologous tissue for a  
4 duraplasty because he wasn't convinced that maybe the  
5 device would be effective.

6 But so a total of 111 patients were  
7 treated with a DuraSeal. All 111 were available at  
8 the first follow-up time point at seven days. One  
9 hundred nine were available at the six week visit, and  
10 at the final visit at three months, 107 patients were  
11 available for follow-up, giving us a 98 percent  
12 compliance rate.

13 One patient fell out after seven days  
14 because of a death at 30 days. An additional patient  
15 didn't make it into this group, although it was  
16 followed to completion because she didn't make it into  
17 the time constraints that we gave for the six-week  
18 visit, but she was followed up shortly thereafter, and  
19 made her three-month visit.

20 There was an additional death at 85 days  
21 postoperatively, and two patients, although they were  
22 followed to the six weeks, did not make their final

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1 three-month visit. So overall I think a rather  
2 exceptional compliance rate for a study of this sort.

3 Patient demographic we as expected for  
4 this study population. It's important to point out  
5 that over half of the patients had a smoking history,  
6 and in speaking to the complexity and severity of the  
7 cases that these kinds of medical centers attract, 86  
8 percent had serious cardiovascular co-morbidities with  
9 an ASA score of two or greater.

10 The indications for surgery are, again, as  
11 you might expect at some of these major medical  
12 centers, with tumors, AVM, microvascular  
13 decompressions, Chiari, aneurysms, epilepsy.

14 Next.

15 But what's interesting to point out is  
16 that unlike what the ratio of procedures' surgical  
17 locations in the general population, we have nearly 50  
18 percent of our cases were infratentorial, and it's the  
19 infratentorial group that all neurosurgeons worry  
20 about the most because of the high risk and propensity  
21 to CSF leaks and related complications.

22 In addition, the surgeries at these

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1 different centers tended to be long. The average  
2 duration of surgery was nearly four hours, and over 90  
3 percent were longer than two hours, with a full 30  
4 percent of greater than four hours and up to seven  
5 hours. So these were long and involved procedures.

6 As expected, there was a distribution  
7 between craniotomy, where the bone is replaced, and  
8 craniectomy, where the bone is removed and left out.  
9 And nearly 50 percent of the surgeons chose some sort  
10 of autologous duraplasty material to close the dura to  
11 their satisfaction.

12 At the surgical procedure, 60 percent of  
13 the patients after the surgeon had done his best to  
14 repair it in a watertight fashion, 60 percent of the  
15 patients' dural repairs leaked spontaneously, and the  
16 other 40 percent leaked after a Valsalva maneuver.

17 The DuraSeal was applied in a single  
18 application once, and only five percent of the time  
19 did it require two applications, and 95 percent of the  
20 time it was rated by the neurosurgeons as easy or very  
21 easy to use, and this is without any lead-in patients  
22 or any training prior to the first case.

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1           None of the patients who were treated with  
2 the DuraSeal leaked after the application. Two  
3 patients, however, did not have their Valsalva  
4 maneuver elevated to an appropriate level to 20. It  
5 was only brought up to ten, and these we then  
6 considered were not evaluable by our protocol, and  
7 therefore, on an intent to treat analysis 98 percent  
8 of our patients were successfully sealed with a  
9 DuraSeal application.

10           In terms of adverse events, we created a  
11 very inclusive approach. Each and every untoward  
12 event was captured, and we did not cascade the events  
13 in individual patients. So every time there was an  
14 adverse event, even in the same patient, it was  
15 reported separately as an adverse event.

16           Importantly, there were no unanticipated  
17 adverse device effects. There were no device related  
18 adverse events. The majority of these events were not  
19 serious, but in keeping with the complexity of the  
20 cases, there were a significant percentage of patients  
21 who had a serious adverse event, but none of these  
22 were inconsistent with the type of surgeries performed

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1 or the complexity of the cases.

2 In this slide and the following slide,  
3 we've taken all of the adverse events, and I attempted  
4 to order them in descending order of seriousness, and  
5 as I said, these are all typical for the patient  
6 population that we were studying, but in terms of  
7 serious adverse events, I need to point out that most  
8 of the panel members are already aware there were  
9 eight surgical site infections.

10 And later on in this presentation Dr. van  
11 Loveren will be speaking to address this observation.

12 Next.

13 Each and every adverse event was reviewed  
14 by an independent clinical events committee, which  
15 consisted of three neurosurgeons who had no  
16 relationship with any of the participating sites. And  
17 it was their independent conclusion that the events  
18 that they reviewed were all consistent in type of  
19 severity considering the disease state and the  
20 procedures performed; and that no concerns were raised  
21 for patient safety because of use of the device, and  
22 none of the events were determined to be device

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1 related.

2 Pain assessments and modified Rankin  
3 scales were also acquired during the study, and these  
4 evolved and improved over time, as would be expected  
5 with this study population.

6 There were no metabolic abnormalities.  
7 All of the wounds uniformly were well healed at the  
8 three-month final follow-up, and there were no  
9 unexpected findings on CT scans.

10 Interestingly, at the three-month follow-  
11 up there was nearly a 75 percent reduction in the  
12 extra dural space, suggesting that DuraSeal was,  
13 indeed, absorbing as expected.

14 So, in summary, in terms of the primary  
15 endpoint and achieving success of a watertight dural  
16 closure, we did this in 98 percent of cases, well  
17 exceeding the 80 percent OPC mark, and there were no  
18 unanticipated adverse device effects and neither were  
19 there any device related adverse events.

20 So I'd now like to turn over the podium to  
21 Dr. van Loveren, who will speak to some of the safety  
22 review.

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1 DR. VAN LOVEREN: Thank you, Dr. Cosgrove.

2 Dr. Becker, members of the panel, I  
3 appreciate your time today.

4 My name is Harry van Loveren. I'm the  
5 Chairman at the University of South Florida,  
6 Department of Neurosurgery. I was principal site  
7 investigator at the University of South Florida. I'm  
8 a member of the Advisory Board for Confluent, and  
9 therefore, my time and travel today are compensated.

10 I want to address the two key safety  
11 findings in this study, and that is the infections  
12 postoperatively and the postoperative CSF leaks, and  
13 then a focused comparison of those results to what is  
14 available in the current literature.

15 In terms of overview of our infection  
16 rate, there were eight patients in this study of 111  
17 that had deep surgical site infections. One of those  
18 had a concurrent meningitis. Seven of those eight  
19 patients underwent removal of their bone flap to  
20 eradicate the infection. One patient was a  
21 craniectomy patient. So there was no bone flap to  
22 remove. All infections resolved.

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1           There was one patient with a superficial  
2 surgical site infection which results with antibiotic  
3 treatment, and there was one interesting patient that  
4 was included with bacterial meningitis, also resolved.

5       The reason I say that patient is interesting is  
6 because it's a patient that had a CSF leak, had a  
7 shunt put in, was asymptomatic regarding any sign of  
8 infection, had one broth culture come back positive  
9 for coag. negative staph. and, therefore, the surgeon  
10 as a precaution decided to use prophylactic  
11 antibiotics, which makes it an automatic inclusion.

12           So clinically we didn't think the patient  
13 was infected from an infectious disease standpoint,  
14 but the patient is included. That's ten patients  
15 total and a nine percent rate of infection.

16           We need to compare that to the literature  
17 comparisons. Finding suitable comparators in the  
18 literature for this type of information are extremely  
19 difficult. Comparing this prospective analysis, which  
20 was very rigorous is difficult when the literature is  
21 ripe with mostly retrospective reports, which are  
22 notorious for underestimating the capture of adverse

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1 events.

2 The definitions are difficult to reconcile  
3 in terms of what type of surgery was done, where was  
4 it done, what are the patient risk profiles and what  
5 is the definition of infection compared to our study.

6 The follow-up intervals in the literature  
7 tend to be short, or the intervals are unspecified,  
8 and there is a serious limitation in the literature  
9 available concerning patient follow-up and compliance.

10 Some of the best compliance data in the literature is  
11 in the range of 75 percent return for follow-up, but  
12 there's a general assumption in the literature in many  
13 of these articles that if a patient is not heard from  
14 again by the treating center and is not referred back,  
15 that there has been no adverse event, and the  
16 denominator stays all patients enrolled rather than  
17 all patients returning for follow-up.

18 The bottom line is that the literature,  
19 therefore, is a very conservative estimate of adverse  
20 event rates, and therefore, potentially biases  
21 comparisons against our study, which I think gives us  
22 a rather robust comparison actually.

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1           The literature was reviewed through common  
2 search engines, Medline, PUBMED, OVID, to find  
3 relevant articles. In relation to infection, we  
4 excluded articles published earlier than 1990 because  
5 that was before the era that antibiotic prophylaxis  
6 became common, and sine antibiotic prophylaxis was  
7 commonly used in our cases, those articles and those  
8 studies had to be excluded.

9           That left a number of retrospective and  
10 prospective studies. The prospective studies tended  
11 to be topic specific. They were focused on  
12 prophylactic antibiotics, preparation techniques for  
13 the surgical sites, or specific risk factor  
14 assessment.

15           Some of those articles dropped out because  
16 the definition of infection or the definition of  
17 surgical site or surgery type was not provided or, as  
18 we said, insufficient follow-up, and that left us with  
19 one very good article that was fairly comprehensive  
20 with well stratified patients and risk factors, and  
21 that's the Narotam article shown there with 2,249 well  
22 analyzed patients, and then a series of studies that

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1 were mostly retrospective looking at duraplasty  
2 materials.

3 If we look at some of the articles that  
4 were not considered good comparators, for instance,  
5 the Young article, although they start out with 800  
6 patients, 400 of those patients are laminectomies,  
7 shunt insertions, stereotactic functional procedures  
8 with no durotomy or one to two millimeter durotomy,  
9 that really needed to be excluded.

10 And when you get down to the 200 to 250  
11 craniotomies that could be compared to our series, the  
12 demographics are not known. The details provided in  
13 terms of assessment definition follow-up is quite  
14 poor.

15 If you look at the Bullock article, for  
16 instance, they start out well with about 400 cases.  
17 They have good follow-up. About 200- cases, again,  
18 are shuts and laminectomies, and then when you look at  
19 the 200 cases that could be applied, the risk profile  
20 is dramatically different from our study.

21 Our study was a very complex set of cases  
22 with an average time of surgery of multiple hours,

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1 high ASA scores, and this is a study where the average  
2 surgical time was about 100 minutes. So it's very  
3 difficult to generate a fair comparison. Again, if  
4 you look at all of the articles available on  
5 duraplasty materials, you can see that infection rates  
6 reported in the literature really are all over the  
7 map, high and low, and a lot of deficiencies found in  
8 the studies, those studies that only looked at deep  
9 wound infections and had no definition inclusion for  
10 superficial infections, those studies that had poor  
11 compliance in the range of 75 percent, but still  
12 maintained that enrollment denominator.

13 Next.

14 So if we look specifically at the Narotam  
15 article, which we used as the best available  
16 comparator in the literature, it's one of the largest  
17 prospective studies undertaken to evaluate operative  
18 sepsis in neurosurgery, 2,249 cases, and the infection  
19 rates were provided by surgery classification, and you  
20 see the five categories of classification: the clear  
21 case, clean-contaminated, clean with foreign body,  
22 contaminated and dirty, and the detailed definitions

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1 of infection were well provided.

2 The clean-contaminated case becomes  
3 important for our series because you've heard this  
4 several times, and you will hear it several more no  
5 doubt. We chose what we perceive to be some of the  
6 best neurosurgeons in the country, and in return for  
7 that, we got some of the worst cases in the country  
8 with the longest operative time and the sickest  
9 patients, and although that's an excellent challenge  
10 for a worst case scenario for this product, it also  
11 means when we compare it to the literature, we really  
12 have to account for that and stratify cases.

13 So if you look at the clean-contaminated  
14 category, a clean-contaminated cases which has a  
15 higher rate of infection is any surgery that lasts  
16 longer than two hours in duration, which was a  
17 significant number of our cases, I think more than 70  
18 percent, and certainly they had a separate  
19 classification for any operation lasting longer than  
20 four hours in duration, and that was a little over 30  
21 percent for our series. And, in fact, some of our  
22 cases went over ten hours, and that is a significant

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1 risk for infection.

2           They had a separate category for cases  
3 where they were an entry into the sinuses,  
4 transphenoidal, transoral procedures. We culled that  
5 out of their data because they were exclusions in our  
6 data as well.

7           Not any study is really perfect, and the  
8 small deficiency of this study was their limited  
9 follow-up to time of hospital discharge or four weeks,  
10 whichever came first, and compared to our very  
11 rigorous three-month follow-up.

12           What we did then is look at their  
13 infection rates for each of the specific categories,  
14 clean, clean with foreign body, clean-contaminated,  
15 and clean-contaminated greater than four hours.

16           The column in blue reports their infection  
17 rates for each category. The next column stratifies  
18 our patients according to the Narotam criterion, and  
19 you can see we have 54 percent of our cases lasting  
20 two to four hours, which is significant; 37, 38  
21 percent of cases in this extreme clean-contaminated  
22 greater than four hour duration surgery.

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1           And if you apply that mathematical  
2           statistic then, you generate for our patients, for our  
3           study group a predicted infection rate according to  
4           Narotam data for our patients of 8.3 percent.

5           To be fair, then, for use of Narotam data  
6           as a comparator, we have to alter our capture of  
7           infections as well because the Narotam study is very  
8           liberal about including patients in the infection  
9           group, and any concern about a wound in the Narotam  
10          data is included as a potential infection.

11          So we had to go back and we had one  
12          patient where there were express concerns about wound  
13          erythema that resolved, and in another patient where  
14          a surgeon cited concern about poor wound healing that  
15          also resolved, and to keep the data fair on both sides  
16          of the equation, we had to add those two patients to  
17          be consistent with Narotam.

18          So that really adds two patients, 12 of  
19          111 with an observed infection rate according to  
20          Narotam data of 10.8 percent, which is not  
21          significantly different than the predictor of 8.3  
22          percent.

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1           We also compared to the best study in the  
2 literature for duraplasty material, and this is our  
3 comparison to that study in which DuraGen was tested,  
4 and you can see in the categories where the patients  
5 are able to be stratified, in clean surgery we had a  
6 comparable infection rate, and in the clean-  
7 contaminated group we had a comparable or favorable  
8 infection rate.

9           Now, one of the criticisms you could make  
10 of this comparison is that the DuraGen study  
11 intrinsically is looking at a subgroup of patients in  
12 whom the surgeon decided they couldn't primarily close  
13 the dura and had to use grafting materials. So to be  
14 fair about that comparison, we went on to restrict  
15 ourselves to a group of patients that are autologous,  
16 and we'll show you that slide later because we do do a  
17 heads up comparison.

18           If you look through the literature, risk  
19 factors for infection are well known and well  
20 described in the literature. Certainly prolonged  
21 surgery, greater than two hours, certainly greater  
22 than four hours are well known risk factors for

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1 infection.

2 American Society of Anesthesia scoring of  
3 greater than two is a risk factor. The presence of any  
4 foreign implant; we did not specifically capture data  
5 on foreign implants. Drains that are left in for  
6 greater than 24 hours. Titanium mesh, methacrylate  
7 cranioplasty adjunct to replacing the bone, we didn't  
8 capture that data. That group of patients does have  
9 an increased rate of infection.

10 The extent of the incision in many of our  
11 durotomies were quite long, up to, I think, 19  
12 centimeters, and sinus penetration which we excluded  
13 and smoking is a significant literature risk factor  
14 for infection.

15 Next.

16 When we did univariate analysis and looked  
17 at our own studies, we found these factors that were  
18 significant in predicting infection: the volume of  
19 DuraSeal used, the duration of surgery, the length of  
20 durotomy, the use of an intraoperative shunt or drain,  
21 the smoking status. But in a multiple regression  
22 analysis, only those factors that have an asterisk

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1 remained significant predictors in our data, the  
2 duration of surgery and the patients' smoking status.

3 And if you look at this, these are our  
4 temptations with infection and the risk factors that  
5 were associated with each patient, and you can see  
6 that the risk factors are rather rampant for long  
7 surgery, elevated ASA scores.

8 So we're taking complex operations in sick  
9 patients.

10 Next.

11 In summary, the observed DuraSeal surgical  
12 site infection rate is what we would expect, given the  
13 patient population. We were addressing the risk  
14 profile of those patients and the complexity of the  
15 procedures performed and the infection rate compared  
16 favorably to duraplasty materials.

17 Next.

18 We also need to look then at the  
19 postoperative CSF leak rate as a safety finding and  
20 look at its comparison to the literature.

21 Post-op CSF leaks by definition in our  
22 study included any leak through the incision and any

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1 pseudomeningoceles that required any invasive  
2 intervention whatsoever, even if it was the simple so-  
3 called tap and wrap that surgeons are familiar with  
4 where a needle is used to aspirate the fluid and that  
5 is placed in a bandage wrap. Any penetration of skin  
6 is considered an intervention and invasive and,  
7 therefore, is a significant pseudomeningoceles.

8 Five patients experienced then CSF leak  
9 for a rate of 4.5 percent. That's only two that  
10 actually have incisional leaks and three that were  
11 included as pseudomeningoceles.

12 One patient is interesting and was  
13 included at FDA insistence, even though the  
14 investigators had some doubts that it should, but so  
15 I'll tell you about that patient. That's a patient  
16 who had infection in the wound in the posterior fossa.

17 The surgeon debrided the wound, and in debriding the  
18 wound, scraped off all of the DuraSeal, scraped the  
19 dura clean and noted that at the end of the  
20 debridement there may have been some evidence of CSF  
21 seepage through the previous suture line, and  
22 therefore as a precaution, the surgeon used a lumbar

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1 drain.

2 So certainly the minute you use a lumber  
3 drain to prevent CSF leakage, you become an included  
4 patient, although that's really quite iatrogenic.

5 Next.

6 If you break the patients down into two  
7 particular risk categories, the risk category well  
8 known and cited already in this discussion by those  
9 cases that are infratentorial where you're in the  
10 posterior fossa; you're at the dependent portion of  
11 the CSF volume, and most prone to leak, and then we  
12 had 58 in the supratentorial category with only one  
13 leak and 53 in the infratentorial category with only  
14 one leak.

15 And if you look at this, we substratified  
16 a bit to look at the high risk categories.  
17 Infratentorial craniectomy, of course, is a very high  
18 risk category because this is now you're at the  
19 dependent portion of the CSF volume at the base of the  
20 skull, and you don't have any bone to put back to  
21 buttress or support the suture line, and that was  
22 especially grueling in this study because when we use

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1 DuraSeal in these situations we were not allowed to  
2 buttress or support the DuraSeal with any other  
3 material.

4 So if you look at that high risk  
5 infratentorial craniectomy group, even though the  
6 numbers are low, 19 cases, we have only one leak, and  
7 that's the iatrogenic leak created by the surgeon  
8 clearing infection.

9 We have a small number of acoustic  
10 neuromas, six. Statistically that's not a relevant  
11 number, but again, we set it there because it's a  
12 group that has a higher risk in the literature for CSF  
13 leak and the rate in those patients happen to be zero.

14 Again, for CSF leak, we have to find  
15 comparators in the literature and we use the similar  
16 research engines, Medline, PUBMED, OVID, and then as  
17 mentioned, we excluded a number of articles that  
18 focused on cases that had unusually high CSF leak  
19 rates, which would be an unfairly favorable  
20 comparator, excluded series on acoustic neuroma,  
21 skull-base approaches, translabyrinthine approaches,  
22 series where there was no emphasis for dural closure,

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1 no mandate to try and close the dura and higher CSF  
2 leak rates.

3 We were still left then with a series of  
4 retrospective and prospective articles, and again, for  
5 similar reasons to the infection articles many dropped  
6 out because of poor follow-up, poor definition of what  
7 is a leak, no information on pseudomeningoceles,  
8 whether they were included, not included, and poor  
9 definition of the operations performed.

10 There is still a major prospective study  
11 with a similar patient population, which we'll  
12 discuss. That's the von Wild data, and some  
13 retrospective studies that looked at similar  
14 breakdowns of procedures in risk categories,  
15 supratentorial versus infratentorial.

16 Next.

17 This is the von Wild paper which was a  
18 suitable comparator, also a prospective, multi-center  
19 trial, a bit weak in compliance follow-up. Seventy-  
20 five percent of patients returned for follow-up at the  
21 six-month period. Every patient enrolled was placed  
22 in the denominator. We've mentioned this before. So

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1 that's a difficult comparator that grossly  
2 underestimates CSF leak, but the best comparator that  
3 we could find.

4 Next.

5 Again, also looking at it in terms of risk  
6 groups, 20 percent of their cases were infratentorial  
7 versus 48 percent of our cases. So we might expect  
8 actually a slightly higher leak rate for our more  
9 complicated cases.

10 Next.

11 But, in fact, we found a lower leak rate.

12 Our leak rate, including pseudomeningoceles is 4.5  
13 percent, and I should mention we are now excluding the  
14 iatrogenic leak.

15 If you include the iatrogenic leak, it  
16 does raise us to 5.4 percent and still well within 95  
17 percent confidence interval compared to the von Wild  
18 study with 12.9 percent leak rate, and on leak rate,  
19 again, if the criticism would be that their patients  
20 all used DuraPatch, which was what was being tested,  
21 then we excluded cases from our group where no patch  
22 was used.

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1                   So now we're looking just at the 50 cases  
2 in our study where the surgeon decided dural closure  
3 could not be performed without an autologous patch,  
4 comparing to their use of DuraPatch. So they are a  
5 better matched set of cases, and then our leak rate is  
6 six percent versus theirs of 12.9 percent.

7                   Next.

8                   So we still have a relatively comparable  
9 or favorable outcome breaking it down that way.

10                  If we look at supratentorial cases in the  
11 literature, again, it's quite a spectrum. There are a  
12 lot of retrospective studies under reported, under  
13 capturing of leak rates. No clarification as to  
14 whether they're going to include or not include  
15 pseudomeningoceles and what the criteria are, and  
16 still we come out with a very comparable leak rate to  
17 the other studies.

18                  And if we look at those studies that  
19 isolate to the more complicated, more risky procedures  
20 of infratentorial procedures, again, our leak rate of  
21 5.7 percent is very comparable, and in fact, if you  
22 look at the one study that's in our same ball park at

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1 5.6, the Manley study, that study was a retrospective  
2 analysis of quality assurance data at a single center,  
3 which could easily underestimate or under capture  
4 events by 30, 40 percent. But in essence, we're very  
5 comparable.

6 Next.

7 This was a Gnanlingham study which looked  
8 at that very high risk group of infratentorial  
9 craniectomy where there's no bone to put back and,  
10 again, we have comparable rates for CSF leak. They  
11 did isolate out pseudomeningoceles. We have very  
12 comparable rates for pseudomeningoceles, and in fact,  
13 you might say favorable.

14 Next.

15 So in summary, for the CSF leak safety  
16 analysis, the observed DuraSeal CSF leak rate compares  
17 favorably to rates reported in the literature, given  
18 similar patient profiles.

19 Next.

20 The overall study summary and conclusions.  
21 We think we have had one of the most complicated  
22 series analyzed submitted in the literature, the worst

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1 cases and the best follow-up in a prospective manner.

2 Fifty percent of our patients required grafting  
3 material. Forty-eight percent were infratentorial.  
4 Nineteen percent were craniectomies. Eighty-seven  
5 percent had elevated ASA scores, and significant  
6 morbidities.

7 Our procedures were remarkably prolonged,  
8 92 percent greater than two hours, some as long as ten  
9 hours; long durotomies, as long as 19 centimeters,  
10 which is a lot for a craniotomy, and yet a very  
11 rigorous assessment with 96 percent of patients  
12 completing the total study.

13 The primary endpoint of intraoperative  
14 dural sealing was achieved 98 percent of the time.  
15 The wound infection rate is comparable to what would  
16 be expected in this risk profile group of patients in  
17 the literature.

18 The postoperative CSF leak rate compares  
19 favorably to what's comparable in the literature, and  
20 the adverse events seen in this study were consistent  
21 in nature, frequency, and severity for patients  
22 undergoing this complexity of cranial surgery.

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1                   And, in fact, the CDC independently found  
2 no evidence of a device related event.

3                   In terms of our risk-benefit conclusion,  
4 of course, we begin with the assumption that dural  
5 closure/sealing promotes wound healing and avoids the  
6 cascade of complications that follow CSF leak and  
7 wound failure. There is no product approved by FDA  
8 for dural sealing as a support to suture closure and  
9 none demonstrated effective.

10                   DuraSeal provides a standardized,  
11 effective, intraoperative, watertight dural closure  
12 without an increase in the risk of adverse events, and  
13 it's on that basis that we ask this panel to approve  
14 this product.

15                   Okay. Safety and effectiveness of  
16 DuraSeal has been demonstrated through valid  
17 scientific evidence. The benefits associated with the  
18 use of DuraSeal outweigh the potential risks  
19 associated with the use of the device, and DuraSeal  
20 dural sealant is an effective adjunct to sutured dural  
21 repair during cranial surgery to provide watertight  
22 closure.

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1 I think we said that.

2 CHAIRPERSON BECKER: Thank you, Confluent  
3 Medical.

4 At this point members of the panel are  
5 able to ask Confluent Medical questions, and I want to  
6 actually ask the first very naive question of the  
7 neurosurgeons.

8 How did you perform Valsalva on an  
9 anesthetized patient and how did you measure ICP  
10 during the Valsalva?

11 DR. TEW: The Valsalva maneuver is a  
12 standard maneuver for neurosurgeons to check  
13 watertight closure, and simply in an anesthetized  
14 patient the anesthetist bags the patient to a certain  
15 level of pressure which is then transmitted into the  
16 intercranial compartment.

17 You don't have a direct measurement of the  
18 intercranial pressure, you know, at surgery, but you  
19 can see the pressure indirectly through the bulging  
20 and leakage through the dura.

21 CHAIRPERSON BECKER: The pressures that  
22 are reported here, you know, your two failures of

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1 patients who didn't get ICPs high enough, that's based  
2 on intrapulmonary pressures or --

3 DR. TEW: Correct.

4 CHAIRPERSON BECKER: Okay. Other  
5 questions?

6 DR. CANADY: Yes. I had a question for  
7 Dr. van Loveren. The only control group we ever have  
8 here is the DuraGen control group. How was that  
9 control group constituted?

10 DR. VAN LOVEREN: Well, we have control  
11 groups for infection, comparators in the literature.  
12 When you look at the --

13 DR. CANADY: I understand, but I'm  
14 interested particularly in the DuraGen group. What  
15 was their --

16 DR. VAN LOVEREN: What was significant or  
17 special about that group?

18 DR. CANADY: Did they leave the leaks  
19 untreated or how was it constituted, that group? How  
20 was it defined?

21 DR. VAN LOVEREN: These were patients who  
22 had a durotomy that could not be suture closed and

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1 required a graft to be placed, and these were then  
2 compared in that study to patients in whom DuraGen was  
3 not used.

4 CHAIRPERSON BECKER: Dr. Germano.

5 DR. GERMANO: I have a question for Dr.  
6 van Loveren.

7 If you could please explain the  
8 discrepancy in reporting of the data on page 27.  
9 There is a report of CSF leak, six patients, 5.4  
10 percent; pseudomeningoceles, two patients, 1.8  
11 percent.

12 On page 39 of your presentation, you  
13 explain that the CSF leak is five because one was  
14 iatrogenic. What happened to the other two  
15 pseudomeningoceles patients? They're not reported  
16 here.

17 CHAIRPERSON BECKER: If I could just  
18 remind people to use the microphone when they ask  
19 questions.

20 DR. GERMANO: Sorry.

21 DR. VAN LOVEREN: On the adverse event,  
22 not every pseudomeningoceles met criteria for

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1 significance if there was no intervention. So the  
2 simple event of having a pseudomeningoceles if there  
3 is no treatment required, no penetration of skin  
4 required, and the pseudomeningoceles is observed  
5 and/or resolved, that is not included.

6 There has to be an intervention because if  
7 you look at other studies, pseudomeningoceles, if you  
8 look at radiographic studies looking for frequency of  
9 pseudomeningoceles, a small SCF collection after  
10 suture closure becomes really rather common.

11 CHAIRPERSON BECKER: Dr. Jayam-Trouth.

12 DR. JAYAM-TROUTH: I have a question. If  
13 normally you have 60 percent of surgical closures that  
14 come to neutral leak spontaneously, you know, all with  
15 the Valsalva manner as you've shown in a nicely done  
16 surgery, my question is then, I mean, is it really all  
17 that necessary, you know, when surgeons do a nicely  
18 done surgery that you need to have a sealant on top of  
19 it? Wouldn't it spontaneously heal?

20 And then you use antibiotics. Wouldn't  
21 you expect that without infection that the healing  
22 rate would be better?

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1 DR. VAN LOVEREN: Well, I think it is  
2 these leaks at the time of closure that are resulting  
3 in all these complications you see in the literature  
4 and in practice, what starts as an interoperative leak  
5 and as a pseudomeningoceles, a wound breakdown, or an  
6 infection, and I don't think that surgeons are walking  
7 away from leaking wounds. They're reaching onto the  
8 shelf for a heterogeneous group of unapproved  
9 materials to buttress that wound. They are doing  
10 something about that wound almost each and every time,  
11 with a lot of heterogeneous, off-label, unproved,  
12 unstudied use.

13 And this is the first, I think, attempt to  
14 bring something standardized to that dural closure.

15 DR. JAYAM-TROUTH: No. My question is in  
16 50 percent of these you put some, you know,  
17 heterogeneous material anyway, and then on top of it,  
18 you put the DuraSeal, and despite showing 100 percent  
19 closure with the DuraSeal, you still had  
20 pseudomeningoceles and you still had CSF leaks.

21 Now, how do you explain? Because if you  
22 say that the DuraSeal lasts for eight weeks and ten

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1 weeks in the system, you know, why is it that these  
2 patients did have the pseudomeningoceles?

3 DR. VAN LOVEREN: Well, I think when you  
4 refer to the heterogeneous material we put down and  
5 then put DuraSeal over it, the only thing we put down  
6 is an autologous, regionally harvested graft of  
7 patient tissue to close the gap because we're only  
8 allowed to accept a two millimeter gap. So there are  
9 no other materials being applied to that opening.

10 And the second part of the question is?

11 DR. JAYAM-TROUTH: When you had a 100  
12 percent leak closure, how do you explain, and if the  
13 material lasts for ten weeks in the system, you know,  
14 then how do you explain the pseudomeningoceles? You  
15 shouldn't have seen a single one.

16 DR. VAN LOVEREN: Well, you're asking why  
17 we didn't achieve perfection. I guess I'd have to  
18 acquiesce that the product is not perfect. If you  
19 look at the individuals', for instance, the leak rate,  
20 if you look at the true leak rate, it's incredibly  
21 low, two patients in the entire study, and in fact,  
22 one of them was found to have hydrocephalus, which was

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1 really an exclusion in this study, but the patient had  
2 hydrocephalus, recognized a month before surgery. The  
3 surgeon thought it had resolved. After surgery when  
4 the patient was leaking, the surgeon decided that the  
5 patient had active hydrocephalus and needed to be  
6 shunted to stop the CSF leak.

7           So I think there are explanations. If you  
8 have a complex case, you are not going to seal every  
9 case. You are going to have problems of wound healing  
10 unrelated to the DuraSeal. You're going to have  
11 problems of hydrocephalus after surgery that may break  
12 the seal, and still we have this incredibly low rate  
13 of CSF leak, and I think we were extremely rigorous in  
14 the inclusion of our pseudomeningoceles patients  
15 compared to literature where often, in fact, most of  
16 the time, a pseudomeningocel is not considered a  
17 leak. So I think that was a very liberal definition.

18           DR. CANADY: You really don't think your  
19 pseudomeningoceles and CSF leak?

20           DR. VAN LOVEREN: I'm saying that --

21           DR. CANADY: I mean, I understand the  
22 study defined it certainly, but you really don't

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1 believe that, do you?

2 DR. VAN LOVEREN: Well, we defined  
3 pseudomeningoceles as a CSF leak.

4 DR. CANADY: Thank you. Okay.

5 CHAIRPERSON BECKER: Dr. MacLaughlin.

6 DR. MacLAUGHLIN: Yes. I have a question  
7 for Dr. Cosgrove.

8 You mentioned in your presentation that  
9 you excluded patients who were planning to have  
10 chemotherapy for their tumors or were on steroid use.

11 Do you see that as standard restriction for the use  
12 of this product? Because a lot of your patients  
13 actually are cancer patients.

14 DR. COSGROVE: Well, in terms of the study  
15 design, we had to be very particular about what  
16 patients we were going to allow in and not, and many  
17 of our patients do have steroids. They're on  
18 steroids.

19 We actually used a criteria. They  
20 couldn't have chronic steroid use greater than four  
21 weeks prior to because that actually is implicated in  
22 delayed wound healing and infections and all of the

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1 systemic immunosuppression. And so for the purposes  
2 of this study that's why we were so particular.

3 I can't say whether we would exclude those  
4 patients. I wouldn't think that's being an exclusion  
5 criteria for ongoing use of it until there was more  
6 data and information.

7 For the similar reasons, it was purely for  
8 a uniform study design, was the issues of chemotherapy  
9 and radiation, and in some instances you can't predict  
10 that because you'll go in and you'll say, "Well, I  
11 think this is going to be this kind of tumor," and  
12 then you come out and it's a malignant glioma and  
13 they're going to need to have radiation, you know,  
14 within the three-month time period, usually within  
15 about two to four weeks.

16 I know there was one patient who actually  
17 was excluded later on. So it could be -- I don't  
18 think it's going to be a major problem moving forward,  
19 but we'll have to study that.

20 DR. MacLAUGHLIN: Thank you.

21 CHAIRPERSON BECKER: Dr. Loftus.

22 DR. LOFTUS: Now, if I may be permitted

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1 three questions of three presenters, is that  
2 acceptable?

3 CHAIRPERSON BECKER: Sure.

4 DR. LOFTUS: First, for Dr. Cosgrove, if  
5 you wouldn't mind, just a question regarding your  
6 study design. You specify, if I understand you  
7 correctly, no gaps greater than two millimeters and no  
8 tears, durotomies, as it were, within three  
9 millimeters of the bone edge. You know, these are two  
10 of the most compelling reasons to use such a product,  
11 and aside from the pragmatic view that by eliminating  
12 these situations you are enabled to surmount your 80  
13 percent criterion, can you just shed some light for me  
14 on why the study design eliminated what would be the  
15 most obvious need for a dural sealant?

16 DR. COSGROVE: Well, first and foremost,  
17 you know, the directive to all of the site  
18 investigators was to perform their best dural closure  
19 using autologous materials as needed. You and I both  
20 know that there are instances where to the best of  
21 your ability you're sewing things in and, you know,  
22 you're doing more damage than good by trying to patch

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1 certain things in or let's just put another stitch in  
2 here to see if I can get watertight, and it just pulls  
3 other things apart.

4           So, I mean, the goal of the neurosurgeons  
5 were to get as good a primary dural closure as  
6 possible. In some instances where you can't tell the  
7 neurosurgeon, you know, against his better judgment  
8 that you should do something different. He may make  
9 the determination that there's no way I'm going to get  
10 a primary closure and there may be a gap here, and we  
11 allowed that gap to be up to two millimeters primarily  
12 because we didn't want -- not greater than two  
13 millimeters -- primarily not because in some ways we  
14 weren't sure that it would seal properly, but when you  
15 spray it on, you didn't want it falling through the  
16 gap into the intradural compartment, and to get it to  
17 polymerize as a layer, two millimeters seemed to be  
18 the appropriate because of the viscosity of the  
19 product, that you could spray it on and it wouldn't  
20 drip. It polymerizes and sets up very nicely.

21           The second issue about close to the bone  
22 edge, the craniotomy margin, I agree with you. It was

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1 primarily though because in order for the compound to  
2 work as designed, it has to have a certain amount of  
3 dura that it can adhere to on both sides of the  
4 durotomy so that it can adhere properly and have the  
5 appropriate coverage.

6 So that was really a number that we sort  
7 of pulled out of the air, three millimeters from the  
8 craniotomy margin in order to be able to spray it on.

9 Now, that's not to say that when you spray  
10 it on it doesn't go right up to the craniotomy margin  
11 and, you know, up on the edges of the bone, but we  
12 thought that it was important to at least have, you  
13 know, flat dura to adhere to enough on both sides to  
14 not get a flat valve effect.

15 DR. LOFTUS: If I may just pursue, I mean,  
16 you know as well as I do that if approved, this is  
17 exactly what surgeons are going to want to use this  
18 for, and it's going to flop down on the surface of the  
19 brain. I mean, there's no way around that as I see  
20 it.

21 I just want to make certain that you feel  
22 that the product is, indeed, safe if it's directly

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1 applied to the surface of the brain.

2 DR. COSGROVE: Oh, yes. I mean it wasn't  
3 so much that there was any concern about the  
4 toxicology of it because I think there's -- and we'll  
5 talk to that afterwards if necessary about the  
6 detailed toxicology studies -- but this is essentially  
7 an inert substance, and it does not promote any  
8 reaction at all, and it was really to get it to form  
9 the seal, to work as designed rather than concerns  
10 about, you know, falling onto the brain and touching  
11 the brain.

12 You obviously though don't want to have a  
13 big lump of tissue, you know, a lump of foreign  
14 material, even though it's absorbable, sitting in the  
15 intracranial compartment after you've done an  
16 operation. I mean, that's like having a hematoma in  
17 there. So it just doesn't make good neurosurgical  
18 sense.

19 And you know, after we have done our  
20 surgeries, typically the brain isn't right up at the  
21 dural surface.

22 DR. VAN LOVEREN: If I could say

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1 something, when I looked at this preliminarily, I  
2 mean, if you look in pigs unfortunately it seals just  
3 fine to bone, and in fact, you'll herniate the pig  
4 before the seal breaks off of the bone. So it will be  
5 effective that way, and it will be used that way.

6 But if we were to allow that in the study,  
7 I think we'd have to stratify for it, and I think  
8 you'd have to stratify the patients to say sealing to  
9 bone rather than sealing to dura. You'd have to do a  
10 separate study. I don't think you can assume how  
11 something seals to dural material is how it seals to  
12 bone. You'd have to prove it.

13 DR. LOFTUS: May I proceed? The next two  
14 are very short.

15 Harry, if I could, Dr. van Loveren, if I  
16 could just ask you, so for the purposes of our  
17 comparison with the literature, I mean, it may seem  
18 pedestrian, but your definition of a deep surgical  
19 site or deep wound infection versus superficial.

20 DR. VAN LOVEREN: Pus deep to the galea  
21 that includes any form of involvement of the bone  
22 flap, bone osteitis, meningitis, anything that is on

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1 the deep surface of the galea. Superficial wound  
2 infections is really the incisional line only.

3 DR. LOFTUS: Okay, and my third question  
4 was for Mr. Ankerud, and that is you present no data  
5 in the trial regarding spinal use of the product, and  
6 I wonder if you propose that the product be also  
7 approved for use in repair of the spinal dura.

8 MR. ANKERUD: No, that is not included in  
9 our proposed indication for this device at this time.

10 DR. LOFTUS: Okay. Thank you.

11 CHAIRPERSON BECKER: Dr. Egnor.

12 DR. EGNOR: This is for Dr. van Loveren.

13 I share Dr. Loftus' concern regarding the  
14 exclusion criteria. For both the comparison for  
15 infection and the comparison for CSF leak to other  
16 published studies, the results are fairly impressive.

17 My concern is that the patients though with the  
18 DuraSeal were the patients who had the very lowest  
19 risk in all of those groups because of the exclusion  
20 criteria.

21 When you have a dural closure in  
22 particular the supratentorial closures where there's a

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1 two millimeter or less residual opening, those are  
2 cases that are essentially closed. As your numbers  
3 noted, virtually everyone leaked, whether Valsalva or  
4 spontaneously anyway.

5 So the question would be: were the  
6 studies that you were comparing to for the infection  
7 and for the CSF leak -- did they have the same  
8 exclusion criteria for their patients as you did for  
9 yours?

10 DR. VAN LOVEREN: When they did not, we  
11 took out patients that were not included in our study  
12 either. I don't think we had a favorable group in  
13 terms of the DuraSeal patients.

14 One of our exclusion criteria was, for  
15 instance, entry into an air sinus, certainly any  
16 transphenoidal procedure, any procedure through a  
17 contaminated space. So to be fair, when we compared  
18 ourselves, for instance, to Narotam data, that's one  
19 of the reasons we could use their data, because they  
20 had those patients stratified, and we could exclude  
21 them because they contribute abnormally to their rate  
22 of infection.

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1           So since they're not in our series,  
2 they're taken out of their series.

3           DR. EGNOR: Do you know that the CSF leak  
4 patients in the studies to which you were comparing  
5 DuraSeal had dural defects that were two millimeters  
6 or less? Because the large dural defects are really  
7 the at risk group.

8           DR. VAN LOVEREN: Well, I think actually  
9 we had a very difficult series because if you look at  
10 other series with CSF leak, a lot of them are  
11 including patients with shunts or stereotactic  
12 procedures where there's a pinhole made in the dura,  
13 very small procedures compared to 19 centimeter  
14 durotomies.

15           DR. COSGROVE: Dr. Egnor, could I also  
16 response?

17           DR. EGNOR: Sure.

18           DR. COSGROVE: You know, I think a two  
19 millimeter opening is not essentially closed, and as a  
20 pediatric surgeon in a posterior fossa procedure, if  
21 the resident said, "Oh, I've closed the dura and  
22 there's only a few two millimeter gaps," you'd go,

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1 "You did what? I mean, go back and do it again."

2 So I don't think in the exclusion criteria  
3 we selected easier cases by any means. I think that  
4 we just tried to do the standard of care, which most  
5 neurosurgeons try and get a watertight dura or  
6 complete dura closure.

7 And then, of course, we demonstrated that  
8 even though we tried to get them to do that, if they  
9 could, there was spontaneous leak in 60 percent, and  
10 then, you know, 40 percent of the time the  
11 neurosurgeon said, "Well, I did a good job there."  
12 Right? And looking pretty good, and then you do a  
13 Valsalva and it leaks, you know, typically along the  
14 suture line and the suture holes.

15 I mean, you know, we say, "Well, that's  
16 as good as it gets," basically, and we would describe  
17 in our operative report we performed a watertight  
18 dural closure, right?

19 So I don't think we preselected. I mean,  
20 I understand that the tougher ones are where the tear  
21 goes out underneath the bone. I understand that, but  
22 that's just not something that then we can evaluate.

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1 We would have to stratify it in a different way and  
2 then have, you know, another cohort completely with  
3 tears that are not able to be primarily repaired, and  
4 so this was one way of trying to keep it a uniform  
5 study population.

6 But I don't think we, with our exclusion  
7 criteria, preselected any great cases.

8 DR. EGNOR: Well, you did. I mean, you  
9 excluded all kinds of things that were at very high  
10 risk for leak like a big, gaping hole in the dura that  
11 you could drive a truck through. I mean, those things  
12 were excluded, and those are the tough cases.

13 DR. COSGROVE: Well, no, but in fact, you  
14 know, as you and I both know, gaping holes tend to  
15 give, in fact, -- well, we don't know the data on  
16 that. There's no data to say that a big hole is worse  
17 than a little hole. In fact, in my experience, in  
18 fact, it's the smaller holes, the little flap valves  
19 where, you know, the patient does a Valsalva. It  
20 squirts out, opens up a little bit, and then the  
21 pressure of the fluid outside now closes the flap  
22 valve, and as they do various things that's how you

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1 get these expanding pseudomeningoceles.

2 If you have a big opening, I mean, the  
3 French never close their posterior fossas at all.  
4 They leave a big hole, you know, so fluid can go in  
5 and out, and then what happens is that there's no  
6 pressure or valve effect.

7 DR. EGNOR: Then why use DuraSeal at all?

8 (Laughter.)

9 DR. COSGROVE: Yes, well, that's a good  
10 point because the French -- I mean, the French never  
11 have a complication, right? Or at least that they can  
12 report.

13 But, no, there's lots of reasons to still  
14 use it because I don't abide by that at all because  
15 there are issues of wound healing. There are issues  
16 of meningismus, meningitis. There's issues of any  
17 infection with an open dura becomes now a deep  
18 intradural infection with meningitis and abscess  
19 formation. There are many, many, many, many good  
20 reasons to close the dura. I'm not abiding by the  
21 French stance.

22 But I'm just saying that there is no data

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1 to my knowledge that characterizes any opening in the  
2 dura as being more dangerous or less dangerous, that a  
3 big hole is not necessarily more dangerous than a  
4 smaller hole, you know, or an intermediate hole. I  
5 don't think -- there's no data in the literature that  
6 has ever characterized that.

7 DR. EGNOR: Well, there may be no data  
8 because it seems obvious.

9 DR. COSGROVE: I don't think it's so  
10 obvious, but I think we get into more problems with  
11 the small pinhole and the valves than, you know, where  
12 you have a bigger opening sometimes.

13 CHAIRPERSON BECKER: Dr. Haines.

14 DR. HAINES: Actually it's for Dr.  
15 Cosgrove.

16 Dr. van Loveren's presentation is one of  
17 the most eloquent expositions of why concurrent  
18 controls would be helpful that I've ever heard, and  
19 could you explain in your deliberations about deciding  
20 not to have concurrent controls in the study why not  
21 use the surgeon's standard practice as the control?

22 DR. COSGROVE: Well, because you can say:

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1       what is that surgeon's standard practice? What is  
2       the next person's standard practice? What is the next  
3       person's standard practice?

4                   DR. HAINES: But that's exactly the point.  
5       It would have produced a comparison for these  
6       patients treated by these surgeons, which it would  
7       have been much less burdensome for us in terms of  
8       understanding the comparison than having to try to  
9       deal with this literature problem.

10                   DR. COSGROVE: Well, yeah. So I'll  
11       address that in a couple of ways. The first issue is  
12       that the standard of care of a specific surgeon is one  
13       thing. The standard of care of that specific surgeon  
14       may change from case to case. So he may use surgical  
15       in gelfoam in one instance, which again I remind you  
16       are not FDA approved.

17                   He may use DuraGen or some other dural  
18       replacement device, not approved for this.

19                   He may use fibrin glue for specific things  
20       that he thinks, you know, but typically in my  
21       experience people don't use the same standard for each  
22       and every case.

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1 DR. HAINES: But at least we'd have some  
2 idea of what that surgeon's chance of getting a leak  
3 or a deep wound infection with this group of patients  
4 was, and we really don't know that now.

5 DR. COSGROVE: Yeah. Well, the problem  
6 is, and this is why we have these communications and  
7 got input from the FDA. You know, it really was  
8 deemed by the FDA unacceptable to compare something to  
9 nonapproved FDA devices, where you don't have safety  
10 and efficacy profiled. You know, this is the problem.

11 This was the problem in trying to get an appropriate  
12 study design.

13 CHAIRPERSON BECKER: Dr. Jensen.

14 DR. JENSEN: A question for Dr. van  
15 Loveren.

16 What imaging was done on the infected  
17 patients, leak patients at the time that it was  
18 recognized that they were infected or had a leak? Was  
19 it MR or CT? And what were these findings when  
20 compared to what you expected based upon the canine  
21 model?

22 Who read the studies? Did you have a

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1       neuroradiology group that looked at those studies of  
2       the infected patients? And were there any findings  
3       that you would not expect based upon the canine model,  
4       i.e., early reabsorption of the hydrogel, eccentric  
5       collections focused on the edge of the hydrogel, et  
6       cetera?

7                   DR. VAN LOVEREN: Well, I appreciate your  
8       interest as a neuroradiologist. I think I would just  
9       word it a bit different, but we had a core lab that  
10      reviewed all of the radiographic studies, and there  
11      were studies taken at routine intervals, CAT scan, and  
12      we were primarily looking at its characteristics of  
13      dissolution on CAT scan and MRI. We had no mandate to  
14      specifically investigate radiographically if there was  
15      suspicion of an infection or of a pseudomeningoceles.

16                   DR. JENSEN: But don't you think that  
17      would have strengthened your position if you had had  
18      good MRs done with a patient with a leak and it showed  
19      that the thickness of the material was what you would  
20      expect at that level or if you had an infection, that  
21      the site was not at perhaps the edge of the hydrogel?

22                   DR. COSGROVE: Do you want me to speak to

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1 that?

2 DR. JENSEN: Whoever would like to, feel  
3 free.

4 DR. COSGROVE: So we had a lot of  
5 discussions about what was the appropriate technique  
6 to image, and the problem is that with the product  
7 being about 90 percent water, being able to  
8 differentiate it from CSF, to be able to differentiate  
9 it from blood breakdown products, air, I mean, we had  
10 Dr. Alex Norbash, who was in charge of the imaging  
11 corps, go through images from Europe and from the  
12 European study looking at both CT and MR images, and  
13 we had a lot of discussion about this point, and it  
14 was really felt that the optimal way for imaging this  
15 was with CT and looking at it over those time points  
16 that we described.

17 Now, in terms of the infections, is  
18 that --

19 DR. JENSEN: Well, you know, based upon  
20 your dog data, you know, you talk about how the gel  
21 looks in contrast to CSF in terms of hyper intensity,  
22 and you showed an MR. So I think clearly MR in this

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1 situation would probably be better than CT in trying  
2 to look for edge enhancement of the hydrogel.

3 And they talk about a uniform enhancement  
4 of the edge of the hydrogel that dissipates over time.

5 So if you're looking for inflammation, right, I mean,  
6 obviously what you're going to be looking for is  
7 enhancement, which is going to be more specific with  
8 MR.

9 And I would think that if you're worried  
10 about an infected collection and you do an MR and you  
11 find that you see just the same enhancement that you  
12 expect with the hydrogel and the collection is either  
13 remote or not positioned on the material or is  
14 positioned subgaleally, then chances are it's not your  
15 hydrogel. It's infection in another site.

16 I mean, it seems to me it would have  
17 provided you more substantial data in arguing that it  
18 was not the hydrogel, which is a site or source of  
19 infection, as opposed to other, you know,  
20 postoperative complications.

21 DR. COSGROVE: I understand many of your  
22 points, and not being a neuroradiologist and not being

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1 an MR specialist, maybe I'll get Pat to address some  
2 of those issues, and he's not a neuroradiologist  
3 either.

4 DR. CAMPBELL: No. Thanks.

5 Those are excellent observations. The  
6 study that I showed with the images of the MR, those  
7 studies were performed both CT and MRI imaging. MRI  
8 was performed using flare, T1, T2, with and without  
9 enhancement, and Dr. Norbash completed that study,  
10 evaluated every time point.

11 He did find that you could differentiate  
12 using the proper imaging the gel from CSF. You could  
13 also differentiate it from a potential infected bed,  
14 and that work is in press or in publication right now.

15 We'll be publishing that in the next year or so. So  
16 that will be available to the general public.

17 DR. JENSEN: Okay. However, working at a  
18 busy neurosurgical site, I can guarantee you that your  
19 patients got MRs. I mean, I can't imagine that  
20 somebody who has an infection didn't get an MR. Do  
21 you have that data?

22 DR. COSGROVE: To be completely

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1 inconsistent, I mean, yes, you're right that a  
2 patients undergoing intracranial procedures typically  
3 do get MRs at times, but it's completely inconsistent.

4 Sometimes it's early on. Sometimes it's at weeks  
5 afterwards. So --

6 DR. JENSEN: Right, but I mean in terms,  
7 again, of your infected patients and your leak  
8 patients. Okay? When you suspect the patient is  
9 infected, I mean, maybe it's just my institution, but  
10 that patient is going to get an MR before they go to  
11 the OR.

12 DR. COSGROVE: Yes.

13 DR. JENSEN: The same with a leak.  
14 They're going to get an MR. So I have to believe the  
15 data is there. The question is whether or not you  
16 chose to collect it and show it to your core group.

17 DR. COSGROVE: Well, anecdotal experience  
18 is there for sure. We did not collect it in a way  
19 that you could make any rigorous conclusions from it,  
20 but I can tell you, you know, the problem patient was  
21 my patient. The big patient, he was about 415 pounds,  
22 and we did an Arnold Kiari (phonetic) on him and said,

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1 "He's the one that got infected, and he's the one who  
2 when we explored him and debride, you know, to see  
3 what the depth of the infection was, went down and you  
4 take out all foreign material and you see what's going  
5 on.

6 So we scraped off all of the remaining  
7 DuraSeal, and after we did that, yeah, it sort of  
8 looked like the things were leaking. So I have an MR  
9 on that guy. This was about four weeks out from the  
10 surgery, three to four weeks out from the surgery  
11 when we took that image, and I'll tell you, well,  
12 first of all, it's difficult in an RL Carey (phonetic)  
13 malformation with all of the soft tissues and al of  
14 those things in the best of times, without DuraSeal in  
15 there, it's hard to interpret.

16 But it was difficult to interpret. It was  
17 a mixture of signals that, you know, the decision to  
18 reoperate was on a clinical basis, and I couldn't tell  
19 what was what because there was a combination of  
20 enhancement, fluid diffusion weighted abnormalities.  
21 It was impossible to tell at that point.

22 DR. CAMPBELL: Can I address one other

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1 issue sideways related to your comment?

2           There's a lot of information in the  
3 literature concerning polyethylene glycol and  
4 infection. Polyethylene glycol has been shown through  
5 many studies to be a poor food source for bacteria.  
6 Polyethylene glycol is synthetic, unlike other  
7 products that could be a food source.

8           Polyethylene glycol also has been  
9 evaluated in our preclinical studies extensively with  
10 no signs of infection. It's widely known and  
11 recognized as safe and nontoxic in the industry, and  
12 we have also completed a study in a similar product we  
13 were developing that uses polyethylene glycol where we  
14 implant a polyethylene glycol product, hydrogel, into  
15 the abdominal cavity of animals and intentionally  
16 created an infection at a rate that would cause  
17 healthy animals to die.

18           Prior to application we determine the LD-  
19 50 for an interperitoneal infection for these animals  
20 and then challenged it with the hydrogel versus non-  
21 hydrogen and found that the presence of the hydrogen  
22 did not potentiate infection, did not change the

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1 survival rate or the abscess formation in those  
2 animals.

3 DR. JENSEN: And so to that, in the  
4 case -- and I assume, Dr. Cosgrove, it was your case  
5 where the DuraSeal was scraped off. Did it come off  
6 as a sheet? Did it scrape off the middle peels? Were  
7 you able to send any of it to the lab to be evaluated?

8 DR. COSGROVE: Cultures were sent of  
9 necrotic and debrided material. It does not come off  
10 as a sheet. It's actually an amazing substance. It  
11 is adherent. It's pliable so that, you know, it  
12 stretches, and what you do if you want to take it off  
13 -- and in this instance it was four weeks out. So it  
14 had already undergone a fair amount of decomposition  
15 and was absorbing on its own. But you just took a cup  
16 curette and you'd have to scrape on the dura and lift  
17 the residual parts of it off, but it does not come  
18 off, you know, as a sheet.

19 CHAIRPERSON BECKER: Dr. Ellenberg.

20 DR. COSGROVE: And in answering your  
21 question about the infection, specimens were  
22 submitted, but in fact the patient had already been

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1 placed on antibiotics prior to the surgery. They tend  
2 to get placed on the antibiotics as soon as they hit  
3 the emergency room, and by the time you take them down  
4 to get the appropriate studies, no matter how many  
5 times you say we should hold off on the antibiotics  
6 before we get specimens.

7 This patient had been on antibiotics.

8 DR. JENSEN: Any microscopic evaluation of  
9 the hydrogel or staining or anything to just see if  
10 there had been any pockets of bacteria or anything?

11 DR. COSGROVE: No, I don't recall the  
12 path. report indicating anything of that sort.

13 DR. JENSEN: Thank you.

14 CHAIRPERSON BECKER: Dr. Ellenberg.

15 DR. ELLENBERG: Are we okay on timing?

16 CHAIRPERSON BECKER: Yeah.

17 DR. ELLENBERG: Okay. If I may, I'd like  
18 to ask three questions of Dr. Cosgrove in the area of  
19 efficacy and three questions on safety. I'd be happy  
20 to stop the questioning and allow another panel member  
21 to break in if the chair so determines that's a good  
22 idea.

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1           My first question has to do with the issue  
2           that Dr. Haines had already raised, the lack of a  
3           control group in the study, and from my reading of the  
4           material in the FDA clinical review, the major  
5           argument considered there on page 25 was the issue  
6           that one would have a heterogeneous control population  
7           if you had a control group and you and the rest of the  
8           sponsor group have referred to that on several  
9           instances.

10           In addition, this morning you've raised  
11           the issue which I did not read in the panel book that  
12           FDA either ruled or has thought it inappropriate to  
13           use a standard of care as a control because the  
14           standard of care might include unapproved use of  
15           products on the market.

16           I want to pursue the issue of the use of  
17           control group, but at this point I think it's  
18           reasonable for the panel to understand the constraints  
19           fully that you had are not using a control group  
20           because what you are offering up, as Dr. Haines has  
21           pointed out, is a very selective review of the  
22           literature to find in the massive numbers of papers

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1 that you've looked at that paper that you can find a  
2 subgroup in. So it's a subgroup of papers. Then  
3 within a paper it's a subgroup there that most closely  
4 matches the group that you're presenting today.

5 So with that in mind, I would like to ask  
6 FDA if there are, in fact, constraints -- and, Dr.  
7 Witten, I would ask you to respond to this -- are  
8 there constraints on having a control group where  
9 standard of care might include the use of an  
10 unapproved device?

11 DR. WITTEN: You can certainly have a  
12 control where the standard of care includes, you know,  
13 the use of various unapproved devices, but then the  
14 question is for us how we would end up interpreting  
15 that. So it's not that you can't use it. It could be  
16 put into the study design, but then the question would  
17 be how we would interpret.

18 Just for example, would the sponsor then  
19 need to show superiority to this heterogeneous  
20 standard of care equivalence to it? What would that  
21 mean?

22 So just I think that --

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1 DR. ELLENBERG: That answers my question,  
2 but let me rephrase that for my benefit and, thinking  
3 aloud, the panel's benefit.

4 My sense of that response is that the  
5 ruling did not have to do with the issue of standard  
6 of care. It went back to the issue of having a  
7 heterogeneous control group. So let me follow on with  
8 that.

9 You in defining the entrance drug criteria  
10 or --

11 DR. COSGROVE: Can I respond to the  
12 question before I lose -- I'm trying to keep track of  
13 all the questions.

14 DR. ELLENBERG: I haven't asked the  
15 question yet.

16 (Laughter.)

17 DR. COSGROVE: Well, I know, but I think  
18 it's very, very important to point out that we as the  
19 investigators were very perplexed, very cognizant of  
20 these issues. I mean of the design study, of a single  
21 arm study. We did not propose this initially. We  
22 proposed a control arm, and we figured that the best

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