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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

NEUROLOGICAL DEVICES PANEL
OF THE
MEDICAL DEVICES ADVISORY COMMITTEE
Fourteenth Meeting

Thursday, May 11, 2000

8:58 a.m.

Conference Room 020B
9200 Corporate Boulevard
Rockville, Maryland

P A R T I C I P A N T S

Committee Members

Cedric F. Walker, Ph.D., Chairman

Alexa I. Canady, M.D. (via telephone)

Constantine A. Gatsonis, Ph.D. (via telephone)

Robert W. Hurst, M.D.

Sally L. Maher, Esq.

David T. MacLaughlin, Ph.D.

Anne Roberts, M.D.

Gail L. Rosseau, M.D.

Anne W. Wojner, M.S.N.

Janet Scudiero, Executive Secretary

FDA Staff:

Celia Witten, Ph.D., M.D.

Peter L. Hudson, Ph.D.

Judy Chen, M.S.

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P R O C E E D I N G S

Call to Order

MS. SCUDIERO: Good morning. We are ready to start. I apologize for the delay. We are trying to trace a couple people.

My name is Janet Scudiero, and I am the Executive Secretary of the Panel, and I also do reclassification and classification in the Division of General Restorative and Neurological Devices.

This morning, our chair is unable to be with us due to weather conditions, and Dr. Cedric Walker will fill in for her. I now have several statements to read into the record.

Deputization to Voting Member Status

and Conflict of Interest Statements

"Appointment to Temporary Chair. Pursuant to the authority granted under the Medical Devices Advisory Committee Charter, dated October 27, 1990 and amended April 20, 1995, I appoint Cedric F. Walker, Ph.D., P.E., as Acting Chair of the Neurological Devices Panel for the duration of this meeting on May 11."

It is signed by Dr. David W. Freigel this morning.

"Appointment to Temporary Voting Status. Pursuant to the authority granted under the Medical Devices Advisory Committee Charter, dated October 27, 1990 and amended April

1 20, 1995, I appoint the following as voting members of the
2 Neurological Devices Panel for the duration of this meeting
3 on May 11, 2000: Constantine A. Gatsonis, Ph.D.; David T.
4 MacLaughlin, Ph.D.; and Anne C. Roberts, M.D. For the
5 record, these people are Special Government Employees and
6 are consultants to this panel or another panel under the
7 Medical Devices Advisory Committee. They have undergone the
8 customary Conflict of Interest Review and have reviewed the
9 material to be considered at this meeting."

10 This was also signed by Dr. Freigel on April 28,
11 2000.

12 I note Dr. Gatsonis is unable to be with us
13 because of weather conditions, and we are going to have him
14 hooked into a speaker phone, but he will not be voting
15 today.

16 We are attempting to get Dr. Canady connected by
17 telephone as well, and she will participate in the meeting
18 like Dr. Gatsonis, but she will be unable to vote today.

19 And now the last statement, the Conflict of
20 Interest Statement that was prepared for this meeting.

21 "The following announcement addresses conflict of
22 interest issues associated with this meeting and is made
23 part of the record to preclude even the appearance of an
24 impropriety."

25 "To determine if any conflict existed, the agency

1 reviewed the submitted agenda and all financial interests
2 reported by the Committee participants. The conflict of
3 interest statutes prohibit Special Government Employees from
4 participating in matters that could affect their or their
5 employers' financial interest. However, the agency has
6 determined that the participation of certain members and
7 consultants, the need for whose services outweighs the
8 potential conflict of interest involved, is in the best
9 interest of the Government."

10 "Waivers have been granted for Dr. Alexa Canady,
11 Richard G. Fessler, and Constantine A. Gatsonis for the
12 interests in firms and issues that could be potentially
13 affected by the Panel's deliberations. The waivers allow
14 these individuals to participate fully in today's
15 deliberations. A copy of these waivers may be obtained from
16 the agency's Freedom of Information Office, Room 12-A-15, in
17 the Parklawn Building."

18 "We would like to note for the record that the
19 agency took into consideration other matters regarding Drs.
20 Robert Hurst, Constantine Gatsonis and Anne Roberts. Each
21 of these panelists reported past or current interests in the
22 firms at issue, but in matters that are not related to
23 today's agenda. Therefore, the agency has determined that
24 they may participant fully in the Panel's deliberations."

25 "In the event that the discussions involve any

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

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

10 Thank you.

11 I will turn the meeting over now to Dr. Walker,
12 who is our Acting Chair for the day.

13 Dr. Walker?

14 **Introductions**

15 DR. WALKER: Thank you, Janet.

16 Good morning. My name is Cedric Walker, and I am
17 the Acting Chairperson of the Neurological Devices Panel. I
18 am professor of biomedical engineering at Tulane University
19 in New Orleans.

20 At this meeting, the Panel will be making a
21 recommendation to the Food and Drug Administration on the
22 approvability of the Premarket Approval Application P990040
23 from Cordis Endovascular Systems for Trufill N-Butyl
24 Cyanoacrylate and Trufill Tantalum Power intended for the
25 presurgical treatment of arteriovenous malformations.

1 Before we begin the meeting, I would like to ask
2 our distinguished Panel members, who are generously giving
3 of their time to help the FDA in the matter being discussed,
4 and the FDA staff who are seated at this table, to introduce
5 themselves.

6 I would like you to introduce yourself by giving
7 your name, your area of expertise, position and affiliation-
8 -and I think that on the speaker phone immediately to my
9 right, so we will start in this direction, we have Dr.
10 Canada.

11 Dr. Canady, are you here?

12 DR. CANADY: I am here

13 DR. WALKER: And I believe we have Dr. Gatsonis?

14 DR. GATSONIS: Yes.

15 DR. WALKER: Good morning.

16 Dr. Canady, will you start and introduce yourself?

17 DR. CANADY: I am professor of neurosurgery and
18 Chief of Pediatric Neurosurgery at Children's Hospital in
19 Detroit, Michigan, Wayne State University.

20 DR. WALKER: And Dr. Gatsonis?

21 DR. GATSONIS: Hello. I am professor of
22 biostatistics at Brown University.

23 DR. WALKER: Thanks.

24 Dr. Roberts?

25 DR. ROBERTS: Dr. Anne Roberts, professor of

1 radiology and Chief of Vascular and Interventional Radiology
2 at UC-San Diego.

3 DR. WITTEN: Celia Witten, Division Director of
4 the Division of General and Restorative Devices Evaluation
5 at FDA.

6 MS. MAHER: Sally Maher, Director of Regulatory
7 Affairs and Clinical Research for Smith & Nephew; and I am
8 here as the Industry Representative.

9 MS. WOJNER: Anne Wojner, President of the Health
10 Outcomes Institute and an assistant professor at the
11 University of Texas-Houston, and I am a Consumer Rep.

12 DR. MacLAUGHLIN: I am David MacLaughlin,
13 associate professor at Harvard Medical School as a
14 biochemist, and I have a research lab at the Massachusetts
15 General Hospital. I am here as a Technical Expert.

16 DR. ROSSEAU: Gail Rosseau. I am a neurosurgeon
17 and Director of Cranial-Based Surgery for Rush University
18 Medical Center in Chicago.

19 DR. HURST: Robert Hurst. I am an associate
20 professor of radiology, neurosurgery, and neurology at the
21 University of Pennsylvania and Director of Interventional
22 Neuroradiology.

23 MS. SCUDIERO: Just one correction for the record.
24 Dr. MacLaughlin is a deputized voting member for today as
25 well as the Technical Expert.

1 Thank you.

2 DR. WALKER: Apparently, FDA looks upon "experts"
3 and "voting members" in two different ways.

4 I would like to note for the voting members that
5 we have present constitute a quorum as required by 21 Code
6 of Federal Regulations, Part 14.

7 Now, it is my pleasure to ask Mr. Stephen Rhodes,
8 the Chief of the Plastic and Reconstructive Surgery Devices
9 Branch, to update the Panel on several matters that were
10 deliberated on at the last two Panel meetings.

11 Mr. Rhodes?

12 **Update Since September 1999 and March 2000 Meetings**

13 MR. RHODES: Thank you, Dr. Walker.

14 Welcome, Panel, and welcome, members of the
15 audience.

16 I just want to give you a brief update on what we
17 have been doing in this area in the last few months.

18 The Panel met in September of 1999 and recommended
19 that human dura be classified into Class II and provided
20 comment on the guidance for preparation of a Premarket
21 Notification Application for processed human dura.

22 At this time, FDA is considering the information
23 provided by the Panel and submitted by dura providers as it
24 prepares a final classification regulation for human dura as
25 a Class II Medical Device.

1 The Panel also provided comment on two guidance
2 documents, one for dura substitutes and one for neurological
3 embolization devices. Based on the Panel's comments, both
4 of these guidances have been modified and are currently in
5 the process of being released to the public.

6 The Panel also recommended reclassifying the
7 totally implanted spinal cord stimulators from Class III to
8 Class II. These devices are indicated for treatment of
9 chronic pain of the trunk and the limbs. This
10 recommendation, the sponsor's petition, and other comments
11 are being evaluated by the FDA also at this time.

12 At the March 31 meeting, the Panel recommended
13 approval with conditions for the Medtronic Activa system for
14 treatment of Parkinson's disease. This recommendation is
15 also being evaluated by the FDA at this time.

16 Thank you for your attention. That concludes my
17 update.

18 DR. WALKER: Thank you, Mr. Rhodes.

19 We will now proceed with the Open Public Hearing
20 portion of the meeting that was scheduled for 9 o'clock, so
21 in spite of our delay, we are only 10 minutes off-schedule.

22 I would ask at this time that all persons
23 addressing the Panel speak clearly into the microphone, as
24 the transcriptionist is dependent on this means to provide
25 an accurate record of the meeting.

1 Prior to the meeting, we received no requests to
2 speak in the Open Public Hearing.

3 Is there anyone here who would like to address the
4 Panel now?

5 [No response.]

6 DR. WALKER: If not, then we can proceed with the
7 Open Public Meeting.

8 Cordis will be the next presenter. We will
9 proceed with the sponsor's presentation on P990040, the
10 Cordis Neurovascular, Inc. Trufill N-Butyl Cyanoacrylate and
11 Trufill Tantalum Powder intended for the presurgical
12 treatment of arteriovenous malformations.

13 After the sponsor's presentation to the Panel, we
14 will have the FDA presentation. After the lunch break, the
15 Panel will deliberate on the approvability of the PMA
16 supplement.

17 Before the Panel votes on the approvability of the
18 PMA, there will be another Open Public Hearing, and a time
19 for FDA and sponsor summations.

20 I would like to remind the public observers at
21 this meeting that while this meeting is open for public
22 observation, public attendees may not participate except at
23 the specific request of the Panel.

24 We will begin with Cordis Endovascular Systems
25 presentation. The first Cordis Neurovascular speaker is Ms.

1 Alina Caraballo, Regulatory Affairs Manager.

2 Ms. Caraballo?

3 Sponsor Presentation on PMA 990040,
4 Trufill N-Butyl Cyanoacrylate and Tantalum Powder

5 MS. CARABALLO: Good morning.

6 First of all, I am the Regulatory Affairs Manager
7 for Cordis Endovascular Systems, and I would like to thank
8 the members of the Panel for being here and also the FDA for
9 working so hard with us on this process that is going to, of
10 course, benefit Cordis, the physician community, and the
11 patient, ultimately.

12 I would like to introduce the members who will
13 speak in behalf of our devices.

14 Dr. Steve Rowland, Vice President of Research and
15 Development for Cordis Endovascular System, will be
16 presenting an overview on the device.

17 Dr. Phil Purdy, who was one of the study
18 investigators at U.T.S.W. Medical Center in Dallas, Texas,
19 will give us an overview on AVM morphology and treatment.

20 Dr. Tom Tomsick, the principal investigator for
21 our study, will present the trial results. He is from the
22 University of Cincinnati in Cincinnati, Ohio.

23 And last, Ms. Lisa Wells, Senior Manager for
24 Clinical and Regulatory Affairs at CES, will give an
25 overview of our training program.

1 Also, as members in the audience, we have Mr. Bret
2 Nevelrider [ph.], who was one of the original project
3 leaders for the project, and if needed, he will speak.

4 Also, Dr. Pedro Cato, who is the current project leader, and
5 Dr. Hoy Leung, who is our statistical person from Quintas.

6 With that, I am going to turn it over to Dr. Steve
7 Rowland who will present the device overview.

8 Thank you.

9 DR. ROWLAND: Good morning.

10 I would like to give you a brief overview of the
11 device, the Trufill n-BCA Liquid Embolic System, as well as
12 give you an overview of the testing that was done on a
13 preclinical basis to characterize the system.

14 [Slide.]

15 First, there are three components to the Trufill
16 System--the n-Butyl Cyanoacrylate Monomer; tantalum powder,
17 which is provided as a radiopacifier; and ethiodized oil for
18 injection, which is provided as a radiopacifier and organic
19 diluent for the system.

20 [Slide.]

21 You can see here from the viewgraph, the three
22 components--you can see the Trufill ethiodized oil, which is
23 in a 10 ml glass ampule; below that is the n-BCA aluminum
24 tube which holds 1 gram of material; and you can see that
25 there is a plastic threaded lure fitting which screws into

1 the end of this aluminum tube and is used to transfer the
2 material through the lure fitting into a syringe. Below
3 that is a microtube which holds the tantalum material and 1
4 gram of tantalum is provided in that microtube.

5 [Slide.]

6 The indications for use for the Trufill n-BCA
7 Liquid Embolic System. Trufill n-BCA Liquid Embolic Agent,
8 radiopacified with ethiodized oil and Trufill tantalum
9 power, is indicated for the embolization of cerebral
10 arteriovenous malformations when presurgical
11 devascularization is desired.

12 Additionally in our instructions for use, we make
13 the statement that the safety and efficacy of the Trufill n-
14 BCA Liquid Embolic Agent as a long-term implant has not been
15 established.

16 [Slide.]

17 Going to the individual components, the n-BCA or
18 n-Butyl Cyanoacrylate monomer, is a clear liquid which is
19 used for delivery under fluoroscopic guidance through an
20 infusion microcatheter.

21 The chemical composition is specified as being
22 greater than 99 percent pure. It is supplied nonpyrogenic
23 and sterile. Polymerization time is certified to be less
24 than 1 second when in contact with plasma.

25 The n-BCA as I showed you earlier is provided in a

1 single-use aluminum tube which contains 1 gram of material.
2 The tube is placed and sealed in a Tyvek/Mylar pouch, and
3 three pouches are provided in each box of n-BCA.

4 [Slide.]

5 The n-BCA polymerization--n-BCA polymerizes
6 straight from a monomer through an anionic initiation to the
7 n-BCA polymer. n-BCA is in the family of cyanoacrylates,
8 which traditionally are known as the superglues. In this
9 application as a liquid embolic agent, the n-BCA can
10 penetrate deeply into the nidus of an AVM and obscure
11 feeding pedicles into the AVM as well as embolize peripheral
12 feeding into the AVM.

13 [Slide.]

14 Next, the tantalum part of the devices. Tantalum
15 powder is a finely-ground powder, gray in color, and it is
16 used with the ethiodized oil to radiopacify the n-BCA. The
17 tantalum that we provide has a minimum of 98.8 percent
18 purity. We specify the size of the tantalum to remain in
19 suspension with n-BCA and ethiodized oil for a minimum of 1
20 minute. It is supplied nonpyrogenic and sterile.

21 As I showed you earlier, it is provided in a
22 sealed, single-use microcentrifuge tube which has 1 gram of
23 material; each tube is also placed and sealed in the
24 Tyvek/Mylar pouch and sterilized, and three pouches are
25 provided in each box.

1 [Slide.]

2 Ethiodized oil is a component that we have added
3 to the system, specifying specifically from CES. The
4 ethiodized oil is a sterile injectable radiopaque agent that
5 is used to radiopacify n-BCA and also to dilute and control
6 the polymerization of the n-BCA.

7 The ethiodized oil that we are using is iodinated
8 poppyseed oil. It meets the U.S. Pharmacopeia 23
9 specifications for ethiodized oil injection, and we specify
10 that the material is compatible with the n-BCA and tantalum
11 powder.

12 This is provided in glass 10 cc ampules, and two
13 ampules are packed per box.

14 [Slide.]

15 Next, an overview of the product usage. The first
16 step is the ethiodized oil and tantalum powder are mixed in
17 an appropriate mixing container. Then, the desired amount
18 of n-BCA is added to the mixing container and mixed well.
19 This mixture is aspirated into an appropriate syringe,
20 typically a 3 ml syringe. The mixture is injected through
21 an infusion catheter under fluoroscopic guidance after the
22 catheter has been placed deep into the nidus of the AVM.

23 As the material is injected into the AVM, this is
24 observed fluoroscopically, and when the injection is
25 completed, the microcatheter is rapidly removed from the

1 site of injection to prevent the catheter from being adhered
2 into place.

3 [Slide.]

4 To summarize the in vitro testing of the n-BCA, we
5 specify the polymerization rate in contact with plasma to be
6 less than 1 second and have shown that to be the case. We
7 have also done studies to show the reproducibility of this
8 material in contact with plasma and with this polymerization
9 rate. We have done sterility testing. Also, we have
10 characterized the packaging integrity and shelf life to
11 support a 2-year shelf life. And biocompatibility testing
12 was undertaken following the ISO 10993 guidance for implant
13 materials, blood contacting, with prolonged exposure of
14 greater than 24 hours but less than 30 days, and passed
15 those tests.

16 [Slide.]

17 Likewise, on the tantalum powder in vitro testing,
18 the tantalum powder that we have sourced has been shown to
19 be compatible with n-BCA in its effect on polymerization
20 time. The sterility of the material has been verified. The
21 packaging and shelf life testing, both accelerated as well
22 as real-time testing, supports the requested shelf life.
23 Biocompatibility likewise was undertaken following the ISO
24 10993 guidelines to the same through prolonged exposure,
25 blood contact and implant materials, greater than 24 hours,

1 less than 30 days and passed those tests.

2 [Slide.]

3 At the request of FDA in the initial deficiency
4 letter we received from our PMA application, we have
5 undertaken additional testing. I won't go into the results
6 of this testing, but I just wanted to go over that this
7 testing has been initiated.

8 Biocompatibility testing form the n-BCA, tantalum
9 and ethiodized oil mixture has been undertaken and, with a
10 couple of exceptions, has been completed, but the results
11 have not been submitted to FDA, so we will not present those
12 results today since they have not had a chance to review
13 them.

14 Additionally, hydrolytic degradation studies have
15 been undertaken. This is looking at the hydrolytic
16 stability under in vivo and also under accelerated time
17 conditions at elevated temperatures, to look at degradation
18 products of the combination of tantalum, n-BCA and
19 ethiodized oil.

20 Additionally, elution studies have been undertaken
21 to show the elution of the ethiodized oil from the mixture
22 of tantalum, n-BCA, and ethiodized oil. Those studies have
23 been completed but not reviewed by FDA.

24 Catheter compatibility testing with Cordis
25 Endovascular System microcatheters has been completed, and I

1 believe those results have been submitted and reviewed in
2 the Panel pack.

3 This completes my summary of the description of
4 the device as well as the testing.

5 I will now turn the presentation over to Dr. Phil
6 Purdy, who will talk to you about the clinical intervention
7 with AVMs using this material.

8 DR. PURDY: Good morning.

9 My name is Phillip Purdy, and I am the Director of
10 Neuroradiology at UT-Southwestern Medical School in Dallas,
11 Texas, and I am one of the investigators on this trial.

12 [Slide.]

13 As per the instructions in the beginning, I want
14 to disclose that I have no stock or options or other
15 financial interest in Cordis or Johnson & Johnson and
16 receive no pay for my appearance here. I am not currently a
17 paid consultant at Cordis. I am the inventor on some
18 unrelated patents, as I say, unrelated to the glue, that are
19 licensed to Cordis from ET-Southwestern.

20 [Slide.]

21 One of the important features to understand in
22 interpreting this data and this trial is the nature of the
23 disease itself. One of the purposes of my talk today is to
24 talk a little bit about AVMs in general as a disease state
25 for those members of the Panel who may not be intimately

1 familiar with it.

2 One of the important features about AVMs is that
3 they are a rare disease. The incidence in the population is
4 somewhere between .02 and .05 percent of the population.

5 The difficulty in running this trial was in part
6 because of the incidence of the disease, and then, when you
7 stack on top of that the difficulty with interpreting the
8 anatomy, defining the appropriate anatomic configuration of
9 the malformation to do it with glue, and then to sign the
10 patient up with an informed consent to participate in the
11 trial, it was by anybody's measure a difficult trial to run.

12 Arteriovenous malformations present clinically
13 with a number of symptom complexes that include cerebral
14 hemorrhage--

15 [Technical interruption.]

16 DR. WALKER: Dr. Purdy, let's take a moment so
17 that Dr. Canady and Dr. Gatsonis can be reconnected to us.

18 Let's take a 10-minute coffee break.

19 [Coffee break.]

20 DR. WALKER: Dr. Purdy, please continue right
21 where you left off.

22 DR. PURDY: Thank you.

23 [Slide.]

24 As I said before, the incidence of AVMs is very
25 rare in the population, and that is one of the features that

1 complicated the acquisition of subjects for this trial.

2 The clinical problems that patients with AVMs
3 present with are, as you might imagine, myriad. They run
4 anywhere from a devastating cerebral hemorrhage or a less
5 devastating cerebral hemorrhage to seizures or headache or
6 progressive neurological deficit or stroke.

7 [Slide.]

8 The treatment of AVMs is an area of some amount of
9 controversy in terms of recent development of radiosurgical
10 techniques to treat AVMs. There are very few people who
11 would hold that primary embolization is at least a regular
12 way that AVMs can be treated, and primarily, I think it is
13 pretty broadly agreed that the current treatment of an
14 arteriovenous malformation involves surgical resection of
15 the AVM, which is a microsurgical dissection that is done
16 over a period of time where the vessels are cauterized
17 around the margin of the AVM.

18 Preoperative embolization is primarily an adjunct
19 to the surgical resection as a means of trying to make the
20 surgical job easier.

21 [Slide.]

22 The goals of preoperative embolization are to
23 eliminate the feeding pedicles; to eliminate the vessels
24 themselves, which will be encountered late during the
25 resection of an AVM--for instance, if you are beginning your

1 resection from the front of the AVM, those vessels coming in
2 from the back of the AVM are going to be bleeding at you
3 throughout the whole procedure unless they are taken care of
4 embolically to begin with; you try to increase the perfusion
5 to the surrounding brain to try to decrease the incidence of
6 what is called "normal perfusion pressure breakthrough
7 bleeding," which is that brain which has not been facing a
8 normal perfusion pressure because of the AVM sumping the
9 blood away now is confronted with a normal perfusion
10 pressure when the AVM is removed, and sometimes those
11 vessels break loose and bleed, and it is one of the causes
12 of postoperative hemorrhage; and also, obviously, to
13 decrease the amount of bleeding at the time of surgery.

14 [Slide.]

15 The currently-approved embolic materials include
16 polyvinyl alcohol, which is small sponge particles that are
17 sized in various sizes. They have some advantages and
18 disadvantages. Some of the disadvantages are that they are
19 not radiopaque; we cannot see those particles on x-ray; many
20 pass straight through the AVM to the lungs, although most
21 often, this is well-tolerated by the patients, but we know
22 it happens, and it is a disadvantage of the particles. The
23 particles, because they are solid, require larger catheters
24 and guidewires than would a liquid embolic material to
25 deliver to the AVM, and that increases the stiffness of the

1 system and may impact the complication rates that are
2 encountered with the catheterization process itself.

3 One of the advantages of PVA particles is that
4 they do enable flow-directed embolization in a way that
5 liquid embolics do not.

6 [Slide.]

7 Coils are comprised of fine platinum wire that has
8 variable degrees of stiffness and comes in variable sizes.
9 These are used to occlude the feeding pedicle or to block
10 shunts within the malformation when the particles are not
11 decreasing the flow, and as a disadvantage, they may leave
12 the nidus of the AVM, actually occluding only the larger
13 feeders, and then collaterals to the AVM can still fill the
14 AVM and cause you to achieve less with your embolization.

15 [Slide.]

16 Another point about n-BCA is that this is an agent
17 that has been around for a long time. It was around when I
18 was in training in the late seventies and early eighties as
19 isobutyl cyanoacrylate, and then n-butyl cyanoacrylate, so
20 it is not new to the market, although it is here for trying
21 to get first-time FDA approval. IT has been used off-label
22 since the 1980s widely in the United States as well as
23 throughout the world for embolization of AVM--and I don't
24 mean that as a defense or anything else--it is a fact that
25 people have been using glue for long time to embolize AVM.

1 So this trial is not our first experience with glue, and
2 should be interpreted in that light.

3 It has always been modified using oil-based
4 contrast material and/or tantalum to opacify it. It is not
5 radiopaque in the regular state, and these materials, though
6 the uses of practitioners, have become well-understood in
7 terms of how to mix them, to modify, to achieve
8 opacification and to affect the polymerization time.

9 [Slide.]

10 Something that affects the statistics that we see
11 with the trial that I think is important as you view the
12 data today is the nature of AVMs themselves. They are a
13 highly variable disease. No two AVMs are alike. It is not
14 like treating a wart or a mole. Every AVM is different.
15 They differ in size, they differ in feeders, they differ in
16 location. Venous drainage and the internal architecture
17 vary considerably from one malformation to another in terms
18 of large or small shunts, aneurysms, and the degree of
19 fragility of the vessels and, therefore, the propensity to
20 hemorrhage.

21 [Slide.]

22 This slide shows some examples of different
23 malformation configurations. This is a patient whose AVM is
24 fed from his posterior circulation. Here is a vertebral
25 arteriogram, posterior cerebral artery, and you see myriad

1 numbers of small feeders coming off of that posterior
2 cerebral along its course. This AVM would be difficult to
3 embolize with glue, and you can appreciate that even though
4 both of these two AVMs are in the same general location,
5 they are very different in their configuration.

6 This is fed off of a pedicle that arises off the
7 posterior cerebral artery. It would be easy to pass a
8 catheter into the pedicle and to embolize that AVM. This is
9 a malformation that is fed off the anterior artery, and the
10 distal anterior cerebral going into the AVM. As the
11 investigators are trying to interpret or present data for
12 this trial, please note that these are from the same
13 patient. So in trying to size that AVM, you have to mental
14 combine the carotid arteriogram and the vertebral
15 arteriogram and combine those two AVMs to try to say what
16 size that AVM is, and that is one of the sources of
17 variability, I think, in some of the data.

18 [Slide.]

19 Another source of variability in the data is
20 looking at an individual arteriogram, how do you say where
21 the malformation starts and where it ends, and also
22 interpreting the concentration of glue to use. There are so
23 many differences in the degree of shunting that the
24 practitioners in our field widely felt the flexibility to
25 mix the glue to suit the malformation.

1 [Slide.]

2 I have a couple of examples to show you of
3 different malformations. This is an 11-year-old girl who
4 has a large fistulous malformation fed off her posterior
5 inferior cerebellar artery. This is a vertebral
6 arteriogram, this is pica, and the entire flow of the basal
7 artery, you will see, or the entire flow of the vertebral
8 artery is going to dump into pica on this sine run [ph.].

9 Here, you can appreciate that there really is no
10 filling of the basal artery as it comes into view here.
11 This is the little bit of flash filling into the distal
12 vertebral artery, this is all pica, and this is largely a
13 big fistula. You can appreciate the rapidity of the flow,
14 and if someone were trying to use glue to embolize this, it
15 would require a very fast polymerization time.

16 Again, just showing it one more time, running it
17 through. I use coils embolizing this, and here you can see
18 the catheter winding its way through pica, and the catheter
19 tip is up here, and I have put some coils there and some
20 there and ultimately, packed that vessel with coils, and
21 only after I have packed that vessel with coils do you see
22 filling into the distal vertebral artery, and now a new
23 shunt is filling off of the basal artery, and that one had
24 to be embolized separately--but if I had had to interpret
25 this arteriogram pre-embolization, I might have missed

1 altogether the existence of these other shunts. So the
2 embolization process itself alters the angiographic anatomy
3 that you see.

4 [Slide.]

5 This is another patient with a frontal AVM, again
6 fed largely off the anterior cerebral artery here in his
7 frontal lobe. The middle cerebral artery, you will note,
8 fills normally here, whereas on the other patient, the basal
9 artery did not fill at all. And here is the AVM in the
10 midline.

11 [Slide.]

12 Notice the difference in this AVM with the flow.
13 You will see all the other vessels in the middle cerebral
14 fill out, even though this is rapidly shunting into the AVM,
15 and you can appreciate the other vessels around the brain
16 still fill. There is the venous drainage going up to the
17 sagil [ph.] sinus. I will show you one more time.

18 [Slide.]

19 Another issue, just so the members of the Panel
20 who don't do this or witness it can appreciate some of the
21 anatomic problems that we have in interpreting an AVM, this
22 is a rotational arteriogram on that same patient, and what
23 you will see is the eyes are over here; the patient is
24 facing to our right; and during the injection, the serum is
25 going to rotate around to where the patient is facing to our

1 left. And just watch the vessels going in there, and you
2 can appreciate some of the technical difficulties that are
3 encountered and also appreciate one of the sources of
4 variability from one AVM to another.

5 [Slide.]

6 This gives you an idea of the three-dimensional
7 anatomy that we are dealing with, trying to read these
8 studies and trying to catheterize these malformations.

9 I'll run that by one more time just to let
10 everybody get some visceral appreciation, anyway. This is
11 entirely variable from one patient to another.

12 [Slide.]

13 This is the catheterization of that patient's AVM.
14 Here is a catheter in the carotid artery entering the
15 interior cerebral and going up into one of those branches,
16 and actually, I don't really, but I don't think this vessel
17 was catheterized any further than that; he tolerated testing
18 with amytol [ph.], and I did this embolization.

19 [Slide.]

20 Here is the view after his embolization, and you
21 can appreciate the neurosurgeon would be facing a lot tamer
22 beast when he or she went into operate on that AVM as
23 opposed to a pre-embolization AVM. In this case, I think,
24 whereas with the other case you would want to use a high
25 concentration of glue, in this case, I think you could do it

1 easily with a 25 to 33 percent glue mixture, because there
2 weren't the internal, really rapid shunts that there were in
3 the other one.

4 The next speaker will be Dr. Tom Tomsick, who is
5 the head of Neuroradiology at the University of Cincinnati
6 and is the Principal Investigator on our trial, and he is
7 going to present the actual study results.

8 DR. TOMSICK: Very good. Again, I am Tom Tomsick
9 from the University of Cincinnati.

10 I would like to disclose that I am a consultant to
11 Cordis Endovascular Systems as well as Principal
12 Investigator in this study.

13 I would hope that Drs. Canady and Gatsonis if they
14 are on the line will be able to follow my presentation with
15 the slide packet that was provided to them. As I go through
16 it, I will call "Next slide," "Next slide," so they know
17 where we are as we go through the presentation.

18 [Slide.]

19 It is my privilege today to report to you the
20 clinical results of the Cordis Endovascular Liquid Embolic
21 System trial. First of all, I think it is important to
22 point out that the trial began in October of 1996, so it has
23 been ongoing for quite some time.

24 Some of the difficulties in conducting the trial
25 were alluded to by Dr. Purdy wherein, halfway through the

1 trial, the trial was actually stopped because of relatively
2 slow accrual of patients. And it is to Cordis Endovascular
3 System's credit, I think, that the trial was resurrected at
4 the request of the Neural Interventional Committee and
5 eventually seen through to completion and our meeting here
6 today.

7 [Slide.]

8 My second slide points out that the study was
9 conducted between October of 1996 to final completion in
10 March of 1999 in 13 major centers around the country.

11 [Slide.]

12 Again, the Cordis Endovascular System Liquid
13 Embolic System trial's primary objective was to verify that
14 the n-BCA/tantalum/ethiodized oil mixture is as safe and
15 effective as conventional treatment--namely, polyvinyl
16 alcohol sponge; Cordis Endovascular System's Trufill PVA--
17 for the obliteration of cerebral AVMs when preoperative
18 devascularization is desired.

19 [Slide.]

20 The primary efficacy hypothesis was that the
21 degree of vascular occlusion with the n-BCA Liquid Embolic
22 System was not inferior to PVA as measured by the percent of
23 AVM nidus obliterated or the number of feeding pedicles
24 embolized.

25 [Slide.]

1 The secondary efficacy hypotheses were that the
2 surgical resection time subsequently would be comparable and
3 that surgical blood loss, as reflected by the volume of
4 blood and fluids or colloid required during surgery would
5 also be comparable.

6 [Slide.]

7 The primary safety outcomes included the incidence
8 of device complications; the incidence of procedural
9 complications; and the incidence of intracranial events. I
10 think it is important to point out that these were
11 determined by the investigator at the site. We also
12 measured subsequently the overall neurologic outcome as
13 manifested by the Glasgow Outcomes Score/NIH Stroke Scale
14 [ph.] Score, and general neurologic examination.

15 [Slide.]

16 The device complications were defined as product
17 malfunctions or unintended occurrences, or user error that
18 caused an adverse event. Examples would be catheter
19 occlusion or a catheter that might be glued in place by
20 acrylic or an early or late polymerization of n-BCA, perhaps
21 failure to access a vessel, or in some instance, pulmonary
22 embolism of the embolic agent.

23 [Slide.]

24 Procedure complications would be adverse events
25 that resulted from the procedure itself, not primarily

1 related to the device, such as vessel perforation in
2 attempts to catheterize, or vessel dissection; AVM rupture;
3 incorrect vessel occlusion; or hemorrhages from nonspecified
4 sources.

5 [Slide.]

6 The primary safety outcomes were also measured by
7 intracranial events and the overall neurologic outcome.
8 Adverse intracranial events might be ischemia or stroke or
9 seizure, or a post-embolization or post-surgical hemorrhage,
10 and the overall neurologic outcome was measured by Glasgow
11 Outcomes Score, NIH Stroke Scale [ph.] Score, and the
12 clinical neurologic exam.

13 [Slide.]

14 This slide shows the study flow chart, which I
15 won't dwell on today, but I would like to point out that
16 after the patient was initially evaluated, and it was
17 determined whether they met inclusion criteria or not, the
18 informed consent was signed, and the objectives of the study
19 were defined by the investigator before the patient was
20 randomized. So the goal of the study was determined prior
21 to randomization and treatment in the study, and I think
22 that that is an important point to emphasize.

23 [Slide.]

24 There were no statistically significant
25 differences in the demographics in the patient populations.

1 The AVM size, if you will, as determined by the Spetzler
2 Grade, was similar in both groups, and there were similar
3 patients distributed across all five of the Spetzler Grades.
4 Mean age and sex were similar in both groups as well.

5 There was a slight trend for patients in the n-BCA
6 group to have experienced intracerebral hemorrhage or
7 subarachnoid hemorrhage prior to treatment, although that
8 was not a significant difference, and again, other
9 neurologic history or physical exam deficits were similar in
10 the two groups.

11 [Slide.]

12 The AVM characteristics in the two groups--we
13 mentioned that the Spetzler-Martin Grade was similar; the
14 volumes of the AVMs were also similar in the two groups--the
15 n-BCA-treated group only slightly larger. Unusually large
16 AVMs were equally distributed in both groups as well, in
17 other words--greater than 6 cm in size, four in each group.

18 A slight difference in deep venous drainage was
19 noted in that in the n-BCA group, there was a slight
20 increase in deep venous drainage, and we do know that deep
21 venous drainage is a component of determinations included in
22 the Spetzler-Martin Grade that theoretically make management
23 more difficult when deep venous drainage is present.

24 [Slide.]

25 This is the accounting slide for the PVA group,

1 wherein 52 patients were randomized to treatment with PVA;
2 two actually crossed over from PVA treatment to n-BCA
3 treatment during the course of study and are considered in
4 further analysis. I would like to point out that one of
5 these two patients was actually the only patient in the
6 entire study who had complete obliteration of the AVM with
7 embolization following crossover and ultimately did not have
8 surgery.

9 Subsequently, there was one patient whose records
10 were truly inadequate in terms of documentation, and that
11 patient was eliminated from further analysis. There were
12 four patients who were treated but not resected for a
13 variety of reasons who did not continue through the protocol
14 analysis. And even after surgery, after the patient was
15 embolized and surgery had been performed, there was one
16 patient who had a postoperative hemorrhage and had a remnant
17 of AVM identified that was then treated by n-BCA.

18 Counting statistics for the n-BCA group, 52
19 patients randomized once again. There were two patients who
20 were not embolized because of an inability to select the
21 appropriate feeding artery pedicles. There was one patient
22 who had no attempted embolization at all because the AVM was
23 determined to be in an unsafe location.

24 [Slide.]

25 While I don't want to dwell on individual patients

1 here today, I'd like to show those two n-BCA failures.

2 These were very small AVMs where the feeding
3 arteries could not be catheterized for appropriate
4 treatment, and although these might be considered n-BCA
5 failures, they did turn out to be management successes,
6 because both patients were treated by surgery without
7 embolization, and they had less than the mean fluoro time
8 for the procedure, they had less than the mean surgery time
9 for the n-BCA group, they had less than the mean blood loss,
10 and their Glasgow Outcome Scores were good in both groups.
11 So although it is an n-BCA failure, they are management
12 successes.

13 [Slide.]

14 The patient who was randomized but not attempted--
15 the patient was randomized on the basis of an outside
16 angiogram wherein the operator thought he would be able to
17 embolize, but when the patient had the higher-quality
18 cerebral angiogram at the operator center, he determined
19 that embolization of this AVM was probably not advisable.

20 [Slide.]

21 Therefore, we had 46 patients continuing in the n-
22 BCA treated group. Two patients actually had initial
23 treatment with n-BCA, and then, a small amount of
24 embolization was done by PVA at the operator's judgment.
25 One additional patient actually withdrew from the study

1 after a single state of embolization where coils only were
2 used--he never had n-BCA injected--and he withdrew from the
3 study.

4 There were two patients who were embolized but
5 ultimately not resected. And ultimately, there was one
6 patient who was eliminated from further analysis because of
7 the prolonged hospital course of management.

8 There was one other patient listed on your
9 accounting slide, I believe, who did not have a
10 postoperative angiogram. So your accounting slide may show
11 42 n-BCA patients; we are going to emphasize 43 n-BCA
12 patients here today, because all of his other data was
13 available.

14 [Slide.]

15 So in terms of primary efficacy outcomes, what is
16 the outcome in terms of the percent of reduction of AVM
17 volume by stage?

18 In the n-BCA group, in 73 stages, the operator
19 defined that 47 percent of AVM reduction was desired. In
20 the PVA group, it was 41 percent. So that actually, there
21 was a slight difference, not significant.

22 In terms of the percent that was achieved as
23 measured by the central core lab, there was virtually no
24 difference between the n-BCA and the PVA groups by stage.

25 [Slide.]

1 If we look at percent reduction of AVM volume by
2 patient, again, we see that the desired percent in both
3 groups is very similar, and there is a 7 percent difference
4 between the PVA group and the n-BCA group which is still
5 within the 95 percent confidence interval for that
6 difference by both ANCOVA and Bootstrap analysis.

7 [Slide.]

8 In terms of number of vessels occluded as a
9 primary efficacy outcome measure, again, looking first by
10 stage, in the n-BCA group, three desired; in the PVA group,
11 a slightly less number desired, 2.5 vessels. In terms of
12 those achieved, slightly greater in the n-BCA group compared
13 to the PVA group by stage.

14 [Slide.]

15 If we look at the primary efficacy outcome, the
16 number of vessels occluded by patient, then, again, a
17 slightly increased desired in the n-BCA group as compared to
18 PVA, and also an increased number of pedicles achieved in
19 the n-BCA as opposed to the PVA group. Again, these were
20 within the one-sided 95 percent confidence intervals by two
21 analyses, once again.

22 [Slide.]

23 The next slide is an outline of the secondary
24 outcome measures by an intention-to-treat analysis of the
25 embolization duration in minutes, fluoroscopy duration in

1 minutes, the resection of AVM in minutes, blood replacement
2 in terms of units, fluid colloid replacement, and cell-saver
3 replacement. And there were no statistically significant
4 differences in any of these measures in the intention-to-
5 treat analysis.

6 [Slide.]

7 If we were to look at per-protocol analysis of
8 patients making it through the study with completed data, we
9 would see that although there is no statistically
10 significant difference between the two groups, there is
11 actually an 18 percent increase in fluoroscopy time in the
12 PVA group as compared to the n-BCA group. And although this
13 may not be a significant difference, we are looking at what
14 the biologic effects of what increased fluoroscopy time in
15 that PVA group theoretically might be.

16 [Slide.]

17 If we look at the total surgical resection time,
18 once again it is somewhat greater in the PVA group, but not
19 statistically significant. You will see in the last
20 quartile of patients, there does seem to be a little
21 divergence again. In point of fact, there are six PVA
22 patients who had surgical resection times that were longer
23 than the longest n-BCA patient. So again, there is a
24 slightly trend for increases in surgical resection time.

25 [Slide.]

1 If we look at blood replacement in terms of units
2 of blood, there were 13 patients in each group that required
3 blood replacement, blood transfusion, and once again, there
4 is a slight trend for increased requirement in the PVA
5 group, but again, obviously, skewed by a small number of
6 patients.

7 [Slide.]

8 If we look at volume of colloid or fluid
9 replacement in the study, the curves are virtually
10 superimposable up until that final tail of the last couple
11 patients. So again, no statistically significant
12 differences in those parameters, but some trends perhaps in
13 the last quartile of patients.

14 [Slide.]

15 If we were to look at the size of particles used
16 in the study and the use of coils in the study, there was a
17 statistically significant difference in coils used with a P
18 value less than .0001, with greater number of coils used in
19 the PVA group.

20 [Slide.]

21 If we were to look at the size of particles used,
22 there were really only 18 patients of the PVA group that
23 could be treated with PVA and less than 500 micron size.
24 Anything larger than 500 micron size could not be injected
25 through the same catheters that glue can be injected

1 through. In other words, you require larger microcatheters
2 to inject larger PVA particles, and we can see that half of
3 the patients, therefore, required larger particles and,
4 theoretically, larger microcatheters. In point of fact,
5 only five patients were treated with PVA only, without coils
6 less than 500 microns in size.

7 [Slide.]

8 In terms of the catheters that were used in the
9 procedure, again, a 3F infusion catheter is a relatively
10 larger, slightly stiffer catheter as compared to the flow-
11 directed catheters, which are softer and smaller in size.
12 n-BCA is typically going to be injected through the flow-
13 directed catheters, and typically was injected in a higher
14 percentage of patients in the study. The larger, stiffer
15 catheters were used in a preponderance of patients in the
16 PVA group. So there is some difference in the types of
17 catheters used in the two groups.

18 [Slide.]

19 Similarly, if we look at the guidewires used to
20 pass the microcatheters, in the n-BCA group, the
21 preponderance of small, .010-inch, guidewires used, as
22 compared to the PVA group, where a preponderance of larger
23 guidewires, almost twice as large in diameter, in the PVA
24 group. So again, we can't totally divorce the agent from
25 the delivery system, and we think it may have some bearing

1 on complications.

2 [Slide.]

3 If we turn our attention now to total
4 complications, total device-related complications were
5 increased slightly in the n-BCA group compared to the PVA
6 group, 15 to 12. Procedure-related complications were
7 greater in the PVA group, however, 40 compared to 24. And
8 these were complications, once again, as determined by the
9 investigator. There was really no adjudication after the
10 fact.

11 [Slide.]

12 Patients experiencing complications--the last
13 slide shows the total numbers in terms of individual
14 patients. There were 12 patients of the n-BCA group who
15 experienced device-related complications, 7 in the PVA
16 group, and an equal number, 17 in both groups, experiencing
17 procedure-related complications. And once again, these
18 differences were not statistically significant.

19 [Slide.]

20 If we look at the device-related complications
21 that were reported in the n-BCA group, we see that we had
22 incorrect vessel occluded in one patient; catheters occluded
23 in two patients; catheters glued in place; complications
24 related to polymerization time. Some of these are obviously
25 going to be unique to n-BCA. However, there were catheters

1 that were occluded in the PVA group by the agent as well.
2 So again, the device-related complications do seem to be
3 increased in the n-BCA group as previously noted.

4 [Slide.]

5 However, if we look at the adverse clinical
6 outcomes that might have resulted from these n-BCA-related
7 device complications, as emphasized on these slides, I have
8 repeated the same complications here, I have repeated the
9 same numbers in the next column, but the clinical
10 complications--in other words, adverse clinical outcome as
11 affecting the patient--were only measured in one patient.
12 So although you may have a device complication--the glue may
13 set up too fast, or it may set up too late, theoretically, a
14 catheter might be blocked--those are things that do not
15 necessarily impact the patients adversely and did not
16 adversely impact the patients in the study.

17 And if we look at the Glasgow Outcome Scores of
18 those patients both pre-embolization and post-embolization,
19 we see that there was really only one change, and that is a
20 patient with an incorrect vessel occluded, and even after
21 surgery, the trends for good outcomes continued.

22 [Slide.]

23 In terms of intracranial events as complications,
24 there were nearly equal numbers of CVA or stroke in both
25 groups; a TIA reported in two PVA patients. When we look at

1 hemorrhages, there was an increased number of hemorrhages
2 reported during embolization in the PVA group; there were
3 essentially equal numbers in the n-BCA and PVA groups after
4 embolization but before surgery; and we did note an
5 increased number of hemorrhages in the PVA group post-
6 surgery. This difference does approach statistical
7 significance.

8 Five patients in each group had seizures post-
9 embolization, but three of them were new seizures in the PVA
10 group as opposed to no new seizures--in other words,
11 patients who had not previously had a seizure--in the n-BCA
12 group. And there were three deaths in the PVA group and one
13 in the n-BCA group.

14 [Slide.]

15 Again, if the system that is used to deliver the
16 agent plays any part in complications, did we see any
17 correlation between perforations or subarachnoid hemorrhages
18 versus the catheter and guidewire types? Well, if we look
19 at the larger, stiffer microcatheters or over-the-wire
20 catheters compared to the softer flow-guided catheters, we
21 do see that there was a slight trend for hemorrhages and
22 perforations to be identified when larger microcatheters
23 were used, with only one truly being identified in a patient
24 who was embolized using a flow-guided microcatheter. Again,
25 I think it is important to recognize that there may be a

1 relation between not so much the device, but some of the
2 delivery systems as well.

3 [Slide.]

4 I would like to turn attention to those patients
5 who had postoperative hemorrhages. This is the PVA group,
6 where eight patients had postoperative hemorrhages. Again,
7 are there any insights as to why this may have occurred?

8 Well, if we look at the mean for all PVA patients
9 in volume or whether deep venous drainage was there or not--
10 zero being no deep venous drainage, 1 being deep venous
11 drainage--if we look at surgery time, if we look at the
12 number of blood units transfused, if we look at coils used,
13 if we look at Glasgow Outcome Scores, larger AVMS did not
14 necessarily show tendencies to bleed postoperatively. The
15 majority were smaller than the mean. Most of the AVMS did
16 have deep venous drainage. Most of them did have increased
17 surgery time. Many had blood transfused, but not
18 necessarily greater than the mean.

19 However, there did seem to be a relationship
20 between the number of coils used--in other words, greater
21 than the mean number of coils seemed to have some
22 relationship to postoperative hemorrhage.

23 [Slide.]

24 If we look at the n-BCA group, there were two
25 postoperative hemorrhages, and only one of those had a large

1 number of coils used.

2 I would like to point out that five of those eight
3 PVA patients did require a repeat craniotomy to remove that
4 hematoma.

5 [Slide.]

6 Again, is there some reason why there might be a
7 difference between postoperative hemorrhages in the study?
8 If this is an idealized AVM, and we were to use a large
9 number of coils to block the feeding pedicles,
10 theoretically, we may just be blocking the arteries going in
11 and not the nidus itself, and arteries that were smaller in
12 the beginning that are not adequately embolized can increase
13 their flow, perhaps deeper, and if the venous drainage is
14 deep as well, perhaps we are predisposing some adverse
15 clinical event by the nature of the embolic device. Again,
16 the stylized, idealized n-BCA embolization theoretically
17 blocks the nidus as well as the feeding arteries.

18 [Slide.]

19 This slide shows outcomes in terms of the Glasgow
20 Outcomes Score. There was a slight difference in patients
21 pre-embolization--in other words, slightly worse neurologic
22 condition in the PVA patients. Post-embolization, those
23 differences equalized a little bit, but following resection,
24 prior to discharge, patients in the n-BCA group were in
25 slightly better neurologic condition than PVA patients,

1 although again not statistically significant.

2 [Slide.]

3 We mentioned that there were four deaths in the
4 study. One patient in the n-BCA group had had a cerebellar
5 hemorrhage. He was embolized, and he was operated on to
6 remove the hematoma, but the AVM was not resected at that
7 time--the hematoma was removed, but the AVM was not
8 resected, and that patient re-bled and expired.

9 In the PVA group, there were three deaths. One
10 was due to intracerebral hemorrhage two days following
11 successful embolization. The two other deaths were of
12 patients who were in relatively poor neurologic condition
13 prior to treatment and continued so after surgery and
14 ultimately expired.

15 [Slide.]

16 If we look at individual factors in terms of
17 advantages between the two agents that might be looked at in
18 the study, in terms of percent nidus reduction, if you
19 remember, by patient, PVA had a slight advantage, although
20 by stage, n-BCA had a slight advantage. In terms of
21 pedicles embolized, n-BCA exhibited an advantage. Total
22 device-related complications, as we noted, were less in the
23 PVA group. Procedure-related complications were less in the
24 n-BCA group. Again, the clinical outcomes from these
25 complications were not very significant, however.

1 There were pulmonary emboli documented in two PVA
2 patients, one clinically, on the table, and one at autopsy.
3 None was documented in n-BCA patients.

4 There were fewer overall hemorrhages in the n-BCA
5 patients. Overall, the Glasgow Outcome Scores were better
6 in the n-BCA patients.

7 The embolization procedure was minimally shorter
8 in the PVA patients.

9 There were more coils used in the PVA patients as
10 compared to the n-BCA patients--and as we said, that was a
11 statistically significant difference and may have some
12 impact on outcomes.

13 Smaller catheters and micro guidewires were also
14 used in the n-BCA patients. Fewer units of blood were
15 transfused, less cell-saver replacement, and less
16 fluoroscopy time. But again, the only statistically
17 significant difference was the fewer coils used, and the
18 post-surgical hemorrhages approached statistical
19 significance.

20 [Slide.]

21 In conclusion, we feel that the n-BCA Liquid
22 Embolic System is equivalent to PVA in achieving the primary
23 and secondary efficacy endpoints and that the clinical
24 safety endpoints are indeed comparable.

25 Thank you.

1 MS. WELLS: Good morning.

2 My name is Lisa Wells. I am Senior Manager of
3 Regulatory and Clinical for CES, and I will be giving CES'
4 final presentation for the day. I will be talking about the
5 n-BCA Liquid Embolic System training course.

6 [Slide.]

7 Just a quick course overview. This course covers
8 the use of the Trufill n-BCA Liquid Embolic System for the
9 presurgical embolization of cerebral AVMs, and that is
10 consistent with our indications for use.

11 The course is designed to strengthen each hospital
12 representative's understanding and technical expertise, and
13 it includes a didactic session, case studies, and a hands-on
14 workshop.

15 I believe it is dated May 1st--it is an amendment
16 to your panel pack--and that includes an overview of the
17 training course. That training course was given to
18 participants in our clinical trial, so we are able to use
19 that course as a valuable foundation for this course in that
20 this course will have a similar structure, but we are
21 obviously able to gain from the experience of the clinical
22 trial.

23 [Slide.]

24 The course objectives are actually fairly simple.
25 We expect that each participant in this course will be able

1 to thoroughly describe the Trufill n-BCA Liquid Embolic
2 System, its components and compatible accessories, select
3 appropriate mixtures, mix the system components and deliver
4 them to the target site. Also, we will expect each
5 participant to have a thorough understanding of the
6 potential complications of the n-BCA procedure, ways to
7 prevent them and ways to manage them.

8 [Slide.]

9 The course faculty will consist of those who are
10 most experienced with our system. At least initially, that
11 will consist of a few of the clinical trial investigators.

12 [Slide.]

13 Now I will go into a little bit more detail on the
14 course itself. It will start out with a didactic session
15 and a review of the system components. We will obviously
16 review the system components that have been described
17 earlier--n-BCA, tantalum power, and ethiodized oil. We will
18 also go into access and delivery devices, other accessories,
19 and importantly, we will also review incompatibilities. For
20 instance, it is known that n-BCA is incompatible with
21 polycarbonate.

22 [Slide.]

23 Then, we will go into preparation and delivery
24 methods; room set-up; common mixtures--these are mixtures
25 that were used during the clinical trial and are included in

1 our instructions for use. I will go over that a little bit
2 more later.

3 We will review polymerization expectations, what
4 to expect with lower versus higher n-BCA concentrations,
5 slow versus fast-speed injection techniques, and low versus
6 high flow rates.

7 We will be able to bring in cases from the
8 clinical trial to evaluate and compare these different
9 expectations.

10 [Slide.]

11 In the complications section, we will be looking
12 at those complications that Dr. Tomsick reviewed.
13 Specifically, we will include early and late polymerization,
14 vessel perforation and dissection, catheter occlusion,
15 catheter glued in place. We will also review hemorrhage and
16 ischemia, and this is where it will be very important to
17 include a very careful study of cases where these
18 complications have occurred.

19 [Slide.]

20 Then, we will go on to the fun part, which will be
21 the hands-on session. For this session, we will be using an
22 in vitro model that was developed at CES. It was developed
23 based on pioneering work of other researchers in the field,
24 and this model can be used with a video camera or under
25 fluoroscopic guidance, and we will be using both modalities

1 for the training session. It features pulsatile circulatory
2 flow and various AVM configurations.

3 [Slide.]

4 This is a very simple schematic.

5 [Slide.]

6 This is the AVM itself, and this is a polymeric
7 network. You can see the direction of flow through the
8 system. I would like to point out that the fluid that we
9 use with this model is the non-Newtonian [ph.] fluid that
10 was described by Jungreis and Kirber [ph.] in their 1991
11 AJ&R [ph.] article, and that is included in your panel pack
12 as well.

13 [Slide.]

14 This is a picture of the tabletop set-up.

15 [Slide.]

16 I also wanted to spend a little bit of time to
17 share with you--this is an actual one of our AVM models, and
18 I think you'll appreciate the fact that we have spent a
19 great deal of time and effort in trying to develop a model
20 that very closely approximates the actual clinical
21 condition.

22 Here is a network of vessels down to half-a-
23 millimeter. You will see the larger vessels here, and these
24 are aneurysms embedded in the model.

25 We think this model will work very well for this

1 purpose.

2 [Slide.]

3 All of the participants in the course will be
4 required to perform several simulated embolization
5 procedures looking at, once again, high and low AVM flow
6 rates, high and low-speed injections, and the various
7 recommended mixtures.

8 In discussing the mixtures a little bit, at the
9 beginning of the clinical trial, we did not specify certain
10 mixes for the investigators to use; we were relying on their
11 expertise of years of usage of n-BCA to determine their own
12 mixes. However, we were able to analyze the data after the
13 completion of the trial. We also solicited input from
14 several notable experts in the field, and conveniently, we
15 have two of them with us today.

16 Based on that, we were able to come up with some
17 recommended mixtures for use of the n-BCA, and those are
18 outlined in our instructions for use, and I have them
19 tabulated here.

20 [Slide.]

21 Basically, for intranidal injections without AV
22 fistulae, without high flow rates for more deep penetration
23 of the nidus, we recommend a ration between 25 and 33
24 percent n-BCA.

25 For the situations involving feeding pedicle

1 injections close to the nidus with high flow rates, where
2 venous opacification occurs within one-half second, we
3 recommend a higher percentage of n-BCA, between 50 and 66
4 percent.

5 These were the ratios that were used during the
6 trial, and especially with the higher percentage of n-BCA,
7 we strongly recommend the addition of tantalum powder for
8 increased radiopacity.

9 [Slide.]

10 After all the participants have participated in
11 the didactic and workshop sessions, we will reconvene, there
12 will be a final review of the material and a final
13 discussion, any other questions or comments that the
14 participants might have, and that would be the completion of
15 the course.

16 That is also the completion of our presentation,
17 and on behalf of all the CES participants today, I would
18 like to sincerely thank all the Panel members for your
19 careful consideration of our material.

20 Thank you.

21 DR. WALKER: Thank you, Ms. Wells.

22 I'd like to thank CES for their very concise
23 presentation. This is an opportunity now for any members of
24 the Panel, including Dr. Canady and Dr. Gatsonis who are on
25 the other end of the speaker phone, to ask any questions of

1 the sponsor before we take our break.

2 Are there any questions for the sponsor from
3 members of the panel?

4 DR. GATSONIS: I have some questions, actually.

5 DR. WALKER: Dr. Gatsonis.

6 DR. GATSONIS: These are questions that I was
7 going to ask later on in my presentation, but I might as
8 well ask them at this point, if that is okay--is it?

9 DR. WALKER: Yes, it is.

10 DR. GATSONIS: All right.

11 Just in terms of the analysis for the main
12 endpoint, I notice here that in the SAS output they are
13 using this ? procedure for ? comparisons to
14 compute confidence intervals and all that.

15 Can we have an explanation of what is the set-up
16 here and why the net procedure is being used and how it is
17 being used? My understanding of it is that the net
18 procedure compares several treatments to a control. What
19 are the several treatments or groups that are being compared
20 to a single group here?

21 DR. HOY: My name is Hoy Leung, and I am the
22 Statistical Consultant for Cordis. I received your
23 questions, and I have prepared my answers.

24 To answer your question about the net procedure,
25 this procedure is an option in the output of the SAS in the

1 CLM [ph.] procedure.

2 DR. GATSONIS: Yes, I understand.

3 DR. HOY: And it will automatically adjust for the
4 number of treatment groups against control. In this
5 particular situation, there was only one treatment group
6 against a control, and therefore, there was no adjustment
7 performed.

8 DR. GATSONIS: Okay, fine. Then, the next
9 question is--I mean, essentially, you are just doing a two-
10 treatment comparison there--

11 DR. HOY: Right.

12 DR. GATSONIS: --you are not using--

13 DR. HOY: Right, so it is similar to the T-test.

14 DR. GATSONIS: Okay. So then, the confidence
15 limits that you are presenting are one-sided or two-sided?

16 DR. HOY: For the primary efficacy variables, the
17 confidence limit is one-sided.

18 DR. GATSONIS: Okay. So when you quote there,
19 then, lower confidence limits in the SAS output, what do you
20 mean?

21 DR. HOY: Well, it is the 5 percent on the low
22 side and 5 percent on the high side, but our interest is
23 mainly on the upper limit. So it is a one-sided 95 percent
24 confidence limit.

25 DR. GATSONIS: Okay. May I continue?

1 DR. HOY: Yes, please.

2 DR. GATSONIS: I noticed that you are also doing
3 an analysis with ranks--in other words, you are converting
4 the original observations to ranks, and then you are still
5 feeding them through the general linear model.

6 What is the rationale for that? I mean, if the
7 issue there is the normality assumption of the data, that is
8 not going to be held by the ranks anyway, so I am not sure
9 why you do this analysis. What would have happened, for
10 instance, if it showed you different answers?

11 DR. HOY: The primary analysis was done on the
12 actual data and ANOVA.

13 DR. GATSONIS: Yes.

14 DR. HOY: But we observed that the response data
15 were not normally distributed, possibly due to a number of
16 outliers by the examination of the residual plot. In order
17 to check the robustness of the ANCOVA on this dataset, we
18 performed a rank transformation, and this would essentially
19 eliminate the problems that are caused by the outliers.

20 DR. GATSONIS: But it would not, because in the
21 analysis of covariance, you are using again the general
22 linear model.

23 DR. HOY: Well--

24 DR. GATSONIS: All of the statements you are
25 making, all the probability statements, give the assumption

1 of normality, and I don't know how that assumption applies
2 to the ranks, so I don't understand why you use rank.

3 DR. HOY: Well, the rank transformation will
4 strengthen the distance on the outlier. Although the--

5 DR. GATSONIS: That is correct, but it will not
6 help with the normality assumption or anything of that sort.

7 DR. HOY: That is correct. The assumption of the
8 normality--

9 DR. GATSONIS: If you wanted to use nonparametric
10 analysis, there exist nonparametric comparisons that you
11 could try.

12 DR. HOY: Right. Let me address your question.
13 We noticed that the assumption for the normality was not
14 overcome by the rank transformation, but we are satisfied
15 that the outlier was not the problem, since these two
16 analyses provided similar results. And--

17 DR. GATSONIS: Are you satisfied by that? For
18 instance, in one of the two datasets here, there is a value
19 of 594 as a maximum for the volume. This actually relates
20 to a point that was made by one of the presenters that it
21 seemed that the ranges of the values were the same in the
22 two groups. It seems to me that the range of values in the
23 treatment group was considerably larger.

24 DR. HOY: Right. We actually also used a very
25 simple nonparametric test, the Wilcoxon [ph.] rank test, and

1 we did not find a significant difference either. But to
2 address--

3 DR. GATSONIS: Excuse me. Did you use the
4 Wilcoxon test in the one-sided settings where you were
5 trying to do the bioequivalence, or just the difference of
6 two groups?

7 DR. HOY: It was the one-sided bioequivalence.

8 DR. GATSONIS: Okay. I don't have that reported
9 here.

10 DR. HOY: It is not reported. We did that because
11 the results were similar. But to address your question, the
12 main thing is that the objective of the study is mainly on
13 the estimation of the difference of the treatment means.
14 And the nonparametric procedure would not be really
15 convenient in terms of confusing 95 percent confidence
16 intervals of the treatment means. That is why we did a
17 further step to use the Bootstrap method in order to assure
18 ourselves that the results that were generated by the
19 parametric ANCOVA were not totally out-of-line.

20 DR. GATSONIS: Specifically, then, about the
21 transformations, I mean, when you have data that do not
22 behave exactly normally and so on, you could try other
23 transformations, especially in situations like the kind of
24 response you have, which is a percentage of reduction and so
25 on. There are other transformations that could have been

1 used. Did you consider any?

2 DR. HOY: We did not perform those analyses. We
3 considered those as with any transformation, that it may be
4 better for the purpose of testing hypotheses rather than
5 doing it for a statistical estimation.

6 DR. GATSONIS: And the statistical estimation
7 issue is linked with the confidence intervals. Your basic
8 inference here was one of hypothesis-assessing. The way you
9 phrased it, it was one of looking at equivalence, and it was
10 really basically an estimation hypothesis--sorry--a
11 hypothesis-assessing question that you were addressing. I
12 am not saying that that is the best way to do it, but that
13 is how you set it up originally, so I don't see that
14 estimation per se is the major issue. When you are trying
15 to do the hypothesis-assessing then, or the estimation for
16 that matter, if you are going to put confidence intervals
17 with any belief in the probabilities that you are quoting,
18 somehow, the assumptions ought to be met.

19 Hence, you probably have considered, I am sure,
20 other types of transformations of the data. What were these
21 other transformations beyond the ranks, because the ranks
22 will not do it for you?

23 DR. HOY: As I said, we did not perform any other
24 transformations.

25 DR. GATSONIS: Okay.

1 DR. HOY: One of the problems that we were
2 concerned about was that any other type of transformation
3 could produce a biased estimate which could affect the--

4 DR. GATSONIS: I don't understand the question
5 about the bias. I mean, a transformation would produce a
6 certain type of estimate in its own scale.

7 DR. HOY: The bias is in the statistical sense,
8 not in the general sense.

9 DR. GATSONIS: When people analyze other data--for
10 instance, I can give you an example--when they look at
11 income or something else, they take logs, or they take this
12 or that, and they make comparisons in that scale. The bias
13 question is a different formulation in that context, but
14 your hypothesis test at least will be helped, because you
15 have transformed the data in a more appropriate fashion.

16 Okay. Can I move on, or shall I stop here, Mr.
17 Chairman?

18 DR. WALKER: Yes.

19 DR. GATSONIS: Shall I continue?

20 DR. WALKER: Constantine, let's let the FDA do
21 their presentation after the break, and then perhaps there
22 will be a good opportunity for some more questions on the
23 biostatistics. I know Dr. MacLaughlin had a question for
24 the sponsor as well.

25 DR. GATSONIS: Okay. Can I ask one more question,

1 then, and then we'll stop there, and I'll pick it up later
2 on?

3 DR. WALKER: Fine.

4 DR. GATSONIS: My question is this. The question
5 about the power [ph.] computation--in the original data,
6 there was a power computation that used Blackwelder's [ph.]
7 formula, but it was really about proportions--ill
8 proportions.

9 DR. HOY: Right.

10 DR. GATSONIS: In any of the analyses, I do not
11 see an equivalence type of analysis with proportions. Why
12 did you plan the study with a proportion and then analyze it
13 with something else, with continuous variables? What
14 happened in between?

15 DR. HOY: Let me try to explain this problem.
16 Actually, it is an unfortunate incident. If one looks at
17 the study protocol very carefully, the primary endpoint was
18 percent nidus reduction rather than the percent of patients
19 with treatment success. And in the study protocol, this was
20 stated explicitly as the primary endpoint, and it was never
21 defined the proportion of patients with treatment success.

22 I think what happened was that the original
23 statistician who performed the power calculation may have
24 misunderstood or confused the terminology--percent nidus
25 reduction compared to percent of patients with treatment

1 success--and that caused the incorrect application of the
2 sample size calculation.

3 In hindsight, it may not be possible to provide a
4 sample size calculation before this study, because this is
5 the first controlled study in this indication, and previous
6 data are not available for an estimation of the variance in
7 treatment control. Where indeed, if we want to use the
8 percent nidus reduction as the primary endpoint for the
9 purpose of sample size calculation, we would need the
10 variance of the treatment using this primary efficacy
11 variable.

12 DR. WALKER: Dr. Gatsonis, I know you have some
13 other questions, but I think we should give other Panel
14 members an opportunity to voice their questions and
15 concerns, and then perhaps we can go back to yours after the
16 FDA presentation.

17 Would that be okay?

18 DR. GATSONIS: Yes. Sorry I took so long.

19 DR. WALKER: Fabulous.

20 Dr. MacLaughlin?

21 DR. MacLAUGHLIN: Thank you very much, Dr. Walker.

22 I actually have a couple of questions, one very
23 simple one of Dr. Rowland.

24 As I read the materials, it seemed to me as though
25 there was not a source established yet for the ethiodized

1 oil that you would be providing. Am I correct in saying
2 that, and have you solved that?

3 DR. ROWLAND: Yes. Just last week, we received a
4 letter of intent from the supplier of the original
5 manufacturer of the ethiodized oil, and we are right now
6 just finalizing the terms of that distribution agreement.

7 DR. MacLAUGHLIN: And this is the same material
8 that you tested for the compositional analyses and so on?

9 DR. ROWLAND: Yes, it is.

10 DR. MacLAUGHLIN: Thank you.

11 The other question I have is for Dr. Tomsick. I
12 am not a clinician. I was very intrigued by the fact that
13 some of the patients who undergo this embolization procedure
14 actually with PVA or with the n-BCA don't get resected. I
15 know it is not a large number of your group, but why does
16 that happen, and how long do they go on--which I have to say
17 is a concern of mine, and I will tell you later--how long do
18 they go on unresected--is it forever?

19 DR. TOMSICK: Yes, there were a number of patients
20 unresected in both groups and for a variety of reasons. One
21 patient had one-stage embolization, and during a second
22 stage of embolization underwent a tolerance test, an amytol
23 [ph.] test, for injection of a feeding artery, and it was
24 decided that embolization of that blood vessel might be
25 unsafe. Subsequently, discussion with the family regarding

1 further embolization and surgery was undertaken, and they
2 decided to go no further. So in terms of the clinical
3 indication, the patient withdrew from the study.

4 There were--

5 DR. MacLAUGHLIN: Could I follow up for just one
6 second?

7 DR. TOMSICK: Sure.

8 DR. MacLAUGHLIN: Would you consider as a
9 clinician that patient at decreased risk of any problem, or
10 can you say?

11 DR. TOMSICK: There is a little difference of
12 opinion on that issue about partially-embolized AVMs.
13 Again, my personal philosophy is that a partialized AVM is a
14 wounded AVM and perhaps even at higher risk, depending on
15 the indication for that embolization.

16 For instance, on the one hand, if a patient had a
17 hemorrhage, and I could define a bleeding point on his
18 angiogram, and I could eliminate that bleeding point with a
19 glue or a PVA injection--more likely a glue injection--I
20 believe I can reduce some of the risk of further hemorrhage.

21 But again, partially embolizing an AVM and leaving
22 the rest untreated may actually be somewhat risky. There
23 are some studies, or some observations, although not large
24 studies, that suggest that.

25 DR. MacLAUGHLIN: Thank you.

1 I have a question of Ms. Wells. When you
2 described the course, it seems to me--I'd like a little more
3 information about who the students might be. How do you
4 select them? What are the entry criteria, number one; and
5 number two, what are the exit criteria? Do you have any
6 sort of proficiency testing? I understand you are dealing
7 with a group of highly-trained physicians who are doing this
8 already, but where do you draw the line? I think the parent
9 institutions will draw their own lines, and certainly,
10 prudent clinicians will, too, but where do you folks stand
11 on that?

12 MS. WELLS: Those are excellent questions--in
13 fact, those are the same questions that we are toiling with
14 ourselves.

15 We intend to start out with those practitioners
16 who perform the most embolizations, at least in starting out
17 the course. There have been discussions on trying to limit
18 course entry to those physicians who come from institutions
19 that do a minimum number of embolization procedures, and I
20 don't know as of yet what the number should be, and we are
21 hoping to gain input from, for instance, ASITN or other
22 organizations to tell us what the criteria should be if we
23 should in fact enforce that.

24 As far as exit criteria, I think it is important,
25 and we are discussing having a test of some sort for the

1 physicians to complete as far as we would have a visual
2 expectation in terms of embolization during that workshop
3 session, and they would have to meet that expectation and
4 perform that competency test.

5 DR. MacLAUGHLIN: The other thing is that it seems
6 to me this is an optional activity; correct? Let's say I
7 were a surgeon, and I wanted some material. Could I order
8 it, or do I have to go through this? Is it connected to the
9 purchase of the material or the release of the material to
10 your institution?

11 MS. WELLS: The way we plan to set p the course,
12 we will need to train a minimum of one physician from each
13 hospital ordering the product, and that will be at a
14 minimum.

15 DR. MacLAUGHLIN: Thank you.

16 MS. WELLS: Thank you.

17 DR. WALKER: Are there any other questions from
18 members of the Panel for the sponsor before we take our
19 break?

20 Dr. Canady, I hope you are still there.

21 DR. CANADY: I am still here. No questions.

22 DR. WALKER: Okay.

23 Seeing no questions, then, why don't we take about
24 a 10- to 15-minute break. That will give the FDA a chance
25 to get their presentation lined up, and we'll begin once

1 again at 10:45.

2 [Break.]

3 DR. WALKER: Ladies and gentlemen, let's get
4 settled down so the FDA can do their presentation.

5 We have Dr. Gatsonis and Dr. Canady back on the
6 line. We will now have the FDA presentation on this PMA.

7 The first FDA presenter is Dr. Peter Hudson, and
8 he will be followed by Ms. Judy Chen.

9 Dr. Hudson?

10 **FDA Presentation**

11 DR. HUDSON: Thank you, Dr. Walker.

12 Good morning. I am Peter Hudson, the lead
13 reviewer of Cordis Endovascular's Pre-Market Approval
14 Application for the Trufill n-BCA Liquid Embolic Agent.

15 The sponsor's investigational device exemption
16 study protocol was approved on February 9, 1996. On October
17 15, 1998, the FDA approved the sponsor's request for future
18 expedited processing of their PMA. On December 2, 1998, FDA
19 approved the sponsor's format for a modular PMA submission.

20 DR. GATSONIS: I cannot hear Dr. Hudson.

21 DR. WALKER: Dr. Hudson, could you speak into the
22 microphone?

23 DR. HUDSON: I am sorry. Can you hear me now?

24 DR. GATSONIS: That is much better. Thank you.

25 DR. HUDSON: The sponsor submitted the final PMA

1 module on July 16, 1999.

2 I will discuss the device description and
3 indications for use and then present FDA's preclinical and
4 clinical summary reviews of the product.

5 Dr. Kevin Lee has provided the information for the
6 clinical presentation.

7 Ms. Judy Chen, FDA's Statistical Reviewer, will
8 then provide the statistical presentation.

9 I want to thank Dr. George Matamol [ph.], Mr.
10 Keith Foy [ph.], Dr. Dan Weil [ph.], Ms. Kathleen Swisher
11 [ph.], and Mr. John Glass for all the support and review of
12 the application.

13 [Slide.]

14 The sponsor's device contains n-Butyl
15 Cyanoacrylate. Cyanoacrylate devices have been approved or
16 cleared for use as tissue adhesives, skin protectants, or
17 dental cements. This product will be the first
18 cyanoacrylate approved for embolization of cerebral
19 arteriovenous malformations.

20 [Slide.]

21 The sponsor proposes the following indications for
22 use. Trufill n-BCA Liquid Embolic Agent, radiopacified with
23 ethiodized oil and Trufill tantalum powder is indicated for
24 the embolization of cerebral arteriovenous malformations
25 when presurgical devascularization is desired.

1 In addition, the sponsor proposes to include the
2 following statement regarding the long-term implantation on
3 their label: "The safety and efficacy of the Trufill n-BCA
4 Liquid Embolic Agent as a long-term implant has not been
5 established."

6 [Slide.]

7 The device is composed of n-Butyl Cyanoacrylate,
8 or n-BCA, tantalum powder, and ethiodized oil. The n-BCA
9 monomer is described as a clear, free-flowing liquid. It is
10 packaged in 1-ml crimped sealed single-use aluminum tubes
11 and sterilized. Three 1-ml tubes will be provided per
12 package. Tantalum powder is provided in 1-cc polyethylene
13 microcentrifuge tubes and is sterilized. Three 1-cc tubes
14 will be provided in each package.

15 The ethiodized oil is described as a sterile,
16 radiopaque reagent and is provided in two 10-ml ampules in
17 each package. Under recommended procedure in the product
18 instructions for use, the sponsor states that the n-BCA and
19 ethiodized oil are to be mixed with tantalum powder if
20 necessary using a 1 to 10-cc syringe and 50-ml sterile glass
21 beaker.

22 The purpose for adding the ethiodized oil and
23 tantalum powder is to radiopacify the device. The oil also
24 acts to slow the polymerization of the n-BCA.

25 The sponsor did not specify a ratio of the device

1 components of revaluation in the investigation. Of the 75
2 embolization procedures done with n-BCA in the study, data
3 regarding the volumes of the components used was collected
4 on 34 procedures. Ratios used varied from 10 to 70 percent
5 n-BCA and 30 to 80 percent ethiodized oil by volume.

6 Information regarding effectiveness and safety
7 analyses was requested from the sponsor to determine if a
8 recommended ratio might be identified. However, the number
9 of procedures was conducted and the number of variables too
10 high to derive much guidance.

11 The most common ratio used in the study was 2 or 3
12 to 1 ethiodized oil to n-BCA. In terms of volume, the ratio
13 means that patients most commonly received 4.2 to 6.3 ml of
14 ethiodized oil and 2.1 ml of n-BCA.

15 The use of embolic agents is governed by a number
16 of factors such as flow rate, the anatomic setting, the
17 presence of AV fistulae, the location of the injection, the
18 diameters of the feeding pedicle and nidus, and the
19 tortuosity or linearity of the pedicle.

20 The instructions for use state that training in a
21 recognized neuro-interventional program is required, as is
22 training in the sponsor's program.

23 Panel Question 1 will ask for your commentary
24 regarding instructions for use, physician training, and
25 potential additional preclinical or clinical evaluations to

1 be done so as to better define the recommended ratio of
2 device components for use in the embolization of AVMs.

3 [Slide.]

4 Now I will present the preclinical information
5 regarding the chemistry of the device and the
6 biocompatibility experimentation conducted today.

7 The n-BCA is intended for delivery under
8 fluoroscopic guidance through an infusion catheter. n-BCA
9 polymerizes rapidly upon contact with the aqueous
10 environment via an exothermic reaction.

11 Hydroxyl ions are believed to be the initiator for
12 the reaction.

13 The material polymerizes rapidly and serves to
14 block or occlude the blood vessel leading to the
15 malformation.

16 [Slide.]

17 These are the release specifications for the n-BCA
18 as it is currently manufactured. It is 99 percent pure,
19 nonpyrogenic, and it polymerizes within one second.

20 The degradation of polymers like cyanoacrylates to
21 smaller oligomers involves a hydrolysis reaction in which
22 one molecule of formaldehyde is formed for each oligomer
23 formed. Degradation of cyanoacrylate derivatives yields
24 cyanoacrylate as well as formaldehyde, both of which are
25 tissue-toxic.

1 The sponsor was requested to conduct a systematic
2 hydrolytic degradation study that identifies possible
3 degradation products of the device as it will be used in the
4 body, that is, all the components included.

5 The sponsor has been identifying and quantitating
6 breakdown products of the combined devices.

7 [Slide.]

8 These are the current release specifications for
9 the tantalum powder used in the device. Tantalum is
10 described in the scientific literature as being almost
11 completely immune to chemical attack at temperatures below
12 150 Centigrade and is attacked only by hydrofluoric acid or
13 acidic solutions containing a fluoride ion and/or free
14 sulphur trioxide.

15 The purpose of the addition of tantalum to the n-
16 BCA and ethiodized oil is to augment the radiopacity of the
17 device.

18 [Slide.]

19 In the instructions for use, the sponsor
20 recommends mixing the n-BCA with ethiodized oil. The
21 sponsor determined that the addition of ethiodized oil and
22 tantalum powder extended the polymerization time of the n-
23 BCA. Ethiodized oil contains--and the sponsor has already
24 mentioned that they adhered to the USP specifications for
25 ethiodized oil--it contains 37 percent iodine organically

1 combined with the ethyl esters of fatty acids. These are
2 primarily poppyseed oil.

3 When ethiodized oil is used as a drug, it is a
4 diagnostic agent intended for use in hysterosalpingography
5 and lymphography. As a drug, it is contraindicated in
6 patients with a history of sensitivity to iodine and is
7 contraindicated for intravascular, intrathecal, or
8 intrabronchial use.

9 [Slide.]

10 Ethiodized oil and tantalum may be released from
11 the polymerized device over time. FDA has requested that
12 the sponsor conduct experiments to determine how much of the
13 ethiodized oil and tantalum elutes from the device as it is
14 intended to be used in the body. These experiments are
15 ongoing.

16 [Slide.]

17 The sponsor conducted two experiments to determine
18 the polymerization time of the entire device--the accurate
19 and repeatable polymerization rate studies.

20 First, the sponsor observed the polymerization in
21 an in vivo animal model. The experiment was a qualitative
22 assessment of the use of the device. The physicians were
23 satisfied with the devices used and polymerization rate.

24 Secondly, the investigators measured the
25 polymerization rate in guinea pig plasma and bovine plasma.

1 With a 1-to-1 ratio ethiodized oil to n-BCA, they observed
2 that the material polymerized within one-third of a second.

3 To determine whether the n-BCA, ethiodized oil,
4 and tantalum powder mixture was compatible with currently
5 available catheters, the sponsor also evaluated the device
6 with various catheters in an in vivo model. The
7 investigators found that the material was compatible with
8 the catheters and that it did not adversely influence the
9 injection rate.

10 [Slide.]

11 The sponsor conducted these biocompatibility tests
12 on the cured n-BCA alone--that is, polymerized material was
13 extracted as recommended by standard biocompatibility
14 protocol and evaluated. Tantalum powder and ethiodized oil
15 were not mixed with the n-BCA.

16 In addition to the standard hemolysis assay, the
17 sponsor also conducted a second hemocompatibility assay with
18 noncured n-BCA and found that the various blood cell counts
19 did not differ between the subject device and the control
20 device, which was the contour embolyte particulate sponge.
21 However, it is important to note that the noncured material
22 tested in the hemocompatibility assay did cause red blood
23 cell lysis in comparison to the control.

24 [Slide.]

25 The sponsor conducted these biocompatibility tests

1 on the tantalum powder component by itself. It passed all
2 of the tests. Notably, the tantalum powder did not elicit
3 cytologically any signs of irritation in the 7- and 30-day
4 implantation assays.

5 [Slide.]

6 The sponsor has not conducted a subchronic or
7 chronic toxicity test of the device components or of the
8 combined sterile finished device. These tests evaluate
9 single or multiple exposures of the device or extracts of
10 the device during a period of time up to 10 percent of the
11 life span of the test organism. For rates, the period of
12 time is approximately 90 days.

13 The sponsor was requested to either conduct
14 implantation biocompatibility testing of a sufficient period
15 of time or provide relevant information regarding long-term
16 biocompatibility.

17 The device is not intended for long-term
18 implantation, but due to unforeseen anatomical or clinical
19 issues, it may be left in permanently and therefore should
20 be evaluated with this likelihood in mind.

21 In response, the sponsor provided histology
22 reports of some of the tissue explants of patients treated
23 either with n-BCA or PVA. The reports indicate no
24 significant histological difference in tissues treated with
25 either device up to 3 days, but the information does not

1 adequately address the long-term implantation concerns.

2 The sponsor is in the process of conducting a
3 literature search and summary of preclinical and clinical
4 findings to address the issue.

5 The sponsor did conduct short-term implantation
6 studies of the n-BCA or tantalum as individual components.
7 The tantalum powder passed the 7- and 30-day implantation
8 evaluations. For the n-BCA experiments, the sponsor
9 implanted cured n-BCA for 7 and 30 days and evaluated the
10 tissue sites for comparison to PVA particles as a control.
11 The results showed that PVA particles caused an
12 insignificant histotoxic effect under macroscopic
13 examination after 7 and 30 days of implantation in the
14 paravertebral muscles of the rabbit.

15 Microscopically, the PVA particles caused a
16 moderate at 7 days to slightly irritating effect at 30 days
17 on the tissue. The sponsor's device caused some
18 insignificant macroscopic reaction at 7 days but was
19 classified as a severe irritant upon microscopic inspection
20 at 7 days.

21 The report states that the test sites showed
22 substantial acute and chronic granulomatous inflammation
23 with necrosis. At 30 days, the subject device caused an
24 insignificant macroscopic response and was classified as a
25 moderate irritant microscopically.

1 Panel Question 2 requests your discussion
2 regarding appropriate cautions with respect to long-term
3 implantation.

4 [Slide.]

5 The sponsor conducted biocompatibility evaluations
6 on the individual components. FDA requested that the entire
7 device as it would be placed in the body be tested for
8 biocompatibility. The sponsor has been conducting those
9 evaluations.

10 Finally, the sponsor had conducted only the Ames
11 mutagenicity test on the individual components. FDA
12 requested that additional genotoxicity evaluations be
13 conducted on the final complete device. Those studies are
14 also ongoing.

15 [Slide.]

16 Now I'll go over the clinical data.

17 The purpose of the clinical study was to determine
18 if n-BCA used with tantalum powder is as safe and effective
19 as polyvinyl alcohol particles for the embolization of
20 cerebral arteriovenous malformations when preoperative
21 devascularization is desired.

22 [Slide.]

23 Two treatment groups were studied in the
24 investigation--patients treated with the subject device or
25 polyvinyl alcohol particles. A total of 104 patients, 52

1 patients per group, were enrolled in the study at 13
2 investigational sites. The devices were randomized for each
3 investigational site. Patients undergoing staged
4 embolizations were randomized for the first treatment but
5 were subsequently treated with the same device.

6 The study is single-blind with the respective
7 randomization due to the characteristic nature of the
8 embolic materials used.

9 [Slide.]

10 Patients were suspected of requiring a presurgical
11 embolization for a cerebral AVM if they presented with a
12 documented cerebral AVM or with neurological symptoms
13 including headaches, seizures or bleeding.

14 CT or MRI visible hemorrhage from a ruptured AVM
15 or of an unruptured AVM and cerebral angiography were used
16 to determine the existence of a cerebral AVM.

17 In general, patients who met the following
18 inclusion criteria were enrolled in the study: patients
19 with angiographically documented cerebral AVM of Spetzler-
20 Martin Grades III, IV or IV; and patients with Spetzler-
21 Martin Grades I or II cerebral AVMs and in whom the benefits
22 of embolization outweighed the risk, or the AVM was located
23 in an area which was difficult to surgically access.

24 [Slide.]

25 In general, patients excluded from the

1 investigation were pregnant patients who had cerebral AVMs
2 but were asymptomatic; patients who had a previous
3 embolization with cyanoacrylate and/or PVA; patients with a
4 known sensitivity to contrast reagents, for example,
5 iodothalamate.

6 [Slide.]

7 The sponsor determined to investigate whether n-
8 BCA was equivalent in performance to PVA. PVA is recognized
9 as a conventional therapy for embolization of AVMs.
10 Blackwelder's [ph.] method for demonstrating therapeutic
11 bioequivalence was used to calculate the sample size for the
12 study. The calculation relied upon assuming that difference
13 in performance of less than 20 percent would be considered
14 to indicate device equivalency.

15 [Slide.]

16 The primary efficacy endpoint in the study was
17 stated as the degree of intended vascular occlusion is no
18 worse than with PVA. Occlusion was defined as the percent
19 nidus reduction and number of vessels occluded.

20 Pre- and post-embolization angiograms were sent to
21 a core laboratory for determination of the number of vessels
22 embolized and the percent nidus reduction achieved.

23 In the original protocol, the percent differences
24 rating between treatment groups were to be evaluated using a
25 nonparametric statistical test. That is, the results were

1 to be treated as a binary outcome. In the clinical study
2 summary for the PMA, the comparison for determination of
3 equivalency was based upon using the results percent nidus
4 reduction and number of vessels occluded as continuous
5 variables.

6 [Slide.]

7 The secondary efficacy endpoints were the length
8 of time to resect the AVM; the number of transfusions
9 required; and the total blood loss during the surgery.

10 The secondary efficacy hypotheses were that the
11 subject device would be equivalent to PVA with respect to
12 these endpoints using Blackwelder's [ph.] statistics.

13 The secondary efficacy endpoint success and
14 failure criteria were not prospectively stated.

15 [Slide.]

16 The sponsor sought to compare the incidence of
17 device-related complications, procedure-related
18 complications, intracranial events, and unanticipated
19 adverse events between the experimental device and control
20 for the primary safety endpoint.

21 [Slide.]

22 Examples of device-related complications are:
23 early or late polymerization; catheter occlusion; glue
24 solidification inside the catheter; catheter rupture;
25 breakage of guidewire, and failure to access the vessel.

1 Examples of procedural complications are:
2 pulmonary embolization; vessel perforation; vessel
3 dissection; incorrect vessel occlusion; AVM rupture,
4 vasospasm, and hematoma.

5 Examples of intracranial events are: ischemia;
6 subarachnoid hemorrhage; temporary ischemia; parenchymal
7 hemorrhage; seizure, and death.

8 On the case report form, the physician could
9 indicate as to whether the complication was definitely,
10 possibly, or not device-related; or if the complication was
11 procedurally-related.

12 [Slide.]

13 Fifty-two patients were enrolled into both the PVA
14 and n-BCA treatment arms. Two PVA patients were excluded
15 from analysis. These patients were initially randomized to
16 PVA but were treated with n-BCA after initial embolization
17 attempts with PVA were unsuccessful at reducing the blood
18 flow rate.

19 Of the 102 patients remaining, 87, or 85.3
20 percent, completed the course of treatment; 42 of the 52 n-
21 BCA patients, or 81 percent, and 45 of the 50 PVA patients,
22 or 90 percent, finished the course of treatment.

23 Fifteen patients were discontinued from the
24 patient--10 n-BCA patients and 5 PVA patients. The most
25 common reason for discontinuation was that the patient was

1 not resected. Four patients in each group did not undergo
2 surgical resection.

3 [Slide.]

4 Other notable reasons for discontinuation were:
5 death--there were two deaths prior to surgical resection,
6 one in each group; and inappropriate vessel occlusion, in
7 which in this case the patient who was treated with n-BCA
8 developed a neurologic deficit with aphasia and hemiparesis.
9 A small amount of glue had refluxed into the middle cerebral
10 artery and embolyzed in the branches of the middle cerebral
11 artery.

12 [Slide.]

13 Fifty-nine percent of the patients were male, and
14 41 percent were female. The majority of the subjects were
15 Caucasian, 78 percent.

16 The Spetzler-Martin Grades of the two groups were
17 similar. Grade III AVMs were the most common malformations
18 embolized in both cohorts. Twenty n-BCA patients and 17 PVA
19 patients had Grade III AVMs. The mean lesion volume of the
20 n-BCA group was 22.2 cubic cm with standard deviation of
21 47.34. The mean lesion volume of the PVA group was 21.7
22 cubic cm with a standard deviation of 26.39.

23 The location of the AVMs of the two cohorts were
24 also similar, with no distinctive differences. But
25 significantly more coils were used in the PVA group than in

1 the n-BCA group. Seventy-one percent of the PVA
2 embolization stages were done with coils, whereas 19 percent
3 of the n-BCA procedures were done with coils.

4 [Slide.]

5 Percent reduction in lesion volume calculated on a
6 per-patient basis revealed that embolization with PVA
7 achieved a mean 86.9 percent reduction, and embolization
8 with n-BCA achieved a mean 79.4 percent reduction. 2.15
9 vessels on average were occluded with PVA per patient,
10 whereas 2.2 vessels on average were occluded with n-BCA.

11 Panel Question 3 will ask you to discuss whether
12 you believe the sponsor has demonstrated that the device is
13 effective with this indication.

14 [Slide.]

15 No statistical differences were noted between the
16 two treatment groups with respect to the secondary endpoints
17 of time of resection or the number of transfusions required.
18 However, as the sponsor has noted, there were more
19 transfusions done with the PVA group than with the n-BCA.

20 [Slide.]

21 There were 12 device-definitely-related
22 complications associated with the use of n-BCA, and 5
23 device-definitely-related complications associated with the
24 use of PVA. Eleven of the 12 n-BCA complications were due
25 to early or late polymerization, catheter occlusion, and the

1 catheter being glued inside the vessel.

2 The higher incidence of glue-like device-related
3 complications observed should be taken into consideration
4 when discussing any recommendations you may have for the
5 sponsor's physician training program.

6 [Slide.]

7 These are examples of complications that were
8 designated as procedurally-related by the physician. The
9 incidence of procedural complications was similar between
10 the two groups.

11 [Slide.]

12 Finally, there were fewer intracranial events
13 observed in the n-BCA group.

14 Panel Question 4 will ask whether you believe the
15 information provided from the clinical study has
16 demonstrated that the device is safe for this indication.

17 Ms. Judy Chen will now discuss the statistical
18 issues of the study's results.

19 MS. CHEN: I am Judy Chen, the Statistical
20 Reviewer for this submission. I will present my point of
21 view of this submission.

22 [Slide.]

23 This is the objective of the study's device
24 equivalence. It is a multi-center randomized controlled
25 study of 104 patients, comparing patients treated with

1 experimental n-BCA to patients treated with control
2 polyvinyl alcohol.

3 [Slide.]

4 The hypothesis as stated is that we would like to
5 show that the experimental device is at least as good as the
6 control device in terms of proportion of successes.

7 The tolerable difference is 20 percent, which
8 means that the experimental device can be as much as 20
9 percent lower in success rate as compared to the control
10 device, and that would still be considered as equivalent,
11 but the measurement is in terms of proportion of successes.

12 With these criteria, the sample size of 52
13 patients in each of the two treatment groups will provide
14 adequate statistical power to rule out a difference of 20
15 percent or higher in proportions of successes.

16 [Slide.]

17 But there are two major ambiguities in this study.

18 The first one is the device is not clearly
19 defined. The mixing ratio of ethiodol and n-BCA was not
20 specified. It varies everywhere.

21 Second is the change of primary effectiveness
22 endpoint. As planned the primary endpoint and the sample
23 size power calculation are all using the variable proportion
24 of successes, but then, in analysis, the endpoint becomes
25 percent of reduction of lesion volume. These are two

1 entirely different endpoints, which leads to the question,
2 of course, why the endpoint was changed, and also, more
3 importantly, the tolerable difference defined in the
4 protocol, 20 percent, which is in terms of proportion of
5 successes, has now become percent of reduction of lesion
6 volume. That is a completely different measurement. So
7 that now we don't have any prespecificity data to rely on.

8 Of course, with all that change, the power
9 calculation doesn't apply anymore, so is the sample size
10 large enough? That is the question.

11 [Slide.]

12 The data we have from the sponsor show that the
13 incidence of device-related complications is higher in the
14 experimental group--it is 12 out of 52; and in the control
15 PVA, it is 5 out of 50. The sponsor did try to break down
16 or separate patients by mixing ratio group, but not all
17 patients had the mixing ratio data, so that out of the 104,
18 there are only 32 patients who could be broken down into
19 Group 1 and Group 2. Group 1 patients had n-BCA less than
20 30 percent, and Group 2 had n-BCA higher than 30 percent.
21 And the complication rates are different. In Group 1, 9 out
22 of 22 patients had complications, and in Group 2, 3 out of
23 10.

24 [Slide.]

25 The effectiveness was first analyzed by analysis

1 of covariance, and no statistically significant treatment
2 difference was detected in percent lesion volume reduction,
3 number of occluded vessels, and others. However,
4 equivalence cannot be determined on the ground of
5 "statistically not significant" alone.

6 [Slide.]

7 No statistically significant treatment difference
8 alone does not adequately support equivalence, which can be
9 due to any one or a combination of the following reasons:
10 If the study is not large enough; if the study is not well-
11 conducted; if the endpoint cannot be accurately measured; or
12 it could also be due to the devices are equivalent.

13 Equivalence may be further evaluated via
14 confidence limit.

15 [Slide.]

16 This is what the sponsor produced. The Bootstrap
17 one-sided 95 percent upper confidence limit--on percent
18 reduction in lesion volume, the mean difference is 7.7
19 percent; the upper limit is 18.5 percent. So the question
20 here is now whether a difference as high as 18.5 percent in
21 percent reduction in lesion volume is tolerable.

22 [Slide.]

23 Actually, there is no conclusion that can be drawn
24 from this study, but the questions that I have are: Can the
25 safety and effectiveness of the device be determined in the

1 presence of the following difficulties. The effect of the
2 mixing ratio cannot be clearly investigated because a lot of
3 data are missing; also, as we have mentioned, is the
4 prespecified tolerable treatment difference of 20 percent in
5 proportions of successes applicable to the difference in
6 reduction in lesion volume?

7 Thank you.

8 DR. WALKER: Thank you, Dr. Chen.

9 Does any Panel member have questions for the key
10 presenters from the Food and Drug Administration?

11 DR. GATSONIS: I have a question for Dr. Hudson.

12 DR. WALKER: Dr. Gatsonis, go ahead.

13 DR. GATSONIS: Ms. Chen just addressed the issue
14 of the 20 percent in reduction in tolerable difference--at
15 least, that is how I heard it. The question is what is the
16 FDA's point of view, then, on what is a tolerable
17 difference, as it were. In other words, suppose the
18 endpoint is exactly as the sponsor has it now at this point--
19 -does the FDA have a point of view on what is an appropriate
20 delta?

21 DR. HUDSON: Yes, that is a good question. I
22 think that with the people on the Panel here, a clinical
23 tolerable difference--we might ask them if they believe 20
24 percent is a reasonable clinical tolerable difference.

25 DR. GATSONIS: I cannot hear you at all.

1 DR. HUDSON: I am sorry. It is a good question.
2 The people here on the Panel are probably the experts at
3 doing a lot of these procedures, so I guess I'll leave it to
4 them to comment on.

5 DR. GATSONIS: Just to add a [?] , it is
6 unfortunate that the original sample size calculation was
7 done with a 20 percent reduction in the proportion, and
8 then, the sponsor used 20 percent reduction in the
9 continuous measures. It seems that somehow, neither of
10 these figures were justified.

11 DR. HUDSON: Yes, that is probably right. That is
12 the meat of the issue, I think.

13 DR. GATSONIS: Yes.

14 DR. WALKER: Dr. Gatsonis, any other questions?

15 DR. GATSONIS: No. Thank you.

16 DR. WALKER: Does any other Panel member have
17 questions for the Food and Drug Administration?

18 Dr. Roberts?

19 DR. ROBERTS: I don't know if you know the answer
20 to this; maybe someone from the company will have to answer
21 this. One of my questions is in terms of the early and late
22 polymerization, which is one of the safety issues in terms
23 of device-related complications, did that translate into any
24 adverse effects on those patients?

25 DR. HUDSON: I think we'll defer to the sponsor

1 for that.

2 DR. TOMSICK: Tom Tomsick, addressing that
3 question.

4 One of my slides in my presentation, Dr. Roberts,
5 did touch on that issue wherein we looked at the device-
6 related complications enumerated in one of the columns, and
7 then, the clinical complications, the clinical adverse
8 outcomes. There were four patients with devices glued in, I
9 believe, three with early and two with late polymerization,
10 or perhaps the reverse of that, but none of those patients
11 suffered immediate adverse clinical outcomes.

12 In terms of post-surgical outcomes, one patient
13 ultimately had a postoperative hemorrhage, and I don't know
14 if that can be said to be related or not.

15 But in the early and late polymerization groups,
16 no immediate adverse clinical outcomes were evidence.

17 What late polymerization did prompt, however, is
18 some glue was thought to end up in a vein or be polymerizing
19 relatively late, surgery was expedited in those patients,
20 but there were ultimately no adverse clinical outcomes.

21 DR. ROBERTS: I've got some problems with the way
22 that these--we've got two separate sets of figures on these
23 complications. The FDA complications for device-related are
24 12 for the cyanoacrylate and 5 for the polyvinyl alcohol.
25 Your presentation shows 15 and 12. Procedure-related, I

1 count up as 14 in the FDA's numbers and 21 for PVA. For
2 intracranial, I get 10 and 21.

3 I don't know who is counting and what we are
4 counting anymore.

5 DR. TOMSICK: Well, from the standpoint of the
6 submission, the counting was very conservative. And
7 remember it was at the study site, and there was no
8 adjudication, so if someone called it a device-related or a
9 procedure-related complications, that's the way it went, and
10 it may not have been such, and I think when the FDA reviewed
11 that data, if I'm not mistaken, they made some subsequent
12 decisions on what truly was device- and what wasn't device-
13 related.

14 DR. ROBERTS: So is that correct, that the FDA's
15 number--or, basically, are you going back over what was
16 submitted and making your own determination as to what was
17 and what wasn't?

18 Dr. HUDSON: That's right. There were two
19 categories of device-related complications--device-
20 definitely-related complications or possibly-related
21 complications. I think the sponsor's slides showed that
22 there were 15 and 12, and ours shows 12 and 5. The 12 and 5
23 refer to definitely-related complications.

24 DR. ROBERTS: It's a big difference.

25 DR. WALKER: Are there any other questions from

1 the Panel?

2 Yes, Dr. Hurst.

3 DR. HURST: I am looking at those differences as
4 well. Do any of those differences that we see translate
5 into an increased incidence of real patient-related
6 complications? I think Dr. Tomsick addressed that most of
7 the ones that they had looked at here did not translate into
8 any real adverse effects in terms of patients. So in other
9 words, the glue might not have polymerized exactly at the
10 point where it was judged perfect or judged what they
11 wanted, but that didn't necessarily translate into a patient
12 complication.

13 Do you have a feeling that some of these device-
14 related complications did translate into that?

15 DR. HUDSON: No, no. I think the literature on
16 cyanoacrylate shows that inappropriate glue problems
17 sometimes occur.

18 DR. HURST: Okay.

19 DR. HUDSON: I think that that is what the data
20 really reflects.

21 DR. HURST: Okay. So that although we may get
22 different numbers, both the FDA and the sponsor seem to
23 agree that there are very few, if any, real adverse patient-
24 related events as a result of these device-related
25 complications.

1 DR. HUDSON: As a consequence of the--

2 DR. HURST: Correct; yes.

3 DR. HUDSON: Yes.

4 DR. HURST: Okay.

5 DR. WALKER: Any others?

6 [No response.]

7 DR. WALKER: I do have one question for Dr. Chen,
8 perhaps, from FDA.

9 In looking at the three components of the system--
10 the glue, the oil, and the tantalum--it seems to me that
11 only one of those is the active ingredient. You had some
12 concerns about the mixing ratios--

13 MS. CHEN: That's right.

14 DR. WALKER: --but would it be easier to look at
15 this data instead, not as mixing ratios, but simply as the
16 amount of active ingredient that is administered and look
17 only at the n-Butyl Cyanoacrylate and view the other two
18 components simply as inert ingredients that went along for
19 the ride? If you did the analysis in that way, would it
20 clear up some of the statistical uncertainties?

21 MS. CHEN: The data was analyzed by the sponsor.
22 Your question about grouping the other way in this matter
23 probably could only be determined by the clinical criteria.
24 What I have seen is what is done by the sponsor, and that is
25 only grouped in separation according to the proportion of n-

1 BCA.

2 DR. WALKER: Okay.

3 MS. CHEN: That is active--that is not my--

4 DR. WALKER: You think they did just consider the
5 active ingredient.

6 MS. CHEN: Yes.

7 DR. WALKER: Okay, fine.

8 All right. We are running a little bit ahead of
9 time, and what I propose we do now is move directly into the
10 Open Panel Discussion portion of the meeting, which includes
11 reviews from three members of the panel who have done some
12 extra homework on that; and then, around noon or whatever
13 seems to be an appropriate break point, we will then take an
14 hour off for lunch rather than going to lunch now.

15 Is that okay with the panel?

16 [Affirmative responses.]

17 DR. WALKER: All right. The three voting members
18 of the Panel who will open this part of the meeting with
19 their remarks are Dr. MacLaughlin, Dr. Hurst, and Dr.
20 Gatsonis.

21 Dr. MacLaughlin will give his remarks on the
22 preclinical aspects of the PMA; Dr. Hurst will provide a
23 clinician's remarks; and Dr. Gatsonis will give the Panel
24 his perspective on the statistical evaluation.

25 After those three presentations, the Panel will

1 discuss and deliberate on the information in the submission
2 and on the information presented by the sponsor and the FDA.
3 At that time, the Panel can ask the sponsor or FDA more
4 questions; and after that general discussion, we will move
5 on to the five specific questions that the FDA had for the
6 Panel, and that probably won't happen until well after
7 lunch.

8 So, Dr. MacLaughlin, if you wouldn't mind starting
9 us off now with your part, we'll run through that, and
10 eventually go to lunch.

11 **Panel Deliberations**

12 DR. MacLAUGHLIN: Well, you have seen some really
13 high-tech presentations. This one is going back to the
14 Stone Age. We in Boston have not yet caught up with the
15 rest of the world.

16 [Viewgraphs.]

17 Let me begin my remarks by saying a couple of
18 things. As a technical reviewer, I can appreciate, after
19 really a lot of reading and research that I have done on
20 this subject, that it is incredibly complicated. And it is
21 complicated by virtue of the anatomy and the definition of
22 the problems and the judgment of the operators. I think I
23 really fully appreciate that.

24 I understand what a really great burden that puts
25 on groups who define a device, and I am prefacing some of my

1 remarks here before this machine comes on to make that
2 point. That is really the crux of my critique of what we
3 are going to see here. It is not that the device doesn't
4 function--it certainly does; there is a long history of it,
5 actually.

6 So, in order to keep things short and sweet, I
7 just want to briefly outline the sorts of things that folks
8 did with this preclinical testing. They do rational and
9 reasonable things in a very logical way--how do you make the
10 stuff; is the material reliable; is the supplier reliable;
11 does the material meet specific criteria for packaging,
12 sterility, long-term stability?

13 I am actually fairly pleased with that; that seems
14 to be perfectly reasonable and well-done, as is the
15 performance criteria in vitro. How liable is it to mix the
16 materials and get polymerization? How long does it take?
17 What is the effect of the oils? What is the effect of the
18 tantalum? All that seems very straightforward to me, and
19 reasonable as far as it goes.

20 I do have a question, though, about the role of
21 the tantalum in the radiopacity studies that you folks
22 provided. There isn't enough detail for me to see what the
23 exact compilation was in those fluoroscopic pictures. Maybe
24 someone could comment on that for me later.

25 At any rate, a lot of this in vitro testing seems

1 very reasonable to me. The safety and toxicity studies,
2 too, as far as they go for their design, seem reasonable in
3 concept. This really gets to the crux of my criticism of
4 the preclinical materials.

5 What has been done with the individual components
6 makes the assumption that this is the worst-case scenario, I
7 think, reasonably stated, 100 percent oil, 100 percent n-BCA
8 is the problem. And we can address that by doing all of the
9 toxicity and safety testing in that way. And actually, I
10 don't completely agree with that for the reasons I'll state
11 in a minute.

12 Let me just say that there were a number of issues
13 outstanding in the PMA that required the sponsor to make
14 some comments and address, and a lot of those were resolved,
15 actually--some very technical issues about what the Material
16 Safety Data Sheets looked like; they had to document some of
17 the details of production and manufacture. All of that was
18 done to my satisfaction, at least, and I thought that was
19 not unreasonable.

20 The analyses also included some of the technical
21 data, again, about pyrogenicity of some of the components;
22 the appropriate suspension test had to be done so that you
23 fall within that one-minute time frame; and actually, a lot
24 of cytochemical, systemic and intracutaneous toxicity
25 testings were done to GLP standards, and that was done, and

1 in fact, they passed, as was alluded to by Dr. Hudson, a lot
2 of those standards. So those kinds of toxicity studies were
3 done.

4 What I see, though, from my perspective as a basic
5 scientist looking at this issue is the question of
6 definition that has been raised here in a number of
7 circumstances. I think that what I conclude from this is
8 that it is probably not reasonable to put on a device like
9 this a single ratio of components for use.

10 As a nonclinician and after reading and hearing
11 presentations, I realize that that is actually not
12 appropriate. What you do is sort of art and science, a
13 mixture of what the clinician feels is best, that changes a
14 lot with the patient.

15 So the issue of definition raises itself, and I
16 prefer to look at it in a slightly different way in the
17 context of the preclinical testing.

18 The second issue relates to the time the device is
19 in place. To me, that is an issue for safety. So the
20 sponsor provides an algorithm based on a lot of data,
21 actually, about what is the customary use in the majority of
22 circumstances; how much oil, how much n-BCA. And I
23 understand that.

24 I also understand, though, that if one targets the
25 device for those ratios and conducts safety and toxicity

1 studies about those, we will miss the safety and toxicity
2 questions that arise when people are using a lot less, a lot
3 more. To me, that is an answerable question and one that I
4 think deserves the attention of the sponsor.

5 It is really not a device to me; it is a series of
6 devices, isn't it? It depends on the judgment of the
7 clinician, which I think they should have. How do you put
8 this mixture together for this patient this day? I think
9 that that latitude should be there.

10 Therefore, how do you make an assessment of how
11 safe the product is? You test the limits. You do more
12 testing, is my suggestion, than you are now doing with
13 mixtures. I think it is safe to say, because this is a
14 highly reactive material, that when it polymerizes, we can't
15 always predict the safety of different formulations.

16 So I have proposed that more safety data needs to
17 be accumulated of the type you are now doing, using
18 different formulations than you are now doing. Some people
19 will use 100 percent n-BCA, and they will say this is right.
20 If I am not mistaken--and a clinician, please help me--but I
21 am thinking, hey, in one circumstance, maybe this is what we
22 should do; in another, we need to be much more slowly
23 polymerizing the material.

24 So being able to test the safety and toxicity of
25 those formulations to me seems an achievable goal, and I